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Abstract

In recent years, numerous studies have established a connection between blood pressure and nociception. While this connection is well documented in the literature, its underlying physiological mechanisms have yet to be elucidated. Much attention has focused on the relationship between cardiovascular regulatory centers and nociception, yet the intricacies of this relationship have not been fully explored. Therefore, the purpose of this investigation was to examine the role of the baroreflex system as a modulator of pain perception. Twenty normotensive males participated in two laboratory sessions. Time to cold pain threshold and pain tolerance was measured at rest during the first visit. On visit two, blood pressure was orthostatically manipulated via tilt table at postures 90°, 120°, and 180°. Orthostatic manipulation significantly lowered systolic blood pressure (SBP), pain threshold, and pain tolerance from seated baseline at 120° and 180°. The regression models for baroreceptor reflex sensitivity (BRS) assessed during seated baseline and at 120° and 180° revealed a significant negative beta weight for the effect of SBP. A significant negative beta weight for the effects of BRS, SBP, and their interaction was observed at 90°. In conclusion, orthostatic baroreceptor activation appears to exert an inhibitory effect on the brain that decreases pain sensitivity.

Keywords

Pain Threshold, Pain Tolerance, Blood Pressure, Baroreceptors

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Orthostatic-induced Hypotension Attenuates Cold Pressor Pain Perception

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ABSTRACT

Wonders, KY and Drury, DG. Orthostatic-Induced Hypotension Attenuates Cold Pressor Pain Perception. *JEPonline* 2010;13 (1): 21-32. In recent years, numerous studies have established a connection between blood pressure and nociception. While this connection is well documented in the literature, its underlying physiological mechanisms have yet to be elucidated. Much attention has focused on the relationship between cardiovascular regulatory centers and nociception, yet the intricacies of this relationship have not been fully explored. Therefore, the purpose of this investigation was to examine the role of the baroreflex system as a modulator of pain perception. Twenty normotensive males participated in two laboratory sessions. Time to cold pain threshold and pain tolerance was measured at rest during the first visit. On visit two, blood pressure was orthostatically manipulated via tilt table at postures 90°, 120°, and 180°. Orthostatic manipulation significantly lowered systolic blood pressure (SBP), pain threshold, and pain tolerance from seated baseline at 120° and 180°. The regression models for baroreceptor reflex sensitivity (BRS) assessed during seated baseline and at 120° and 180° revealed a significant negative beta weight for the effect of SBP. A significant negative beta weight for the effects of BRS, SBP, and their interaction was observed at 90°. In conclusion, orthostatic baroreceptor activation appears to exert an inhibitory effect on the brain that decreases pain sensitivity.

Key Words: Pain Threshold, Pain Tolerance, Blood Pressure, Baroreceptors.

INTRODUCTION

Zamir and Shuber (56) were the first to report an association between high blood pressure and hypoalgesia in humans. Since then, numerous studies have documented the phenomenon of hypoalgesia in hypertensive individuals (for review, see Ghione 1996) (22), as well as in borderline hypertensive individuals (21, 39, 43, 44) and in those at increased risk for hypertension (8). Conversely, a connection between hypotension and hyperalgesia has also been widely reported (23, 32, 34, 45). While this connection between blood pressure and nociception is well documented in the literature, its underlying physiological mechanisms have yet to be elucidated. Much attention has focused on the connection between cardiovascular regulatory centers and nociception. Specifically, several lines of research have identified the baroreflex system as an important modulator of nociception (15, 24, 27, 37, 38).

Together with the autonomic nervous system, the baroreceptor reflex is an important regulatory mechanism in the short term control of blood pressure and heart rate. Arterial baroreceptors located in the aortic arch and carotid sinus are stimulated during systole by distension of the arterial wall created by the pressure pulse wave (28). At rest, increases in blood pressure stimulate a negative feedback loop, or baroreflex. In turn, baroreceptor output elicits an increase in parasympathetic activity and a decrease in sympathetic activity, thereby reducing arterial blood volume and consequently, blood pressure. Autonomic changes related to baroreceptor control are typically studied by evaluating the R-R intervals and changes in blood pressure. Baroreflex sensitivity (BRS) is often used to quantify baroreceptor function, and is classically defined as the slope of the relationship between the R-R interval per unit of blood pressure change, plotted during both increases and decreases in blood pressure (48, 51, 52).

In addition to its role in blood pressure regulation, baroreceptors are known to modulate central nervous activity by exerting an inhibitory effect on the brain (20, 26, 40). Anatomically, baroreceptors converge in the brain at the same place that nociceptive impulses are processed (4, 55). Specifically, the first synapse of the baroreceptor reflex is located in the nucleus of the solitary tract (NTS) within the medulla oblongata (6). The NTS projects into the periaqueductal grey and the locus coeruleus; both of which are involved in the modulation of nociceptive pathways (6, 30). Thus, stimulation of the NTS produces an antinociceptive effect (1). Therefore, it is quite possible that the relationship between blood pressure and nociception may be due to inhibitory influences from brain areas that are involved in cardiovascular regulation and pain modulation. This inhibitory effect has been attributed to a decrease in pain sensitivity in humans (36).

The intricacies of the relationship between pain perception and blood pressure have not been fully explored. Investigators have used drugs (12, 15, 36), psychological stress (9), and baroreceptor stimulation (17, 29, 35) and other means to manipulate the relationship between blood pressure and pain perception. Exercise (25, 34) and lower body negative pressure (46) have also been used to elicit systemic pressure changes for the study of pain perception. Although orthostatic manipulation is a relatively rudimentary means of introducing a cardiovascular challenge, this form of blood pressure variation is very common in the human experience. Therefore, it represents a practical method to study the subtleties of the baroreceptors as they relate to pain perception. The purpose of this investigation was to study the differences in resting pain perception induced by orthostatic manipulations in blood pressure.

METHODS

Subjects

A total of 20 normotensive males were included in this study (Table 1). Exclusion criteria comprised acute or chronic pain of any kind and the use of psychoactive drugs, analgesics, or medication affecting the cardiovascular system. Subjects were asked to refrain from caffeine, nicotine, alcohol, and strenuous exercise for at least 4h before their arrival at the laboratory. All methods were approved by the Wright State University Institutional Review Board prior to the onset of data

Table 1. Subject characteristics.

Characteristic	Value
Age (years)	22.4 ± 0.3
Percent body fat (%)	19.8 ± 2.1
BMI (in kg/m²)	25.9 ± 1.1

Values are means ± SE.

collection. The estimated sample size required to detect significant differences using four levels of posture as an independent variable and blood pressure, BRS, and pain as dependent variables was calculated based on: 1) an alpha level of 0.05; 2) a power level of 0.80; and 3) a moderate effect size (11). It was estimated that approximately 17 to 18 subjects would be needed to detect significant differences.

Procedures

Subjects reported to the laboratory on two separate occasions within a one-week period with each session being completed at approximately the same time of day. On day one, basic anthropometric measurements (height, weight, and body composition) were collected. The subject was then prepped for a 12-lead electrocardiogram and continuous blood pressure monitoring. Continuous systolic and diastolic blood pressure (SBP and DBP, respectively, in mmHg) measurements were obtained using a Biopac Systems NIBP 100B blood pressure monitor. This non-invasive blood pressure monitor generates a continuous arterial pressure signal via the tonometric measurement technique. The tonometric signal is equivalent to the continuous arterial pressure signal produced by an arterial, in-line, pressure transducer (5). The cuff was placed at the distal edge of the radius bone of each subject's dominant arm, directly over the radial artery. A 12-lead electrocardiogram recording by means of polygraph (Cardioline WS2000, Remco Italia) connected with a microcomputer was used for measurement of heart period at a sampling rate of 1000 Hz. Heart period, or cardiac interbeat interval (IBI, in msec), is defined as the length of time between successive R-waves (7).

BRS, expressed as the change in IBI per mmHg blood pressure change, was measured using the technique of Steptoe and Sawanda (51). As such, ascending BRS was determined by identifying sequences with at least three consecutive increases in SBP accompanied with increases in IBI, and calculating regression lines. Since a time lag of one heartbeat is known to produce the best estimate of BRS (52), each systolic value was paired with the heart period from the immediate following cycle. Descending BRS sensitivity was assessed in an analogous manner by identifying consecutive decreases in IBI associated with decreases in SBP. Minimal criteria for changes in blood pressure and IBI were applied as 1 mmHg and 2 msec, respectively. Mean sensitivity values were computed separately for ascending and descending sequences, as well as for all detected reflex sequences.

Pain threshold and pain tolerance were measured via the cold pressor test (16, 54). The apparatus for the cold pressor consisted of a container filled with ice and water that was maintained between 1°C and 3°C. The use of a water circulator (Micro-Mark 83345) prevented the water from warming near the subject's hand. In order to control for possible variations in skin temperature, subjects placed their non-dominant hand and forearm in a water bath of 37°C for 3 min prior to testing. At the onset of the test, subjects were instructed to submerge the non-dominant hand to a marked line at the level of the styloid process of the ulna, and to remain still. Subjects were asked to indicate when the sensations in their hand first became painful (pain threshold) and to also indicate when they were no longer willing or able to tolerate the pain by saying "stop" (pain tolerance). A maximum time limit of 5

min was imposed, though subjects were not informed of this limit prior to testing. A 10-cm line visual analogue scale was presented to each subject at 30-second intervals during the cold pressor test in order to quantify the intensity of experienced pain.

After the completion of the prepping procedures, the subject sat quietly for 10 min to ensure a resting physiological condition. At the conclusion of this 10-min period, nociceptive variables (pain threshold, pain tolerance, and pain intensity ratings) and cardiovascular variables (SBP, DBP, IBI, and BRS), were obtained in the seated position and served as seated baseline measurements for statistical analyses. After seated baseline measurements were determined, the subject remained seated and nociceptive and cardiovascular variables were again measured at 20 min and 40 min.

On the second visit, a Bailey 9500 Series Tilt Table was used to orthostatically manipulate blood pressure. The nociceptive and cardiovascular variables previously described were collected at three different postures; 90°, 120°, and 180°. The order in which these postures were introduced was randomized and 20 min was given for blood pressure to stabilize between each trial.

Statistical Analyses

Descriptive statistics have been computed as means and standard deviations. A repeated-measures ANOVA using within subjects main effect was used to determine if posture significantly altered cardiovascular and nociceptive variables. Moderated regression analysis was used with BRS, SBP, and their interaction serving as predictors. Four separate models were computed based on the BRS assessed at seated baseline and during each posture. The main effect predictor variables were centered prior to analyses. Significant effects of the interaction term were considered indicative of a relationship between BRS and pain perception by blood pressure. To test for possible interaction effects, regression lines were computed for the regression of pain intensity on BRS at two levels of SBP (one standard deviation above the mean and one standard deviation below the mean) (10). Interaction effects were determined by the computation of regression lines for pain intensity on BRS and the slopes of these levels were tested for significance. A significance level of $P < 0.05$ was used for all statistical analyses.

RESULTS

Seated baseline and tilt table data are presented in Tables 2 and 3. Orthostatic manipulation significantly lowered SBP from seated baseline at 120° and 180° ($F_{(3,17)} = 12.33$, $P = 0.015$ and $F_{(3,17)} = 12.42$, $P = 0.012$, respectively), while DBP was

Table 2. Cardiovascular variables.

	SBP (mmHg)	DBP (mmHg)	Heart Rate (bpm)
Seated baseline	124.5 ± 2.2	80.1 ± 3.2	82.4 ± 2.8
90°	126.7 ± 2.3	81.9 ± 1.4	84.8 ± 3.2
120°	120.1 ± 2.4*	82.5 ± 1.6	83.4 ± 2.5
180°	119.6 ± 2.3*	73.9 ± 1.7*	76.7 ± 2.4

Values are means ± SE. Abbreviations: SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure. *Significantly lower than seated baseline ($P < 0.05$).

only significantly decreased from seated baseline at 180° ($F_{(3,17)} = 10.22$, $P = 0.024$). Pain threshold and pain tolerance values were significantly decreased from seated baseline levels at the 120° ($F_{(3,17)} = 10.59$, $P = 0.02$ and $F_{(3,17)} = 13.81$, $P = 0.016$, respectively) and 180° postures ($F_{(3,17)} = 10.26$, $P = 0.033$ and $F_{(3,17)} = 9.53$, $P = 0.04$, Figures 1 and 2, respectively).

Table 3. Nociceptive variables.

	Pain Rating	Pain Threshold (sec)	Pain Tolerance (sec)
Seated baseline	7.4 ± 0.8	67.4 ± 8.4	189.8 ± 18.6
90°	6.9 ± 1.0	50.4 ± 7.6	158.4 ± 21.0
120°	7.9 ± 1.1	37.1 ± 5.9*	121.9 ± 19.4*
180°	8.5 ± 0.7	30.8 ± 4.6*	132.2 ± 19.8*

Values are means ± SE. *Significantly lower than seated baseline ($P < 0.05$).

Results of the moderated regression analyses with BRS,

SBP, and their interaction are presented in Tables 4, 5, 6, and 7. The regression models for BRS

assessed during seated baseline and at the 120° and 180° postures revealed a significant negative beta weight for the effect of SBP (Table 4, 5, and 6, respectively). The model with BRS measured at the 90° posture produced significant negative beta weights for the effects of BRS, SBP, and the interaction term (Table 7).

Table 4. Moderated regression analysis for the prediction of pain perception by BRS during seated baseline, SBP, and their interaction ($R = 0.64$).

Predictors	Standardized β -weights	P
<i>BRS</i>	-0.19	0.075
<i>SBP</i>	-0.33	0.042
<i>Interaction</i>	-0.22	0.061

The regressions of pain perception on BRS at high and low SBP levels (one standard deviation above the mean and one standard deviation below the mean, respectively) are displayed in Table 8. All simple slopes were negative. An inverse relationship was found between SBP and the

simple slopes, with high SBP being associated with decreased simple slopes.

DISCUSSION

The primary finding of this investigation lies in the negative correlation between BRS and the intensity of experienced pain. Because the baroreceptors are stretched and therefore stimulated with an increase in systemic pressure, these findings indicate that thermal pain sensitivity is decreased during periods where blood pressure is elevated. This is in agreement with other investigations (14, 15) where augmentations in BRS have been found to be associated pain inhibition. The degree of pain inhibition appears to change with natural variations in baroreceptor activity across the cardiac cycle. During the systolic phase, baroreceptors are maximally active. Thus, the systolic phase is associated with a reduced nociceptive response compared to the diastolic phase of the cardiac cycle, when baroreceptors are only marginally active (17-19).

Table 5. Moderated regression analysis for the prediction of pain perception by BRS during 120°, SBP, and their interaction ($R = 0.58$).

Predictors	Standardized β -weights	P
<i>BRS</i>	-0.22	0.097
<i>SBP</i>	-0.26	0.044
<i>Interaction</i>	-0.17	0.120

Table 6. Moderated regression analysis for the prediction of pain perception by BRS during 180°, SBP, and their interaction ($R = 0.61$).

Predictors	Standardized β -weights	P
<i>BRS</i>	-0.18	0.11
<i>SBP</i>	-0.28	0.038
<i>Interaction</i>	-0.20	0.068

A possible explanation for this hypoalgesic effect may lie within the anatomy and physiology of the structures involved with the baroreflex. The NTS is the central termination site of baroreceptor afferents. Exogenous angiotensin II in the NTS attenuates the baroreceptor reflex via activation of endothelial nitric oxide synthase (33). Other researchers have reported a relationship between the reduction in

baroreflex gain and a heightened hypoalgesia (24). Interestingly, circulating angiotensin II increases during dynamic exercise (50) and in forms of secondary hypertension (49), two conditions associated with hypoalgesia.

In the current study, blood pressure was manipulated through an orthostatic challenge. In so doing, we were able to significantly change blood pressure without the concomitant sympathetic alterations in the cardiovascular systems that are often associated with physical exertion or pharmacological intervention. This was done in an attempt to isolate the relationship between blood pressure and pain perception as it relates to body positions often encountered through daily living. In a similar investigation of pain perception and orthostatic manipulation, Shimoda and Ikuta (47) compared the heart rate variability

Table 7. Moderated regression analysis for the prediction of pain perception by BRS during 90°, SBP, and their interaction ($R = 0.58$).

Predictors	Standardized β -weights	P
<i>BRS</i>	-0.27	0.033
<i>SBP</i>	-0.38	<0.01
<i>Interaction</i>	-0.37	<0.01

scores and spontaneous baroreceptor sensitivity of 20 healthy male volunteers in a horizontal position and a 70° head-up tilt. The authors concluded that electrical current pain thresholds studied were lower at 70° as compared to the horizontal posture. They concluded that the heart rate variability and baroreceptor sensitivity scores observed indicated a decrease in parasympathetic tone that ultimately led to lower pain perception scores that are consistent with theories related to

Table 8. Simple slopes and P-values for the regressions of pain perception on BRS at high and low SBP levels.

SBP Level	Seated baseline		90°		120°		180°	
	Simple Slope	P	Simple Slope	P	Simple Slope	P	Simple Slope	P
Low	-0.02	0.74	0.082	0.053	-0.027	0.51	-0.007	0.074
High	-0.092	0.099	0.24	<0.01	-0.064	0	-0.01	0.11

Abbreviations: High SBP; one standard deviation above the mean, Low SBP; one standard deviation below the mean.

and baroreceptor sensitivity scores observed indicated a decrease in parasympathetic tone that ultimately led to lower pain perception scores that are consistent with theories related to

hypertension induced hypoalgesia.

The connection between high blood pressure and hypoalgesia has been widely reported (8, 21, 22, 39, 43, 44). This phenomenon may be detrimental to those with hypertension who may unintentionally endure more pain than necessary during a cardiovascular event. In the current investigation, both time to pain perception and time to pain tolerance were significantly lower in positions that correspond with a decrease in systolic pressure. Although these findings are tracking a cardiovascular change related to a decrease in pressure versus an increase, the relationship between blood pressure, baroreceptor sensitivity and pain perception is still reaffirmed by these data.

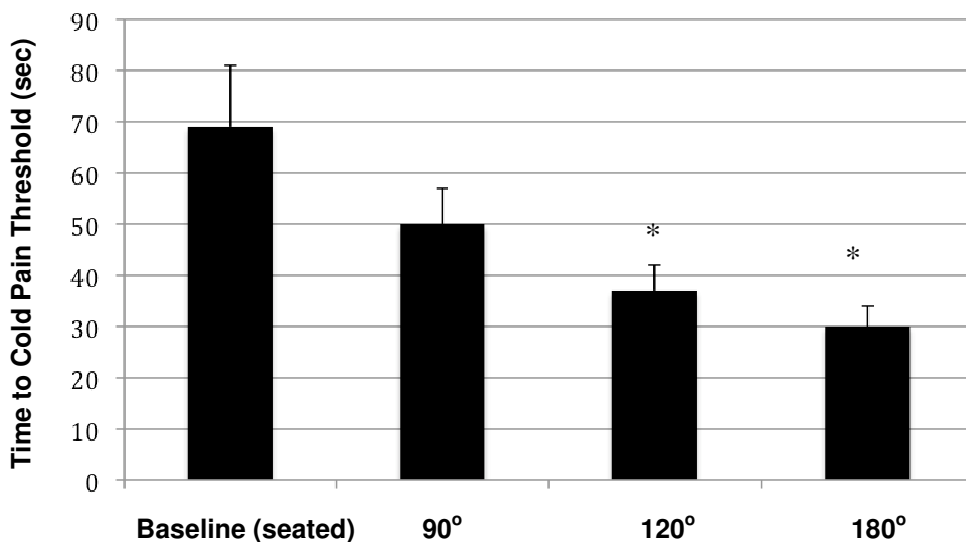


Figure 1. Pain Threshold. *P<0.05 vs. baseline

In individuals with high BRS, small blood pressure fluctuations result in strong reflex responses and a more pronounced pain inhibition. Thus, it can be expected that the relationship between blood pressure and BRS sensitivity would be less pronounced in individuals with blood pressure in the lower end of normotensive range. This was the case in the present study, given that we found a negative relationship between BRS and the intensity of the experienced pain.

Multiple regression analysis using SBP as a covariate revealed that this effect was most pronounced when SBP values were above 130 mmHg. As SBP decreased, BRS was attenuated. Research on the antinociceptive effect of baroreceptor activation has been conflicting. Rau et al. (39) reported an increase in pain threshold following baroreceptor stimulation for mechanical, but not thermal pain. In contrast, Angrilli and coworkers (3) found a reduction in perceived pain intensity during baroreceptor stimulation in subjects with blood pressures at the higher end of the normotensive range. No such effect was found for individuals with lower blood pressure. In addition, Duschek and colleagues (13) reported an inverse association between BRS and pain experience that was attenuated as SBP decreased below 130 mmHg.

The above findings are consistent with reports describing a baroreceptor 'set-point' which can be set and reset over time (2). Numerous studies on hypertensive subjects have established that pain perception appears to be altered in this population. As resting blood pressure rises, patients have a diminished ability to sense pain. Although this relationship is not completely understood, some researchers have attributed this phenomenon to a resetting of the baroreceptors (2, 19, 53). In the presence of noxious stimulation, increases in blood pressure stimulate the baroreceptors that produce a global modulation of central nervous system activity and decreases in cortical arousal. This cortical-inhibitory effect reinforces the gains in blood pressure (15). In addition, cortical inhibition produces a generalized inhibitory effect, resulting in a decrease in spinal somatic sensory pathways and attenuated behavioral reactions to painful stimuli (14).

Although no attempt was made to monitor the activity of the otoliths found in the inner ear, several researchers have observed a vestibulosympathic reflex in animals and in humans (31, 41, 42).

Although this relationship has not been fully explored, it is worth mentioning here as a potential variable that may have played a role in explaining our findings. The fact that we did not observe any differences in our baseline values (seated) as compared to 90° (standing) may be partially explained by the similar position of the head in both of these positions. Although one might expect more muscular involvement in the 90° standing position as compared to the seated baseline measurement, these differences are likely to be nominal given the skeletal support of the legs in an extended position while being strapped to the tilt table. Consequently, the cardiovascular and vestibular factors affecting our subjects in these two positions were indeed very similar. Future investigations into the relationship between orthostasis and pain perception may benefit by including variables associated with the vestibulosympathic reflex.

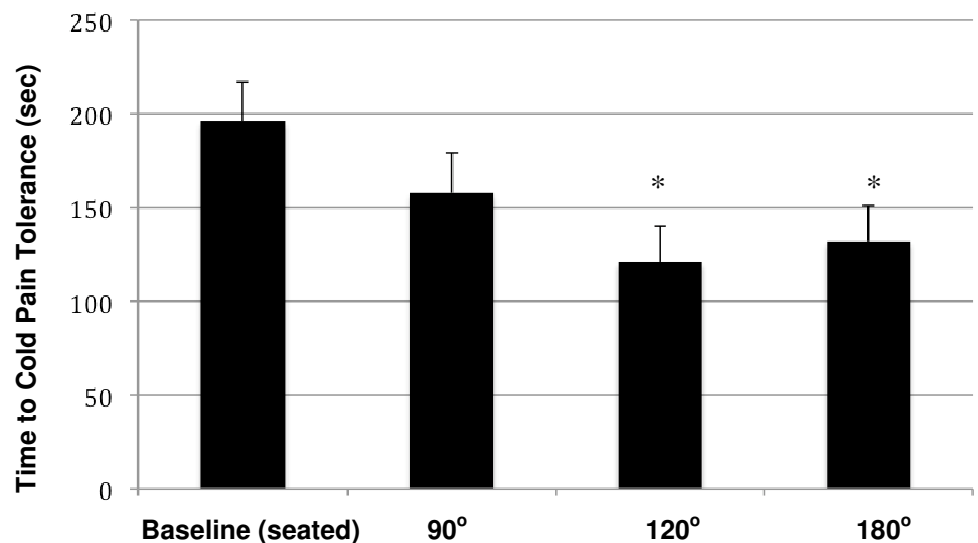


Figure 2. Pain Tolerance. * $P < 0.05$ vs. baseline

these differences are likely to be nominal given the skeletal support of the legs in an extended position while being strapped to the tilt table. Consequently, the cardiovascular and vestibular factors affecting our subjects in these two positions were indeed very similar. Future investigations into the relationship between orthostasis and pain perception may benefit by including variables associated with the vestibulosympathic reflex.

CONCLUSIONS

In summary, baroreceptor activation through orthostatic manipulation appears to exert an inhibitory effect on the nervous system that decreases thermal pain sensitivity. This effect seems to be most pronounced when SBP rises above 130 mmHg. These results are consistent with other investigations that have demonstrated a connection between blood pressure control and pain perception.

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