

**The Relationship Between Sex Differences and Lower Body Negative Pressure with Very Short-Term Blood Pressure Variability with Acute Oral Capsaicin in Humans**

**Grace Herzog**

**Saratoga Springs High School**

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**ABSTRACT**

Cardiovascular disease (CVD) results in 17.9 million deaths annually and its numerous risk factors are highly researched in attempts to prevent prevalence. Hypertension, defined as high blood pressure (BP), is a well-researched risk factor of CVD; however, the very short-term oscillations of BP, known as blood pressure variability (BPV), lack significant documentation. Sex differences contribute to CVD risk, as females are less prone to CVD, possibly due to females observing lower BPV than their age-matched male counterparts. Capsaicin, a hot pepper extract, has been suggested as a therapeutic for hypertension, and thus may also affect BPV, as well as possibly attenuate sex-specific differences. Lower body negative pressure (LBNP) is a method of altering blood flow that has been shown to reduce BP. This study aimed to examine the sex-specific effect of capsaicin and LBNP on very beat-to-beat BPV. 38 young human participants were recruited to participate in a counterbalanced, placebo-controlled study where BP values were recorded via Mobilograph. Procedures were repeated at an LBNP condition in addition to the baseline condition. When examining BPV in the placebo baseline condition ( $p=0.0528$ ) and capsaicin condition ( $p=0.1781$ ), there were no statistically significant sex differences. In the LBNP group, the placebo condition ( $p=0.13969$ ) and capsaicin condition ( $p=0.154$ ) had no statistically significant sex differences. Furthermore, LBNP did not significantly improve the efficacy of capsaicin independent of sex ( $p=0.7666$ ). This study

concluded that there were no sex-specific BPV differences in a placebo baseline condition and that capsaicin and LBNP did not attenuate any sex-specific differences.

## **INTRODUCTION**

Cardiovascular disease (CVD) is characterized by plaque buildup within arterial walls and results in fatal conditions. CVD is caused primarily by unhealthy lifestyles; specifically lack of exercise, unhealthy eating habits, and obesity. It is currently the leading cause of death in the United States, as it is responsible for 25% of deaths [10]. CVD is categorized into four main conditions: coronary artery disease (CAD), cerebrovascular disease, peripheral artery disease, and aortic atherosclerosis. CAD results from heart failure and is responsible for a third of CVD-related deaths. Cerebrovascular disease is caused by blocked arteries and can result in ischemic strokes. Peripheral artery disease is a condition developed by minimal blood flow, leading to claudication, also known as limb pain. Aortic atherosclerosis is characterized by thoracic and abdominal aneurysms which are caused by weakened arterial walls [6]. Currently, CVD is treated by lifestyle changes, medication, and surgery. However, CVD prevention is the most effective treatment [11]. The development of CVD can be predicted, and avoided, based on the maintenance of risk factors such as hypertension [9].

BP is defined as the force of circulating blood on artery walls [9]. Elevated BP, otherwise known as hypertension, can be caused by bad diet habits, smoking, obesity, stress, and diabetes. It is the most preventable and influential risk factor of CVD [7]. Hypertension is categorized into two stages based on the severity of a patient's routine BP measurements. Stage 1 is defined as a BP measurement of 130-139/80-89 mmHg. Stage 2, the more severe stage, is categorized as  $\geq 140/\geq 90$  mmHg [12]. Elevated mean BP is associated with CVD development; however, this may underestimate intermittent-labile hypertension, characterized by the peaks and dips of BP levels [5].

The long-term oscillations of BP, also known as blood pressure variability (BPV) measured in routine office visits, are an independent novel risk factor of CVD. BPV, unlike mean BP measurements, considers excessive fluctuations of BP [5]. Beat-to-beat intervals, known as very short-term BP measurements, show similar associations with CVD as long-term BPV [8]. BPV is a risk factor for hypertension-related morbidity and mortality and can be affected by age, sex, as well as mean BP [1]. Sex differences contribute to developing hypertension and, therefore, CVD, as young males are more prone to these conditions [2].

Age is also an influential factor in the development of hypertension, as individuals over the age of 40 are more susceptible to high BP levels than their younger counterparts. Before menopause, females have significantly lower BP than males. However, after the end of menstrual cycles,

females' BP levels are elevated more in comparison to males. Likewise, there are age-related sex differences in BPV since older women have higher levels than older men [13].

Lower body negative pressure (LBNP) is a technique used to redirect blood flow. This physiological response is stimulated when an individual, from their pelvis down, is inserted into a chamber with a vacuum pump that removes air. LBNP induces venous pooling as blood shifts away from the individual's chest [3]. LBNP reduces central blood volume, defined as the volume of blood cells and plasma, which decreases blood pressure. LBNP's effects on other cardiovascular measures, such as very short-term BPV, lack significant documentation [6].

Capsaicin, a hot pepper extract, is known to decrease BP by increasing relaxation in mesenteric arteries through the activation of a non-selective cation channel that attenuates anti-inflammatory responses, specifically transient receptor potential vanilloid subtype 1 (TRPV1). This stimulation releases nitrite oxide and other mediators which relaxes arterial smooth muscle. This muscle makes up artery walls, which is why BP then lowers [14].

## **Hypothesis**

This study hypothesized that:

- i) Capsaicin would decrease very short-term BPV in females and males in baseline and LBNP conditions

- ii) Males would have a lower very short-term BPV measurement than females in baseline and LBNP conditions
- iii) Sex would alter the response of capsaicin in terms of very short-term BPV in baseline and LBNP conditions
- iv) Capsaicin will be more effective in BPV regulation in the LBNP condition in comparison to the baseline condition
- v) Sex will be responsible for a greater difference in the efficacy of capsaicin in the LBNP condition than in the baseline condition

### **Statement of Purpose**

The purpose of this study was to investigate capsaicin's effect on very short-term BPV in young men and women; therefore, gaining a better understanding of capsaicin's effect on the cardiovascular system. This current research evaluates BPV in younger individuals because there is less knowledge of CVD risk factors in these low-risk individuals. This study also uses very beat-to-beat intervals as an assessment of BPV as there is less documentation on the relationship of very short-term BPV with sex differences. Furthermore, this study assesses the effect of LBNP on very short-term BPV and whether it makes capsaicin more effective or attenuate more sex differences with BPV regulation. Studying the physiological effects of LBNP can add to the current understanding of clinical measures that may help regulate BPV and other CVD risk



factors. This study adds to the current knowledge on potential improvements on the efficacy of capsaicin.

## **METHODOLOGY**

### **Study Population**

This prospective randomized placebo-controlled study was conducted at Skidmore College. Subjects gave their written consent to voluntarily participate in the study while remaining anonymous. The recruited individuals were 18-35 years old. There was a final population of 14 young females and 27 young males. Individuals with any illness were excluded from the study as well as aged individuals, which were defined as 65 years or older. Participants received a \$25 Amazon gift card after completion of the study.

### **Data Collection**

All eligible individuals were required to rest in a supine position for 10 minutes prior to using a Mobilograph, characterized as a peripheral oscillometric sphygmomanometer cuff, and BP cuff which were used to record BP values. The BP cuff was applied with a maximum of 250 mmHg before being released where BP measurements were then taken. Individuals were randomly split into placebo and capsaicin conditions and were given either placebo or capsaicin capsules to

consume 30 minutes prior to their visits. The experimental condition consumed two 390mg capsaicin extract pills and the placebo condition consumed two 500mg fiber powder pills. The subjects completed their second visit using the same data collection techniques where their beat-to-beat BPV was calculated with the average real variance of BP values. In addition to a baseline condition, these procedures were repeated while participants were undergoing a low level of LBNP.

### **Statistical Analysis**

Data is expressed as mean  $\pm$  standard deviation. To analyze the quantitative data, Statistical Analysis Software (SAS) was used. The average real variance of recorded BP measurements was used as the BPV. The websites Statistics Kingdom and Data Classroom were used to analyze and perform data analysis. A Two-Sample T-Test test was used to evaluate sex, treatment, and condition relations within and between subjects' effects. Possible statistical significance was characterized at  $p < 0.05$ .

### **RESULTS**

In the placebo condition, there were 27 males and 15 females; thus, males made up 64.3% of the population and females 35.7%. In the capsaicin condition, there were 27 males and 14 females; so, males accounted for 65.9% of the group and females 34.1%. Participants were aged 18-25

years old. The ideal BPV measurement was defined as 10% to 20% of BP values. When examining sex differences in terms of beat-to-beat BPV in the placebo baseline condition ( $p=0.0528$ ), males had a greater average BPV than females (Figure 3). In the capsaicin baseline condition (Figure 4), there was no statistical difference ( $p=0.1781$ ) between males' and females' BPV. In males, capsaicin decreased the average BPV while in females, capsaicin increased the average BPV. In both groups, capsaicin helped BPV come closer to the ideal level. This relative value was illustrated via green section included on graphs. When examining sex differences in terms of beat-to-beat BPV in the placebo LBNP condition ( $p=0.1369$ ), males had a greater average BPV than females (Figure 5). In the capsaicin LBNP condition (Figure 6), there was no statistical difference ( $p=0.154$ ) between males' and females' BPV. Capsaicin decreased the average BPV (Figure 1), of males and females combined of BPV in the baseline condition ( $p=0.8487$ ). In the LBNP condition, capsaicin had a slightly greater effect on reducing the average BPV (Figure 2), independent of sex ( $p=0.7666$ ). In males, capsaicin decreased the average BPV while in females, capsaicin increased the average BPV. This relationship was observed in both conditions, however less significant in the LBNP condition. In both groups, capsaicin helped BPV come closer to the ideal level. The differences of capsaicin's effect on average BPV in both groups of sex were calculated in both conditions. In females, there was no significant difference between placebo baseline and placebo LBNP ( $p=0.4039$ ). Likewise, in females, there was no significant difference between capsaicin baseline and capsaicin LBNP

( $p=0.7164$ ). In males, there was no significant difference between the placebo baseline and the placebo LBNP ( $p=0.486$ ). Furthermore, the same relationship was observed in the capsaicin-treated group ( $p=0.4951$ ).

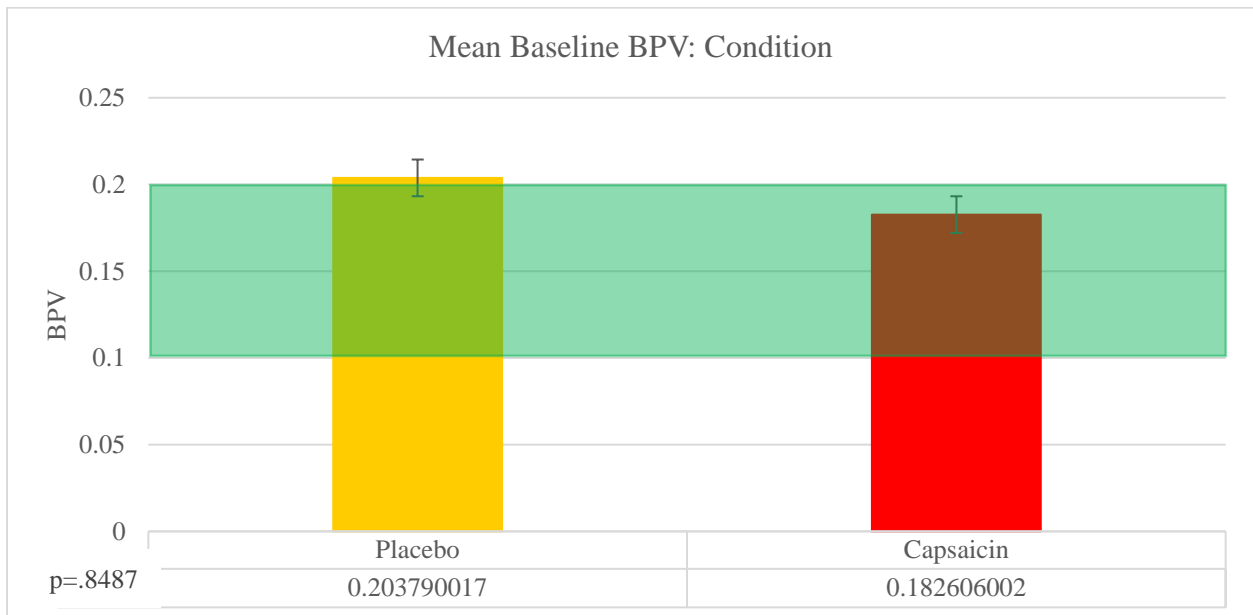


Figure 1: Representation of average BPV, independent of sex, in placebo and capsaicin groups in the baseline condition.

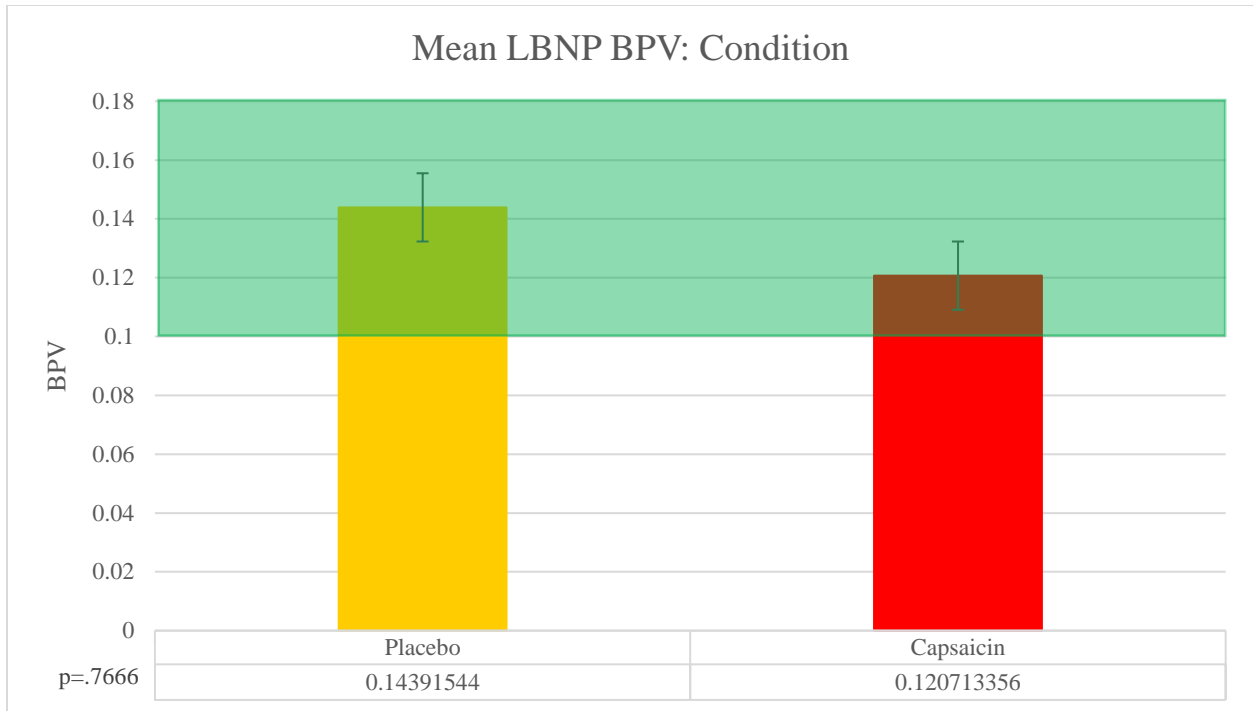


Figure 2: Representation of average BPV, independent of sex, in placebo and capsaicin groups in the LBNP condition.

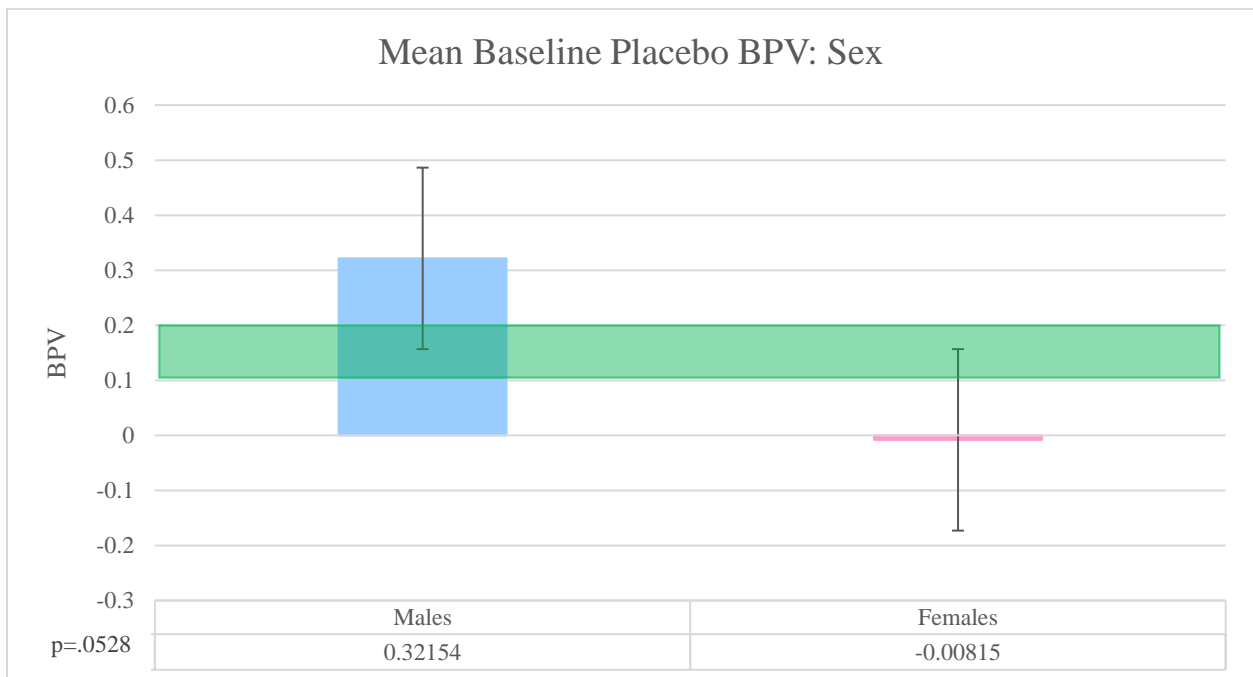


Figure 3: Representation of average BPV sex differences in the placebo-treated baseline condition.

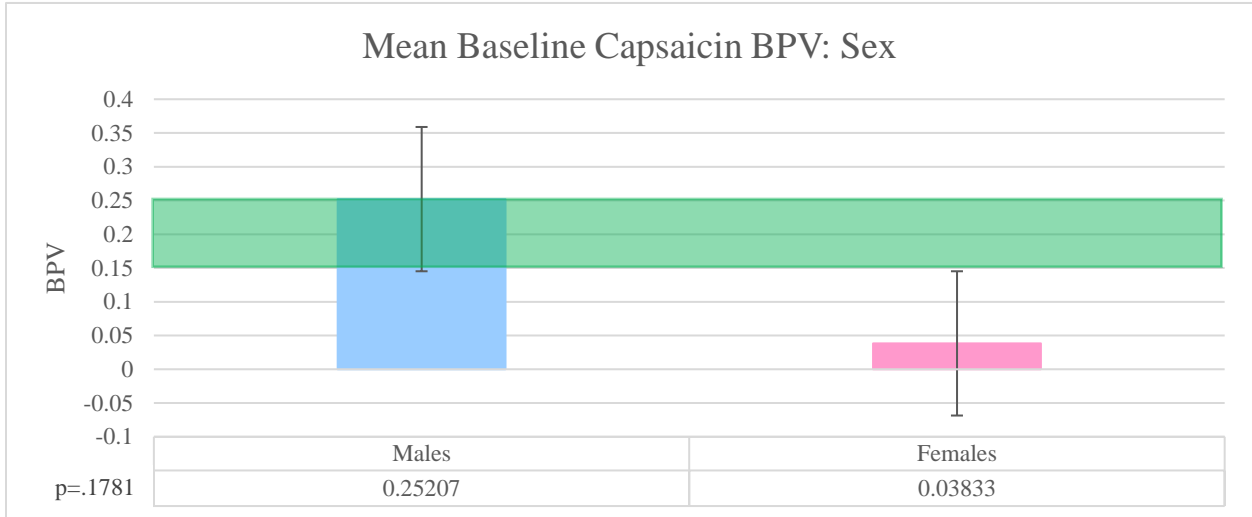


Figure 4: Representation of average BPV sex differences in the caspsaicin-treated baseline condition.

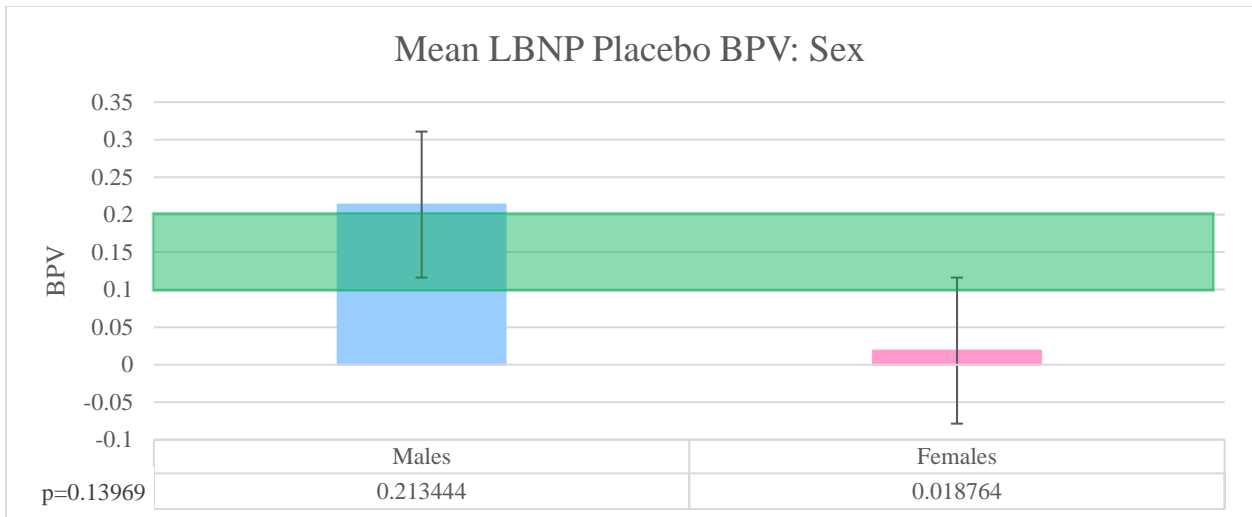


Figure 5: Representation of average BPV sex differences in the placebo-treated LBNP condition.

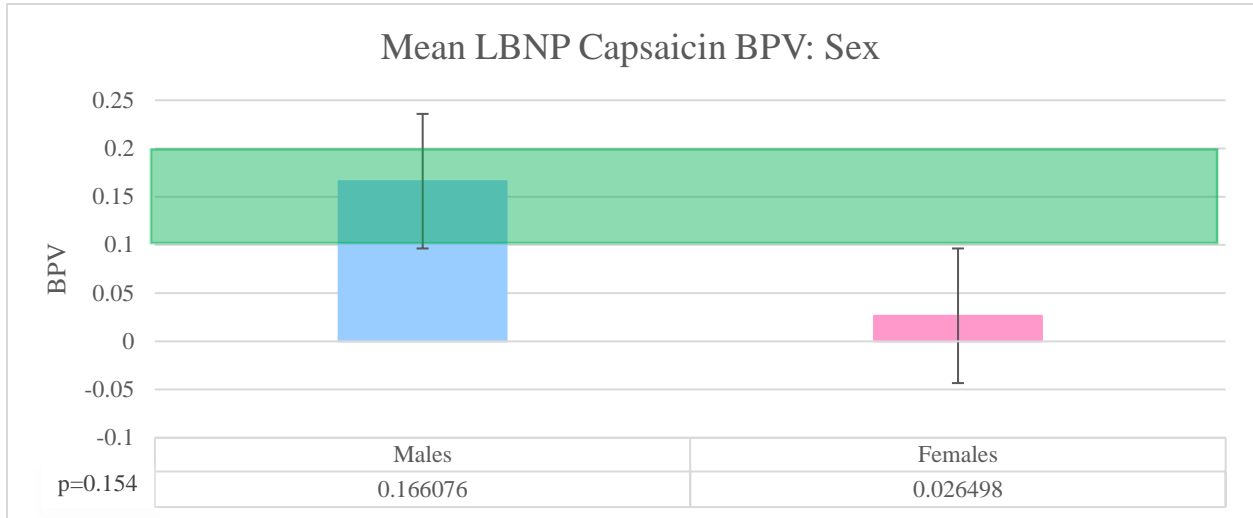


Figure 6: Representation of average BPV sex differences in the capsaicin-treated LBNP condition.

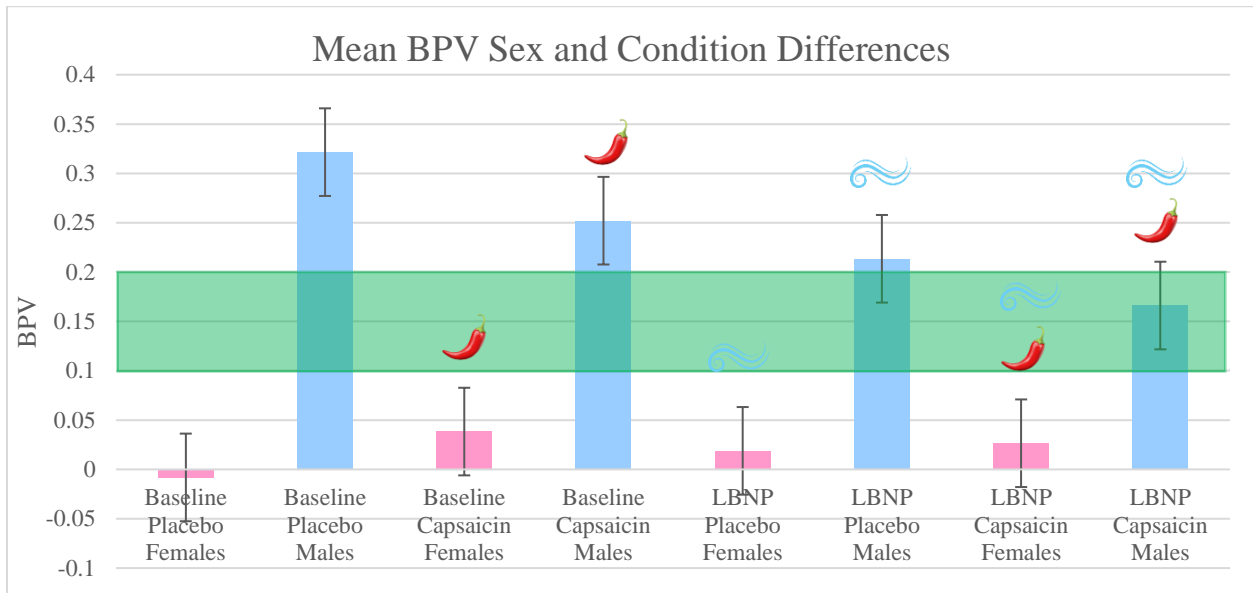


Figure 7: Representation of average BPV based on sex in different treatment and condition groups.

## **DISCUSSION**

This study aimed to determine whether sex alters the response of capsaicin in terms of BPV and whether there are BPV sex differences independent of capsaicin. Additionally, this study assessed the effects of LBNP on BPV, specifically the efficacy of capsaicin. This research has concluded that there was no significant difference between the placebo and capsaicin condition independent of sex in a baseline condition. Furthermore, there was no significant difference, yet one stronger than that of the baseline condition, in the LBNP condition when examining treatment groups. Additionally, there was a close relationship observed between males and females in the placebo baseline condition, with males having a higher BPV than females. With individuals treated with capsaicin in the baseline condition, there was less of a difference between the males and females than the difference between these groups with placebo-treated subjects. Furthermore, there was not a significant relationship between males and females in the placebo LBNP group, however, males observed a higher average BPV than females. In the capsaicin-treated group in the LBNP condition, there was no statistical difference between sexes, yet males had a high BPV average than females. This difference was more random than the sex difference with the placebo group in the LBNP condition. In males and females in both the



placebo and capsaicin conditions, the LBNP and baseline groups did not have a statistical difference. So, LBNP did not significantly change the average BPV in these groups. However, in the female capsaicin, male capsaicin, and male placebo groups, the LBNP conditions had a lower BPV average. This relationship, however, was not observed in the female placebo group, as the LBNP condition had a higher mean BPV than that of the baseline condition. This study supports that capsaicin helps regulate BPV, regardless of sex. The limitations of this research include the lack of accountability for high-risk individuals and assessing longer increments of BPV. This study also did not evaluate the long-term effects of capsaicin, only short-term ones. This study found no statistically significant relationship between males and females in a placebo baseline condition, independent of capsaicin, which opposed previous literature. This finding may have resulted from the selected population, specifically, the lack of females in comparison to males. This study increases the knowledge of capsaicin's effects on the cardiovascular system, specifically regarding very short-term variability.

## **CONCLUSION**

In summary, CVD is a prevalent and fatal illness that can be prevented through the research of risk factors including beat-to-beat short-term BPV. Capsaicin's effects on the cardiovascular system requires more research as it has been proven to have numerous health benefits and may

facilitate with CVD prevention more significantly than currently believed. Capsaicin is an affordable and easily accessible therapeutic unlike common hypertension medication. It could be easily administered during office visits, which are available to more people, rather than expensive treatments. A bottle of one hundred oral acute capsaicin pills is about five dollars, as opposed to common hypertensive medication which can average to eight-hundred dollars annually. Not only is capsaicin significantly cheaper, but it can also be consumed without prescriptions and found at common chain convenience stores unlike most hypertensive medications. Furthermore, this study supports the idea that LBNP can potentially lower mean BPV, while not statistically significant, regardless of sex in a placebo condition. This finding adds to the current knowledge on clinical measures that can be taken to improve the efficacy of common and cheap hypertension therapeutics. Further studies are needed to assess sex differences in terms of very short-term BPV in high-risk individuals which may prove to be significant. Additional research is also needed on the comparison of significance between different recorded increments of BPV. More research is needed on the effects of LBNP on regulating BPV and other CVD risk factors as well as improving the efficacy of capsaicin. Along with capsaicin, other common at home therapeutics, such as olive leaf extracts, have been known to decrease BP and therefore require further investigation. Research on sex differences with medication is also necessary to indicate if types of medication attenuate to sex differences. To

summarize, the study of cheaper, and more accessible, hypertension treatments is extremely beneficial to individuals with restricted medical access and financial means.

### **Significance**

Significant documentation on BP in low-risk individuals is minimal. This study used young individuals who make great test subjects as they have a decreased risk of health issues that can influence BP, specifically hypertension. Research with this age group is important as it adds to the knowledge of BPV development with increasing age. Very short-term BPV was also assessed as its relationships with common therapeutics have not been significantly studied. Therefore, while these findings were insignificant, the results of this study prove that the effectiveness of capsaicin's effect on BPV is not changed by sex differences. Furthermore, this study supports LBNP as a method to help regulate BPV independently and in addition to capsaicin.

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