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Relationship between Resting Systemic Arterial Blood Pressure and Pain Sensitivity Parameters in Young Healthy Indian Medical Students

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ABSTRACT

Background

Pain interests clinicians and researchers alike. Several animal and human studies have attempted to establish and explain the relationship between blood pressure and nociception. Many studies have reported sex differences in pain perception in humans. However, there is no consistent evidence that authoritatively explains the relationship between resting systemic arterial blood pressure and pain sensitivity parameters in human subjects.

Objective

To investigate the relationship between resting systemic arterial blood pressure and pain sensitivity parameters. Secondary objectives were to investigate blood pressure response to cold pain and sex differences in response to cold pain and pain perception.

Method

Out of a total of 331 volunteers, 200 students (100 males and 100 females) were selected for study as per the inclusion and exclusion criteria. Cold Pressor Test was used to apply experimental pain. To study response, cardiovascular parameters (systolic blood pressure and diastolic blood pressure) and pain sensitivity parameters (pain threshold, pain tolerance and pain rating) were measured.

Result

Rise in resting systolic and diastolic blood pressure following Cold Pressor Test was similar between both the sexes ($p > 0.05$). Pain rating was found to be significantly higher in females whereas pain threshold and pain tolerance were significantly higher in males ($p < 0.05$). Resting blood pressure showed a positive relationship with pain threshold and pain tolerance whereas a negative relationship with pain rating.

Conclusion

Resting systemic arterial blood pressure and pain sensitivity are inversely correlated. Females are more sensitive to pain than males.

KEY WORDS

Blood pressure, Pain, Pain threshold, Sex

INTRODUCTION

Several animal as well as human studies have attempted to establish and explain the relationship between blood pressure and nociception.[1,2] Many recent studies have reported sex differences in pain perception in humans.[3] It has been hypothesized that blood pressure is inversely related to pain sensitivity. However, there is no consistent evidence that authoritatively explains the relationship between blood pressure and pain sensitivity parameters in human subjects.

This study was planned with the primary objective of investigating the relationship between resting systemic arterial blood pressure and pain sensitivity parameters. The secondary objectives were to investigate the blood pressure response to cold pain, to investigate the sex differences in response to cold pain, and to investigate the sex differences in pain sensitivity parameters.

METHODS

It was a cross sectional type of observational study. Prior ethical approval to conduct the research was obtained from Sumandeep Vidyapeeth Institutional Ethics Committee (SVIEC). The study was conducted in the clinical laboratory, department of Physiology, Smt. BK. Shah Medical Institute and Research Centre (S.B.K.S. M.I. and R.C.), Piparia-391760, Gujarat, India from June, 2011 to December, 2011.

The undergraduate medical students of S.B.K.S. M.I. and R.C. were invited to participate in the study as volunteers. All the 331 volunteers (173 males, 158 females) were invited to the clinical laboratory, department of Physiology and were explained about the study protocol in detail. They were provided with the Participant Information Sheet (PIS) and Informed Consent Form (ICF) approved by the SVIEC. All the volunteers who agreed to take part in the study by signing the ICF were recruited to detailed history taking and physical examination by qualified medical personnel who was blinded regarded the study details.

Young healthy students of 17 to 25 years of age, who were ready to give a valid consent by signing the ICF, who were right handed (for selection of uniform study sample, as handedness may affect pain sensitivity) and females who were in pre-ovulatory phase of menstrual cycle (for selection of uniform study sample, as pain perception may be different during various phases of menstrual cycle) were included in the study.[4,5]

Students with Body Mass Index (BMI) < 18.5 kg/m^2 or BMI > 24.99 kg/m^2, with any local or bone injury and/or disease in the right hand (as this hand will be immersed in cold water), who were on any diet or exercise regime for weight loss or gain, who were taking any analgesics (as analgesics will reduce pain perception), who were smokers and/or alcoholics, and who were on any medications that can affect the Autonomic Nervous System (ANS) were excluded from the study. Students suffering from any known illness affecting or involving the ANS e.g. Diabetes Mellitus, Thyroid disorder, any cardiovascular or neuropsychiatric disorder, any menstrual irregularities or disorders were also excluded from the study.

As shown in the CONSORT (Consolidated Standards of Reporting Trials) diagram (Schulz, Altman, and Moher, 2010) (fig. 1), out of a total of 331 students, 200 students (100 males and 100 females) were selected for study as per the inclusion and exclusion criteria.

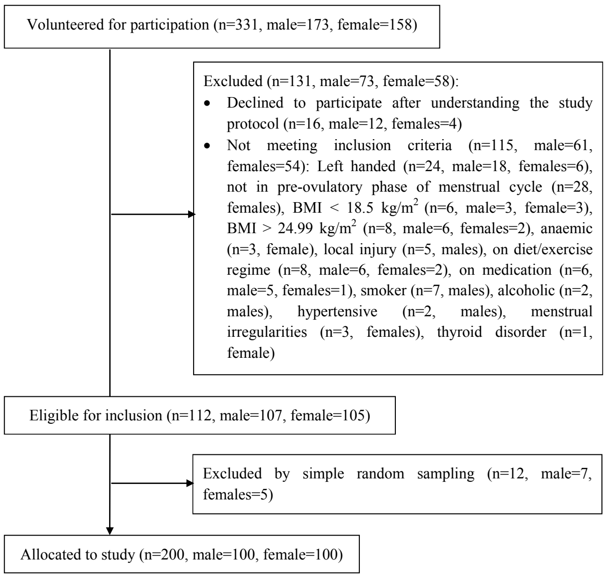

Figure 1. CONSORT diagram showing selection of study participants.

Height measurement: With the participant standing erect on the stadiometer bare footed, height was recorded by placing the horizontal bar of the stadiometer on the vertex of the subject during inspiration.

Weight measurement: With the participant standing erect on the digital standing scale bare footed and wearing light clothes, weight was recorded from the digital scale of the weighing machine.

Body Mass Index: The BMI was calculated using the following formula[6]:

BMI = Weight (in kg)/Height^2 (in m^2).

Cold Pressor Test (CPT) protocol: The participant was asked to sit comfortably in a chair. After 10 minutes rest, systolic blood pressure and diastolic blood pressure were recorded (i.e. resting systemic arterial blood pressure). Then, the participant was asked to immerse his or her right hand into a laboratory water bath (palm facing down, water level up to 5 cm above wrist) having ice cold water. The temperature of water bath was monitored by a laboratory thermometer throughout the test and temperature of water was maintained between 4°C and 8°C by placing additional ice in the bath if needed.[7]

As soon as the participant immersed his or her hand in the bath, two stop watches were started. On first feeling of pain by the participant, one stop watch was stopped and the time was recorded as pain threshold. When the pain became unbearable, the participant withdrew his or her hand from water and the second stop watch was stopped. This time was recorded as pain tolerance. Subject was asked to rate the intensity of pain during the test on a scale of zero to ten, zero being no pain at all while ten being the worst imaginable pain (by Visual Analog Scale).[8] Immediately after the test, systolic blood pressure and diastolic blood pressure were recorded. Blood pressures were recorded using a standardized mercury sphygmomanometer.

The principles of the Declaration of Helsinki were adhered to throughout the course of study.[9] All the instruments used for the study were regularly checked and calibrated using the standard guidelines. To ensure minimal subjective or technical errors, all the parameters were recorded by the same person (a qualified medical personnel) using the same instruments for all participants.

Statistical analysis: Statistical analysis was done using SPSS version 20®. Difference between means of the two groups was analyzed for significance using appropriate students t-test. To find out relationship between two parameters, Pearson's correlation was used. The alpha error was set at 5% and p-values < 0.05 were considered significant.

Table 1. Age and anthropometric data of the study participants (Unpaired student's t-test).

Parameter	Male (n=100) (Mean ± SD)	Female(n=100) (Mean ± SD)	t value (two tailed)	p value
Age (in years)	19.52 ± 0.78	19.38 ± 0.82	1.28	0.22
Height (in meters)	1.68 ± 0.06	1.67 ± 0.07	1.08	0.28
Weight (in Kg)	55.52 ± 3.69	54.66 ± 4.70	1.44	0.15
Body Mass Index (Kg/m^2)	19.67 ± 0.61	19.59 ± 0.49	1.02	0.31

RESULTS

Results of our study are presented in table format. Table 1 shows the age and anthropometric data of the study participants. As evident from the p values (all p values > 0.05), male and female study participants were comparable in terms of age, height, weight and BMI.

Table 2 shows blood pressure response to experimental pain by Cold Pressor Test in male and female participants. All participants showed significant rise in resting systolic blood pressure and resting diastolic blood pressure following Cold Pressor Test (all p values < 0.0001).

Table 3 shows sex difference in blood pressure response to Cold Pressor Test. The resting values of systolic blood pressure and diastolic blood pressure were found to be

Table 2. Blood pressure response to Cold Pressor Test (Paired student's t-test).

	Parameters	Before CPT (Mean±SD)	After CPT (Mean ± SD)	t value (two tailed)	p value	Blood pressure reactivity (Post CPT value minus pre CPT value) (Mean ± SD)
Male	Systolic blood pressure (mmHg)	123.9 ± 8.88	132.8 ± 7.51	12.54	p < 0.0001**	9.10 ± 7.2
	Diastolic blood pressure (mmHg)	78.26 ± 6.28	83.59 ± 6.32	9.17	p < 0.0001**	5.76 ± 5.71
Female	Systolic blood pressure (mmHg)	116.53 ± 8.71	125.78 ± 8.15	14.75	p < 0.0001**	9.26 ± 5.88
	Diastolic blood pressure (mmHg)	73.94 ± 7.86	80.26 ± 7.42	10.05	p < 0.0001**	6.88 ± 6.18

*p < 0.05-statistically significant, **p < 0.01-statistically highly significant.

Table 3. Sex difference in blood pressure response to Cold Pressor Test (Unpaired student's t-test).

Parameters	Male (n=100) (Mean ± SD)	Female (n=100) (Mean ± SD)	t value (two tailed)	p value
Resting Systolic blood pressure (mmHg)	123.90 ± 8.88	116.66 ± 8.66	5.836	p < 0.0001**
Resting Diastolic blood pressure (mmHg)	78.26 ± 6.28	73.98 ± 7.89	4.246	p < 0.05*
Systolic blood pressure reactivity (mmHg)	9.10 ± 7.2	9.26 ± 5.88	0.17	0.86
Diastolic blood pressure reactivity (mmHg)	5.76 ± 5.71	6.88 ± 6.18	1.33	0.18

*p < 0.05-statistically significant, **p < 0.01-statistically highly significant. Reactivity = Post test value minus pre test value.

significantly higher in males than females (p values < 0.05). However, blood pressure response to Cold Pressor Test i.e. systolic blood pressure reactivity and diastolic blood pressure reactivity to Cold Pressor Test was similar in both the sexes (p values > 0.05).

Table 4 shows sex difference in pain sensitivity parameters. Males had significantly greater pain threshold and pain tolerance (p values < 0.0001) as compared to females, whereas pain sensitivity was found to be significantly higher in females (p value < 0.0001) when compared to males.

Table 5 shows correlation between resting systemic arterial blood pressure and pain sensitivity parameters. Resting

Table 4. Sex difference in pain sensitivity parameters (Unpaired student's t-test).

Parameters	Male (n=100) (Mean ± SD)	Female (n=100) (Mean ± SD)	t value (two tailed)	p value
Pain threshold (sec)	24.37 ± 5.61	20.28 ± 5.75	5.09	p < 0.0001**
Pain tolerance (sec)	80.58 ± 17.56	60.88 ± 15.57	8.39	p < 0.0001**
Pain rating VAS (0 to 10)	6.35 ± 1.28	7.38 ± 1.22	5.82	p < 0.0001**

*p < 0.05-statistically significant, **p < 0.01-statistically highly significant.
VAS - Visual Analog Scale.

Table 5. Correlation between resting systemic arterial blood pressure and pain sensitivity parameters. (Pearson's correlation)

	Parameters	Pain threshold (sec)	Pain tolerance (sec)	Pain rating
Male	Resting Systolic blood pressure (mmHg)	r = 0.2722 p = 0.0062**	r = 0.3752 p = 0.0001**	r = -0.2144 p = 0.0322*
	Resting Diastolic blood pressure (mmHg)	r = 0.2766 p = 0.0053**	r = 0.1815 p = 0.0707	r = -0.0981 p = 0.3312
Female	Resting Systolic blood pressure (mmHg)	r = 0.458 p < 0.0001**	r = 0.446 p < 0.0001**	r = -0.371 p = 0.0001**
	Resting Diastolic blood pressure (mmHg)	r = 0.225 p = 0.0243*	r = 0.268 p = 0.0069**	r = -0.294 p = 0.0030**

*p < 0.05-statistically significant, **p < 0.01-statistically highly significant.

systolic blood pressure was positively correlated with pain threshold and pain tolerance, but it was negatively correlated with pain rating in both males and females. Similarly, resting diastolic blood pressure was positively correlated with pain threshold and pain tolerance, but it was negatively correlated with pain rating in both the sexes.

DISCUSSION

Pain is a topic of widespread scientific interest and its ramifications have been examined by physiologists, pharmacologists, psychiatrists, psychologists, anesthesiologists, and others who have contributed to a wide literature. It is said that we have different receptors for pain in our body and those receptors respond different, so there are a lot of variations in response to pain stimuli.[10] Pain sensitivity is a physiological phenomenon which allows someone to experience a sensation when something potentially harmful to the body is occurring or may occur. Researchers have shown that people have different degrees of pain sensitivity, and that a number of factors can influence the way in which someone experiences pain. Various parameters like pain threshold, pain tolerance and pain rating are used to determine pain sensitivity.[11]

The main aim of the present study was to determine the relationship between pain sensitivity parameters (like pain threshold, pain tolerance and pain rating) and blood pressure.

In this study, resting systolic blood pressure and diastolic blood pressure was found to be significantly increased after Cold Pressor Test (CPT) in both the sexes (Table 2). However, the magnitude of rise in these pressures following CPT (systolic blood pressure reactivity and diastolic blood pressure reactivity) was statistically similar in both the sexes (Table 3). The characteristic cardiovascular response to the CPT is significant rise in cardiovascular parameters like heart rate, blood pressure, cardiac output and total vascular resistance due to elevated sympathetic vasomotor neuronal activity.[12,13] The increments in resting systolic and diastolic blood pressure values observed in the present study during cold induced pain are in line with those observed by previous studies.[14-16] Victor et al. also reported that the cold induced elevation in cardiovascular parameters was completely due to sympathetic activation as heart rate changes were entirely eliminated by Propranolol adrenergic blockade.[12]

We found significant sex variation in pain sensitivity parameters between both the sexes. Pain threshold and pain tolerance during experimental pain were significantly higher in males as compared to females, whereas pain rating was significantly higher in females when compared to males (Table 4). Similar findings of greater pain sensitivity in females have been reported in previous studies.[17,18] Although, one study reported lower pain thresholds in females than males, the difference statistically insignificant and was likely the result of small sample size (12 males, 12 females).[19] The mechanisms underlying this sex variation in response to experimental pain remain unclear. Multiple mechanisms have been proposed to explain this differing response between the sexes, including genetic factors, hormonal factors, and differing pain modulatory systems. One possible explanation, from psychosocial perspective, involves social role expectancies i.e. the stereotypic feminine role is related to enhanced willingness to report pain, whereas the masculine role is typified by reduced response to pain and stoicism.[20] Sex hormones affect the entire nervous system and their plasma levels fluctuate regularly in both males and females. Also, these plasma levels fluctuate along the entire length of menstrual cycle, after menopause, and during pregnancy. These differences may affect pain perception.[21] For example, elevated estrogen levels were reported to be associated with a lower heat pain and lower heat threshold.[22] Interestingly, the pain modulatory system also varies with menstrual cycle with more effects in the ovulatory phase than the menstrual and luteal phases.[23,24] On the other hand, though the plasma levels of sex hormones fluctuate throughout the entire lifespan in males and there is significant reduction in their testosterone levels with increasing age, males seem to be less affected by such hormonal changes.[21] Berkley found that in response to pain stimulus, female brain showed higher activity in limbic regions (emotion based centers) whereas males showed greater activity in congnitive regions or analytical centres. Apart from this differing activity in brain, sex related difference in descending inhibitory pathway, stress induced analgesia, menstrual cycle, oestrogen receptor, opioid receptors, and melanocortin 1 receptor are other factors which might influence sex related variation in response to pain.[20,25]

In present study, both the resting systolic and diastolic blood pressures were found to be significantly positively correlated with pain threshold and pain tolerance and negatively correlated with pain rating in both the sexes (Table 5). Proposed mechanisms to explain this relationship include baroreceptor activity (hypertensive hypoalgesia), central descending pathways, and beta-endorphin responses.[26,27] Apart from their role in blood pressure regulation, baroreceptors are known to affect central nervous system activity by exerting an inhibitory effect on the brain. Convergence of baroreceptors and processing of nocioceptive impulses occurs at the same anatomical place in brain. Especially, the first synapse of baroreceptor reflex is located in the Nucleus Tractus Solitarius (NTS), which in turn projects to the locus coeruleus and periaqueductal grey matter; both of which modulate the nocioceptive pathways. Thus, stimulation of the NTS by increasing blood pressure produces an antinocicetpive effect. It is quite possible that this inhibitory effect may decrease pain sensitivity.[3] This is supported by animal and human studies that have demonstrated reduced pain sensitivity on baroreceptor stimulation; although in one study, only borderline hypertensives showed analgesia on baroreceptor stimulation but not the normotensives.[4,28,29] Thus, it may be proposed that higher resting blood pressure produces greater baroreceptor-induced analgesia. This explains our finding of lesser pain sensitivity in males as they had higher resting blood pressure than females.

It is equally possible that increased blood pressure and decreased pain sensitivity are mutually independent events mediated by central nervous system (CNS) pathways that modulate somatic sensations and autonomic outflow. For example, stimulation of many brain regions e.g. the central grey matter, can concurrently increase sympathetic outflow and decrease nociceptive transmission the spinal level.[30]

Also, human body responds to the rise in blood pressure by releasing opioids and activating pain modulation pathways. These endogenous opioids may be responsible for the negative relation between blood pressure and pain sensitivity.[31] This is also supported by animal studies in which hypoalgesia induced by hypertension was reversed by opioid receptor antagonists.[32,33] Sheps et al. found that hypertensive humans showed higher circulating ß-endorphin levels than normotensive subjects; this difference partly explains differences in pain sensitivity between hypertensive and normotensive subjects.[34] Thus, studies suggest that decreased pain perception in persons with higher blood pressure may be related to endogenous opioid activity.[34,35] However, further research is still needed to clarify this issue and generate strong evidence.

This correlation between pain sensitivity and blood pressure is also reported in hypotensives with hypotensives exhibiting markedly lesser pain threshold and pain tolerance, and increased sensory and affective pain perception.[36] Thus an inverse relationship between blood pressure and pain sensitivity is suggested across the whole blood pressure range.

Findings of this study differs from two previous studies finding a resting systolic blood pressure-pain relationship only in females.[32,37] One study finding a resting systolic blood pressure-pain relationship only in males.[30] These differences are possibly due to different sample size and methodology difference.

More accurate and reliable data collection could have been possible if automated instruments were used for blood pres¬sure recording. Future research may include use of advanced automated instruments for data collection.

An individual's pain perception might differ in a real life situation as compared to an experimental set up and consequently the relationship between blood pressure pain sensitivity parameters may also differ in real life situations. Further studies may be directed towards finding pain sensitivity in real life situations and normal day to day life.

Moreover, pain response may differ between patients and normal individuals. Also, it may differ in patients with different pathological states. Hence similar studies may be conducted in patients with different diseases.

Finally, we did not investigate the hormonal levels and psycho-social aspects of the participants which could have affected the pain response. Future research may involve these aspects. Moreover, similar studies in other subjects such as in transgenders and homosexuals may generate interesting findings and illuminate our understanding of physiology of pain.

CONCLUSION

In conclusion, there exists an inverse relationship between resting systemic arterial blood pressure and sensitivity to pain in both males and females. Also, females are more sensitive to pain than males. CPT produces rise in cardiovascular parameters such as blood pressure. This study may be clinically helpful in better understanding of pathophysiology of pain.

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