Sensory detection thresholds are modulated across the cardiac cycle: Evidence that cutaneous sensibility is greatest for systolic stimulation

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Abstract

The visceral afferent feedback hypothesis proposes that sensorimotor function is impaired by cortical inhibition associated with increased baroreceptor activation. This study is the first to examine the effects of naturally-occurring variations in baroreceptor activity across the cardiac cycle on cutaneous sensory detection thresholds. In each trial an electrocutaneous stimulus was delivered to the index finger at one of three intervals (0, 300, 600 ms) after the R-wave of the electrocardiogram. Separate interleaving up-down staircases were used to determine the 50% detection threshold for each R-wave to stimulation interval. Cutaneous sensory detection thresholds were lower for stimuli presented at R+300 ms than R+0 ms or R+600 ms. The finding that cutaneous sensibility was greater when stimulated during systole than diastole may be accounted for by a modified afferent feedback hypothesis.

Descriptors: Arterial baroreceptors, Blood pressure, Cardiac cycle time, Sensory detection thresholds

Introduction

The interplay between the cardiovascular system and the nervous system has been a fruitful topic of study in psychophysiology (for review see Vaitl & Schandry, 1995). One of the classic areas of interest concerns how the cardiovascular system influences sensory and motor processes. The visceral afferent feedback hypothesis proposes that natural variations in arterial baroreceptor activation are associated with changes in cortical inhibition, which, in turn, are manifested as differences in sensorimotor performance across the cardiac cycle (e.g., Lacey & Lacey, 1967). The neurophysiological foundations for this hypothesis come from animal research. Bonvallet and colleagues showed that baroreceptor afferents, which project to the nucleus tractus solitarius, can inhibit cortical activity (e.g., Bonvallet & Allen, 1963; Bonvallet & Bloch, 1961; Bonvallet, Dell, & Hiebel, 1954) whereas other experiments indicate that baroreceptor activation can inhibit both sensory (e.g., Gahery & Vigier, 1974) and motor (e.g., Koch, 1932) processes.

Cardiac cycle time studies have tested the visceral afferent feedback hypothesis in humans. The arrival of the pressure pulse wave at the baroreceptors in the aortic arch and carotid sinus distends the vessel walls and generates pulse synchronous afferent firing that is maximal during systole and minimal during diastole (for review see Eckberg & Sleight, 1992). Accordingly, cardiac cycle time studies of sensorimotor function typically deliver stimuli at various points across the cardiac cycle and compare the performance between stimulation points that fall during systole, which occurs approximately 50 ms to 300 ms after the R-wave, with those that fall during diastole, which occurs less than 50 ms and greater than 300 ms after the R-wave. For example, electroencephalographic studies have shown that the amplitudes of auditory and visual evoked potentials are reduced when tones and lights

are presented during systole compared to diastole (e.g., Sandman, Walker, & Berka, 1982; Walker & Sandman, 1979). Similar findings have been reported for pain-related evoked potentials elicited by noxious laser stimulation of the hand (Edwards, Inui, Ring, Wang, & Kakigi, in press).

Psychophysical experiments have examined whether sensory function is influenced by natural variations in arterial baroreceptor activity across the cardiac cycle. The evidence is mixed. Reduced ability to detect near threshold auditory stimuli has been reported when tones were presented during the QRS complex (c. R−40 to R+40 ms) compared to the P-wave (c. R+700 to R+810 ms) of the electrocardiogram (Saxon, 1970). Supra-threshold tones were judged to be quieter when presented in systole than diastole (Cohen, Lieb, & Rist, 1980). Further, recognition thresholds for tachistoscopically presented visual stimuli were highest at R+200 ms and R+600 ms and lowest at R+100 ms, R+500 ms and R+800 ms (Requin & Brouchon, 1964) whereas recognition of visual stimuli was enhanced when stimuli were presented during the P-wave (diastole) compared to the R-wave (diastole) and T wave (systole) of the electrocardiogram (Sandman, McCanne, Kaiser, & Diamond, 1977). In contrast, studies that have employed signal detection theory methods have consistently failed to demonstrate any cardiac cycle related modulation for supra-threshold auditory (Delfini & Campos, 1972; Velden & Juris, 1975) or visual (Elliott & Graf, 1972) sensitivity. In sum, the evidence from intra-cardiac cycle time experiments of auditory and visual perception provides partial support for the visceral afferent feedback hypothesis. Closer examination of the positive and null findings reveals (a) that the effect sizes of the cycle time effect for sensory function are small, and (b) that sample sizes are small (minimum = 4, maximum = 26, median = 13). Therefore, the inconsistent pattern of results may be attributed, at least in part, to low

power. In addition, these studies were conducted several decades ago, and therefore may not withstand current methodological standards. Accordingly, studies with larger sample sizes using improved modern recording techniques should provide a fair and robust test of predictions derived from the afferent feedback hypothesis for sensory function.

Evidence that sensorimotor function is modulated by natural variations in baroreceptor stimulation comes from reaction time and neurophysiological studies. Recent experiments indicate that simple auditory, visual, electrocutaneous and vibrotactile reaction times decreased in a linear fashion across the cardiac cycle (e.g., Edwards, Ring, McIntyre, Carroll, & Martin, 2007; McIntyre, Ring, Edwards, & Carroll, 2008). Other research shows that the nociceptive flexion reflex (e.g. Edwards, Ring, McIntyre, & Carroll, 2001; McIntyre, Kavussanu, & Ring, 2008; McIntyre, Edwards, Ring, Parvin, & Carroll, 2006) and pain-related evoked potentials (Edwards et al., in press) are modulated in a quadratic manner across the cardiac cycle, with responses lower during systole than diastole. Despite the different patterns of modulation (i.e. linear versus quadratic), these reaction time and neurophysiological findings are compatible with an afferent feedback hypothesis that is modified to account for varying transmission and processing delays for different modalities (Edwards et al., 2007; McIntyre et al., 2008).

This report is a follow-up to our earlier report that investigated the influence of high blood pressure on sensory and motor nerve function as well as their relationships to cutaneous sensitivity (Edwards, Ring, McIntyre, Winer, & Martin, 2008). The present report is, to our knowledge, the first to examine cutaneous sensory detection thresholds across the cardiac cycle and thereby determine the effects of natural variations in baroreceptor stimulation on skin sensibility. Based on the theory

that baroreceptor stimulation causes cortical inhibition and the evidence for heightened auditory and visual perception during diastole (P wave), it was hypothesized that cutaneous sensibility would be reduced during systole compared to diastole.

Hypertension is characterized by reduced sensitivity to peripheral stimulation (Ghione, 1996; Waldstein, Manuck, Ryan, & Muldoon, 1991). For example, individuals with high blood pressure have higher detection thresholds for electrical tooth pulp stimulation (Ghione, 1996) and electrocutaneous hand stimulation (Edwards et al., 2008; Rosa, Vignocchi, Panattoni, Rossi, & Ghione, 1994) as well as compromised visual perception (Mazzucchi et al., 1986; Shapiro, Miller, King, Ginchereau, & Fitzgibbon, 1982). If the cardiac cycle effect is attributable to activation of the arterial baroreceptors, it may be expected that absolute blood pressure level, by affecting this activation, should influence any cardiac cycle time effects for sensory thresholds. Accordingly, the present study tested the hypothesis that any cardiac cycle time effect for electrocutaneous sensory thresholds would be moderated by tonic blood pressure levels (cf. Birren, 1965; McIntyre et al., 2006)

Method

Participants

Fifty-nine adults (31 men, 28 women) with a mean age of 38 (*SD* = 7) years participated. Their mean (range) systolic and diastolic blood pressures were 135 (98-164) and 87 (68-111) mmHg, respectively. Further participant details are provided in Edwards et al. (2007).

Apparatus and Measurements

Laboratory blood pressure was measured using an oscillometric sphygmomanometer (Dinamap, Critikon) and a brachial cuff attached to the left arm. An electrocardiogram was recorded continuously at 2000 Hz using three disposable wet gel electrodes (Invisatrace 1680, ConMed) placed in a modified chest configuration; the electrocardiographic signal was amplified and filtered (0.1–100 Hz plus 50 Hz notch filter) by an AC amplifier (ICP511, Grass). The two active electrodes were placed on the right clavicle and on a rib below the heart on the left side of the torso; the ground electrode was placed on the left clavicle.

Stimuli (1 ms square wave pulses at 250 Hz for 60 ms) were delivered electrocutaneously by a constant current stimulator (DS7A, Digitimer) via a surface electrode secured to the index finger of the dominant hand. The stimulating electrode comprised two 10 mm stainless steel disks (Nicolet) secured with tape on the skin of the dorsolateral surface of distal phalanges with the anode medial. Participants sat upright and supported their dominant forearm on a table while their hand rested on a box. This box contained a piezo-oscillator, red and green light emitting diodes, and buttons marked "no" and "yes". A computer was programmed in Spike2 (CED) to record responses and present stimuli using a Power1401 (CED).

Procedure

Participants sat and relaxed during a 5-min rest period while their blood pressure was measured at 30, 150, and 270 s; recordings were averaged to provide measures of resting systolic and diastolic blood pressure. Next, three cutaneous detection thresholds were determined concurrently by interleaving three up-down staircases (Levitt, 1971). Each staircase determined the cutaneous detection threshold at one of

three intervals after the R-wave of the electrocardiogram (R + 0 ms, R + 300 ms, R + 600 ms). A green warning light (1000 ms duration) was illuminated to signify the beginning of each trial, while a red light (variable duration; the light remained illuminated until the participant made a response, up to a maximum of 7500 ms) signified the end of the trial. The illumination of the green light was followed by a one second delay, then the computer program initiated a search for the R-wave of the electrocardiogram. The participant's finger was then stimulated by a series of five square-wave pulses of 1 ms duration at 250 Hz at one of three R-wave intervals (R + 0 ms, R + 300 ms, R + 600 ms). Participants were told that the stimulus could occur at any point between presentation of the green and red lights. At the end of each trial participants pressed the "yes" button if they felt something and the "no" button if they did not feel anything. On the first trial of each staircase, the stimulus intensity was 0 mA. For each staircase, stimulus intensity was increased in 1 mA steps until the participant first detected a sensation (first reversal), and then decreased in 0.4 mA steps until the participant no longer detected a sensation (second reversal). Each staircase then continued in 0.1 mA steps until the three staircases had completed three further ascending and descending series (i.e., six more reversals). The 50% cutaneous sensory threshold (mA) was defined as the average of the peaks and troughs during the second and third series (i.e., third, fourth, fifth and sixth reversal points) of each staircase. The inter-trial interval was 3 s.

Data Reduction and Analysis

The blood pressure recordings were averaged to provide measures of resting laboratory systolic blood pressure, diastolic blood pressure and pulse rate. A 3

Interval (R+0, R+300, R+600 ms) repeated measures MANOVA, , using the

multivariate method, was used to analyse differences in cutaneous sensory thresholds

among the three R-wave-to-stimulation intervals. Significant interval effects were

followed by post hoc comparisons (all possible pairwise comparisons were

computed). Planned orthogonal comparisons were conducted to examine the

patterning of sensory thresholds across the intervals of the cardiac cycle.

Correlational analyses were conducted to examine the associations between

continuous blood pressures and the change in cutaneous sensory thresholds across the

cardiac cycle. Change scores were calculated to reflect the degree of modulation in

sensory thresholds among the three R-wave intervals (R+0, R+300, R+600 ms).

ΔL_{early} was calculated to reflect the difference in sensory thresholds between R+300

ms and R+0 (R+0 – R+300). ΔL_{late} signified the difference in sensory thresholds

between R+300 ms and R+600 (R+600 – R+300). ΔL_{mean} reflected the average

difference in sensory detection thresholds ($\Delta L_{early} + \Delta L_{late}$ / 2). Correlational analyses

were followed by hierarchical regression analyses that adjusted for potential

confounding variables; gender and age (Takekuma, Ando, Niino, & Shimokata,

2000). The data were analysed using Statistica '99. Eta-squared (η^2), a measure of

effect size, is reported. A significance level of .05 was adopted.

Results

Cutaneous Sensibility across the Cardiac Cycle

The primary aim was to assess the effects of the cardiac cycle on skin sensibility. A 3

Interval (R+0, R+300, R+600 ms) repeated measures MANOVA revealed significant

variations in sensory thresholds across the cardiac cycle, $F(2,57) = 5.49$, $p = .007$, η^2

$=$ .16, that were characterized by a quadratic trend, $F(1,58) = 8.67$, $p =$ .005, $\eta^2 =$ .13 (see Figure 1). Newman-Keuls post hoc tests (critical ranges: step 1 = .015, step 2 = .018) confirmed that cutaneous thresholds were lower midcycle (R+300 ms) than early cycle (R+0 ms), p = .05, and late cycle (R+600 ms), p =.004.

Tonic Blood Pressure as a Moderator of Cardiac Cycle Time Cutaneous Sensibility

A secondary aim was to determine whether the cardiac cycle time effect for sensory thresholds was moderated by tonic blood pressure levels. Correlational analyses examined the associations between resting blood pressures and the differences in cutaneous thresholds between mid and early cycle ($\Delta L_{early} = R+0 - R+300$), between mid and late cycle ($\Delta L_{late} = R+600 - R+300$), and their average ($\Delta L_{mean} = \Delta L_{early} + \Delta L_{late} / 2$). Diastolic blood pressure correlated significantly with ΔL_{late} ($r =$ .34, $p =$ .008) and marginally with ΔL_{mean} ($r =$ .24 $p =$ .07). No other coefficients were significant (rs = .01 to .16). Next, hierarchical regression analyses were conducted to control for potential confounding. Gender and age, which can influence electrocutaneous thresholds (Takekuma et al., 2000), were entered in the first step whereas diastolic blood pressure was entered in the second step. These analyses confirmed a robust association between diastolic blood pressure and ΔL_{late} ($B = 0.001$, 95% CI for $B = 0.000$ to 0.002, $\beta =$ .33, $t = 2.41$, $\Delta R^2 =$ .09, $p =$ .02). Similar analyses using systolic blood pressure were not significant.

Discussion

Cutaneous sensory thresholds were lower, indicating that cutaneous sensibility was augmented, when electrocutaneous stimuli were delivered during the systolic phase of

the cardiac cycle compared to diastole. The present study is therefore the first to demonstrate a cardiac cycle time effect for tactile sensation. However, the pattern of modulation observed for cutaneous detection thresholds was contrary to our predictions that were based on cardiac cycle time experiments using other stimulus and response modalities (e.g., Edwards et al., 2001; Edwards et al., 2007). Such a varying pattern of modulation across the cardiac cycle reported here and in previous cardiac cycle time studies (e.g., Edwards et al., 2001; Edwards et al., 2007) suggests that the baroreceptors influence each sensory modality and behavioural measure in a specific way, presumably reflecting the different ascending afferent pathways and brain areas involved.

Arterial baroreceptors are stimulated by the pulse pressure wave distending the arterial wall. At rest, when mean arterial pressure is low, these stretch receptors are stimulated only during systole and therefore activation is pulsatile (Angell-James, 1971; Coleridge, Coleridge, & Schultz, 1987). For data from the current cycle time experiment to constitute evidence of baroreceptor-mediated interference, the pattern of modulation of cutaneous sensibility should conform to that of baroreceptor activity. The pulse pressure wave reaches the aortic arch and carotid sinus at R+90 ms and R+140 ms, respectively (Kroeker & Wood, 1955; Rushmer, 1976). Arterial baroreceptors begin firing at the onset of the systolic upstroke, peak 100 ms later, and continue for 250 ms (e.g., Angell-James, 1971; Coleridge et al., 1987). Accordingly, the integrated baroreceptor output across both locations can be estimated to extend from 90-390 ms after the R-wave, with the greatest output around 250 ms.

The visceral afferent feedback hypothesis (Lacey & Lacey, 1967) proposes that natural variations in arterial baroreceptor activation are associated with changes in cortical inhibition, which, in turn, are manifested as differences in sensorimotor

performance across the cardiac cycle. The quadratic patterning of cutaneous thresholds observed in the present study is not compatible with this hypothesis. Accordingly, an alternative explanation is needed. Several putative mechanisms may be suggested that could help to explain our findings. First, the visceral afferent feedback hypothesis may still apply, but only if an additional delay related to the duration of a perception is assumed. Given that the minimum perceptual duration has been calculated at 170 ms for audition and 240 ms for vision (e.g., Efron, 1970a; Efron, 1970b), it is likely that cutaneous perceptions last *at least* 200 ms. A modified visceral afferent feedback hypothesis could account for the present findings if it is assumed that cutaneous perceptions last approximately 600 ms. With this duration, the timing of higher order processing of cutaneous stimuli overlaps with that for central baroreceptor-related activation. However, the duration of a perception may not be isomorphic with neural processes that are likely to be the target for baroreceptor-related influence. Therefore, this account seems unlikely. Second, another modified visceral afferent feedback hypothesis may explain our findings. In this version of the hypothesis it is assumed that the cortical inhibition associated with baroreceptor activation reduces the amount of inhibition of afferent somatosensory transmission in the spinal cord and/or central processing of somatosensory information in the brain (cf., Dubner & Ren, 1999). Thus, increased cutaneous sensibility may reflect a baroreceptor-mediated *release of inhibition*. Third, the increased cutaneous sensibility observed for stimuli presented at R+300 ms may reflect an *enhancement effect* (Verrillo & Gescheider, 1975; 1976), which is a temporal summation process manifested by the perception of enhanced intensity when an individual is stimulated more than once in close temporal proximity. In the case of the present study, the cutaneous sensation elicited by stimulation of the index finger

may have been incorporated with sensations associated with the heart beat, which occur approximately 100-300 ms after the R-wave (for review see Brener & Ring, 1995). Finally, it is possible that changes in either peripheral or central blood flow could affect neural transmission and/or processing. Clearly, the merits of each of these hypotheses need to be proven by investigation.

The finding that individuals with higher blood pressure had larger reductions in sensory threshold during systole (R+300 ms) compared to diastole (R+600 ms) may suggest that the baroreceptor influence on cutaneous sensibility becomes greater as tonic blood pressure increases. However, this pattern was only significant for the change in threshold between R+300 ms and R+600 ms, and not between R+0 ms and R+300 ms. Accordingly, further studies are required that examine sensory thresholds with small intervals to provide greater temporal resolution to document the cardiac cycle effects on perception.

In sum, the current study revealed that cutaneous sensibility was modulated across the cardiac cycle, with cutaneous detection thresholds higher for diastolic stimulation. The findings add to the literature reporting widespread modulation of the sensory systems across the cardiac cycle. Further studies are required to determine the mechanism underlying variations in perception with changes in cardiovascular activation.

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Figure Caption

Figure 1. Mean (Standard Error) Cutaneous Sensory Thresholds at Three Intervals of

the Cardiac Cycle.