# First evidence of immunomodulation of the renin-angiotensin system through substance P/neurokinin 1 receptor: a case and control study in hypertension and cardiac patients

Ibrahim M. Alanazi,[1] Riffat Mehboob,[2] Ayesha Tariq,[3] Sajid Hameed,[4] Uzma Malik,[5] Noreen Sarwar,[6] Imran Shahid,[1] Khurram Mehboob[2]

[1]Department of Pharmacology and Toxicology, Faculty of Medicine, Umm al-Qura University, Al-Abidiyah, Makkah, Saudi Arabia; [2]Lahore Medical Research Center, Lahore, Pakistan; [3]Department of Cardiology, Mayo Hospital, Lahore, Pakistan; [4]Department of Public Health, Green International University, Lahore, Pakistan; [5]King Edward Medical University, Lahore, Pakistan; [6]Institute of Microbiology, University of Veterinary and Animal Sciences, Lahore, Pakistan

Correspondence: Riffat Mehboob, Lahore Medical Research Center, Lahore, Pakistan.
E-mail: mehboob.riffat@gmail.com

Key words: renin-angiotensin system, substance P, NK1R, hypertension, cardiac diseases.

Contributions: RM, conceived and designed the experiments; AT, performed the experiments; SH, KM, analyzed and interpreted the data; UM, NS, contributed reagents, materials, analysis tools or data; RM, IS, wrote the paper; IMA, AT, performed review and editing of the manuscript.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: this study was approved by the Ethical Review Board of Lahore Medical Research Center. The research followed the declaration of Helsinki.

Informed consent: written informed consent was taken from all participants.

Patient consent for publication: patient consent was obtained from all the patients and they were informed about the study procedure.

Availability of data and materials: the data are available upon request due to privacy/ethical restrictions.

Funding: no funding was received for this study.

Acknowledgments: the authors are thankful to Prof. Dr. Peter Oehme for his experience and guidance throughout the study.

Received: 27 November 2024.
Accepted: 3 December 2024.

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*Licensee PAGEPress, Italy*
*Italian Journal of Medicine 2025; 19:1870*
*doi:10.4081/itjm.2025.1870*



## ABSTRACT

Gaining knowledge about the differences in substance P (SP) and neurokinin 1 receptor (NK1R) levels between cardiac and hypertensive patients may help clarify how these neuropeptides could be involved in the pathophysiology of cardiovascular disorders. This study aimed to investigate the levels of SP and NK1R in individuals diagnosed with hypertension and cardiac conditions. Participants were chosen from a pool of hypertensive (n=30) and cardiac patients (n=35) in addition to a control group (n=12). Each participant was asked for their informed permission before any demographic data, medical history, and pertinent clinical data were gathered. Serum samples were obtained, and the levels of SP and NK1R were measured using the enzyme-linked immunosorbent assay. When compared to the control group, the levels of SP and NK1R in hypertension patients were considerably higher. The findings point to a possible link between SP/NK1R and hypertension. There was a noticeably greater percentage of men (68.6%) among cardiac patients. The levels of SP and NK1R in cardiac patients and the control group did not vary significantly. Among those with hypertension and cardiac diseases, smoking, family history, and a diet heavy in salt were the most common risk factors. The study discovered substantial variations in SP and NK1R levels between hypertensive patients and a control group, suggesting a link between these neuropeptides and hypertension. In the case of cardiac patients, however, no significant variations in SP and NK1R levels were identified as compared to the control group.

## Introduction

Cardiovascular disorders and hypertension are major worldwide health issues that have significant effects on general public health. According to Mills *et al*. (2016), the prevalence of hypertension has increased to epidemic levels, impacting over 1.39 billion individuals in 2010 globally.[1] Cardiovascular diseases (CVDs) are also highly prevalent and account for 17.9 million deaths annually worldwide, making them the leading cause of mortality.[2] This common ailment accounts for a considerable share of morbidity and death and adds considerably to the worldwide burden of CVDs. It is well

known that hypertension and cardiovascular illnesses have a complex relationship in which hypertension poses a significant risk for the onset and advancement of diseases, including heart failure, stroke, and coronary artery disease.[3]

The effects on public health are profound and missed productivity and healthcare expenditures have a significant financial cost. A thorough understanding of the epidemiology, risk factors, and fundamental processes associated with cardiovascular illnesses and hypertension is crucial for efficient prevention and treatment. Proposals like the ones supported by Roth *et al.* (2017) highlight the need for focused treatments that include lifestyle adjustments, early identification, and evidence-based treatment approaches. A coordinated effort is needed to design and execute public health policies and interventions that address the incidence and effect of CVDs and hypertension, given the worldwide scope and severity of this health problem.[4]

A neuropeptide called substance P (SP) is implicated in the transmission of pain, particularly when inflammation is present.[5-8] Neurons, endothelial cells, and immunocytes, including lymphocytes and macrophages, create SP; all of these cells, as well as the surface of cardiomyocytes, express SP receptors.[9-12] We and others have shown that SP has a role in the pathophysiology of several viral, protozoan, and helminth infections in both mice and humans.[13,14-16]

Neurokinin 1 receptor (NK1R), the SP receptor, is a G-protein coupled receptor. Upstream regulators of RhoA activity are activated when SP binds to NK1R.[17,18] It has been shown that signals triggered by G-protein coupled receptor activation cause cardiomyocyte hypertrophy.[19,20] It is known that RhoA activation contributes to the hypertrophy of rat ventricular myocytes in the neonatal stage.[20-27] Furthermore, it has been shown that mice that overexpress RhoA have a fatal dilated cardiomyopathy linked to heart failure.[28,29] As we have previously shown, SP plays a role in the pathophysiology of encephalomyocarditis virus (EMCV) infection in mice.[13] In addition to elevated cardiac SP protein, myocarditis, and cardiomyopathy,[13] and higher viral levels (unpublished findings), EMCV-infected wild-type mice die at a rate of 51%. On the other hand, SP mice showed no pathology after EMCV infection, were fully protected from death, and had much lower viral levels (unpublished data). Three receptors are known to be interacting with SP: NK1, NK2, and NK3 to a lesser degree.[30]

A thorough evaluation of SP's modifying functions in baroreflex has been conducted. Due primarily to SP release-mediated vasodilation and fluid extravasation into the tissues, recent observations have demonstrated that SP may play a significant role in the secondary injury process following traumatic brain injury, particularly with regard to neuro-inflammation, increased blood-brain barrier permeability, and tissue edema.[31-33] Following this secondary pathophysiological process, the blood pressure may rise to an uncomfortable level. Therefore, there are still unanswered concerns about the precise function and importance of SP in baroreflex afferent activity and blood pressure control in both normal and hypertensive settings.

The study aims to establish connections between neuropeptide levels and clinical indicators by measuring SP and NK1R levels in serum samples from hypertensive and cardiac patients, as well as a control group, using enzyme-linked immunosorbent assay (ELISA). This will provide important insights into the potential role of SP/NK1R in hypertensive and cardiac conditions.

## Materials and Methods

Participants were chosen from a pool of hypertensive (n=30) and cardiac patients (n=35) in addition to a control group (n=12) of people without cardiovascular conditions. Each participant was asked for their informed permission before any demographic data, medical history, and pertinent clinical data were gathered. All participants had their blood drawn using a normal venipuncture procedure. Serum was extracted by centrifugation at 4500 rpm for 5 min. To preserve sample integrity, serum was kept apart from blood samples and kept at the proper temperature.

### Substance P and neurokinin 1 receptor enzyme-linked immunosorbent assay

Serum samples were obtained, and the levels of SP and NK1R were measured using the ELISA. We utilized commercially available ELISA kits designed specifically for SP and NK1R following the guidelines provided by the manufacturer. BT Lab Human SP and NK1R ELISA kit were used to measure levels of SP and NK1R in serum samples of participants (Catalogue Numbers: E1528Hu, E6938Hu).

### Statistical analysis

The SP and NK1R levels in hypertension patients, cardiac patients, and the control group were compared using statistical analysis. Statistical analysis was carried out using Graph Pad Prism 8.0.2 (263) (Harvey Motulsky, Washington, USA). To investigate possible connections between neuropeptide levels and clinical indicators, non-pomatric *t-tests* and analysis of variance were used. For mean ± standard deviation and frequency, descriptive statistics were used.

### Ethical considerations

This study was approved by the Ethical Review Board of Lahore Medical Research Center. The research followed the declaration of Helsinki and written and informed consent was taken from all participants.

## Results

### Analysis of substance P and neurokinin 1 receptor in hypertension patients

A total of 30 patients validly diagnosed with hypertension were included in this study. Out of 30 participants, 22 (73.3%) were females and 8 (26.7%) were males. Different demographics of participants were recorded and analyzed with respect to male-female categories. The mean age of patients was 58.2±14.80, and the mean age of females was less than the mean age of males. The difference between their ages was statistically significant (p=0.0187), which shows females are early prone to hypertension. The difference in the age of diagnosis of both groups was also significant (p=0.0158). The mean weight of participants was 81.25±4.43, the difference in weight of both groups was not statistically significant (p=0.1284). The mean blood pressure of participants was 170/80, and the difference in blood pressure between males and females was not significant. The

mean sleeping time of participants was 8.875±0.7906 hours (Table 1).

Out of the involved patients in this study, 20 (66.67%) were those who smoked and had a family history of hypertension. Respectively, 10 (33.33%) and 16 (52.34%) had a high salt diet and a glycemic diet with a high salt diet. So, these results prove that people who smoke, who have a family history of hypertension, and who eat a high salt diet are more prone to hypertension (Table 2).

SP and NK1R were analyzed as markers of hypertension. The mean SP of the control and case group was 615.0±177.2 and 992.1±629.0, respectively. The difference in SP between the control and case groups was statistically significant (p=0.0489). The mean Nk1R of the control and case groups was 2.681±3.147 and 4.437±3.197, respectively. The difference in NK1R between the control and case groups was statistically significant (p=0.0227). This difference between SP and Nk1R in the control and case groups shows that these are associated with hypertension (Table 3).

The mean SP of males and females was 768.9±114.8 and 1073±718.4, respectively. In females, the SP value was greater than in males but the difference between them was not statistically significant (p=0.2484). The mean NK1R of males and females was 4.994±2.474 and 4.235±3.451, respectively; the difference in NK1R between them was not statistically significant (p=0.5743) (Table 4).

Patients of hypertension are distributed with respect to their age in Table 4, along with respective levels of SP and NK1R. Out of all patients, 14(46.6%) were in the group of 40-50 years with SP and NK1R of 278.24±823.7 and 4.86±3.65. The rest of the participants were in other age groups. The difference in SP and NK1R levels among age

**Table 1.** Demographics of hypertensive and cardiac patients.

| Variables | Hypertensive patients | | | | Cardiac patients | | | |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | Total | p | Male | Female | Total | p |
| Frequency (%) | 8 (26.7) | 22 (73.3) | 30 (100.0) | -- | 24 (68.6) | 11 (31.4) | 35 (100.0) | - |
| Age (years) | 68.5±14.75 | 54.45±13.23 | 58.2±14.80 | 0.0187 | 49.04±13.14 | 43.55±7.104 | 47.31±11.76 | 0.0759 |
| Age at diagnosis | 64±14.64 | 49.36±13.51 | 53.27±15.07 | 0.0158 | 46.29±11.45 | 41.27±6.035 | 44.71±10.25 | 0.1823 |
| Weight (kg) | 81.25±4.43 | 74.64±11.52 | 76.40±10.48 | 0.1284 | - | - | - | - |
| Blood pressure | 170/80 | 170/90 | 170/90 | >0.9999 | 170/80 | 170/80 | 170/80 | >0.9999 |
| Sleeping duration | 8.875±0.7906 | 8.682±0.4511 | 8.733±0.5529 | 0.4067 | 8.333±0.5036 | 7.909±0.8608 | 8.214±0.6563 | 0.075 |
| General cardiac disease (%) | - | - | - | - | 20 (57.2) | 10 (28.6) | 30 (85.7) | - |
| Myocardial disease (%) | - | - | - | - | 4 (11.4) | 1 (2.8) | 5 (14.3) | - |

**Table 2.** Risk factors associated with hypertension and cardiac patients.

| Risk Factors | Hypertensive patients | | | Cardiac patients | | |
|---|---|---|---|---|---|---|
| | Yes | No | Total | Yes | No | Total |
| Smoking (%) | 10 (33.3) | 20 (66.67) | 30 (100.0) | 18 (51.5) | 17 (48.5) | 35 (100.0) |
| Exposure to pollution (%) | 12 (40) | 18 (60) | 30 (100.0) | 20 (57.2) | 15 (42.8) | 35 (100.0) |
| Family history (%) | 20 (66.67) | 10 (33.3) | 30 (100.0) | 26 (74.3) | 9 (25.7) | 35 (100.0) |
| Diet factors | Glycaemic diet | High salt diet | Both | Glycaemic diet | High salt diet | Both |
| Total (%) | 4 (13.3% | 10 (33.3) | 16 (52.34) | 19 (54.3) | 9 (25.7) | 7 (20) |

**Table 3.** Substance P and neurokinin 1 receptor difference between the case and control groups.

| Markers | Hypertensive patients | | | Cardiac patients | | |
|---|---|---|---|---|---|---|
| | Control | Case | p | Control | Case | p |
| SP | 615.0±177.2 | 992.1±629.0 | 0.0489 | 615.0±177.2 | 723.6±618.6 | 0.5542 |
| NK1R | 2.681±3.147 | 4.437±3.197 | 0.0227 | 2.681±3.147 | 2.807±6.294 | 0.9622 |

SP, substance P; NK1R, neurokinin 1 receptor.

**Table 4.** Substance P and neurokinin 1 receptor difference between males and females of the case group.

| Markers | Hypertensive patients | | | | Cardiac patients | | | |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | Total | p | Male | Female | Total | p |
| SP | 768.9±114.8 | 1073±718.4 | 992.1±629.0 | 0.2484 | 760.4±736.7 | 643.3±206.3 | 723.6±618.6 | 0.6105 |
| NK1R | 4.994±2.474 | 4.235±3.451 | 4.437±3.197 | 0.5743 | 3.751±7.449 | 0.7476±0.5021 | 2.807±6.294 | 0.1942 |

SP, substance P; NK1R, neurokinin 1 receptor.

groups was statistically insignificant which shows no dependence of SP and NK1R with age in hypertension patients (Figure 1A and B).

## Analysis of substance P and neurokinin 1 receptor in cardiac patients

A total of 35 patients were validly diagnosed with cardiac disorder and were included in this study. Out of these 35 patients, 30 were with general cardiac diseases and 5 were with myocardial disorder. Out of 35 participants, 11 (31.4%) were females and 24 (68.6%) were males. Different demographics of participants were recorded and analyzed with respect to male-female categories. The mean age of patients was 47.31±11.76 and the mean age of females was lower than the mean age of males, but the difference between their ages was statistically insignificant (p=0.0759), which shows females may be prone to hypertension. The difference in the age of diagnosis of both groups was also insignificant (p=0.1823). The mean blood pressure of participants was 170/80, and the difference in blood pressure between males and females was insignificant. The mean sleeping time of participants was 8.214±0.6563 hours (Table 1).

Out of the involved patients in this study, 26 (74.3%) had a family history of cardiac disorder, and 19 (54.3%) had a glycemic diet. So, these results prove that people with a family history of cardiac diseases and who take a high glycemic diet are more prone to cardiac disorders.

SP and NK1R were analyzed as markers of cardiac disorders. The mean SP of the control and case groups was 615.0±177.2 and 723.6±618.6, respectively. The difference in SP between the control and case groups was statistically insignificant (p=0.5542). The mean Nk1R of the control and case groups was 2.681±3.147 and 2.807±6.294, respectively. The difference in NK1R between the control and case groups was also statistically insignificant (p=0.9622). This difference between SP and Nk1R in the control and case groups shows that they might have less association with cardiac and myocardial disorders (Table 3).

The mean SP of males and females was 760.4±736.7 and 643.3±206.3, respectively. In males, the SP value was greater than in females, but the difference between them was not statistically significant (p=0.6105). The mean NK1R of males and females was 3.751±7.449 and 0.7476±0.5021, respectively. Although in males, the NK1R value was greater than in females, the difference between them was not statistically significant (p=0.1942) (Table 4).

Cardiac patients are distributed based on their age in Table 4, along with respective levels of SP and NK1R. Out of all patients, 11 (31.4%) were in the group of 41-50 years with SP and NK1R of 477.54±280.7 and 0.654±0.5. The rest of the participants were in other age groups. The difference in SP and NK1R levels among age groups was statistically insignificant, which shows no dependence of SP and NK1R with age in cardiac patients (Figure 1C and D).



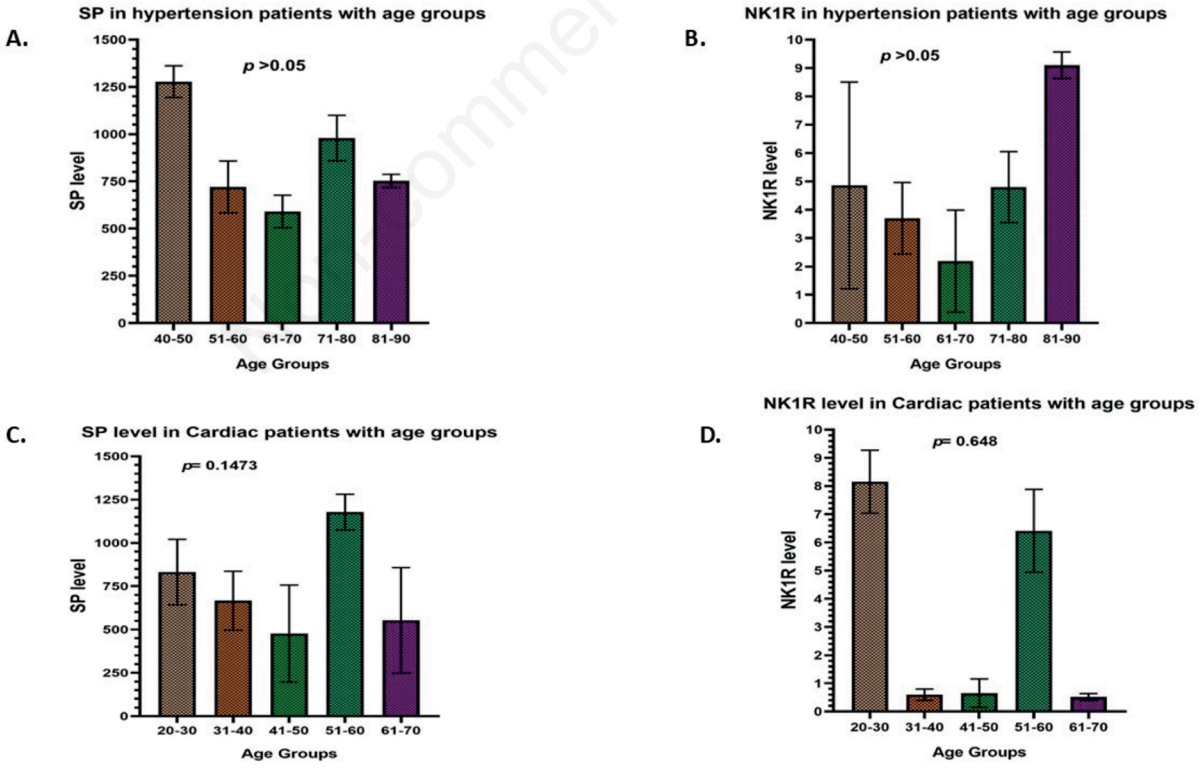


**Figure 1.** A) Substance P (SP) levels in hypertension patients with respect to age groups; B) neurokinin 1 receptor (NK1R) levels in hypertension patients with respect to age groups; C) SP levels in cardiac patients with respect to age groups; D) NK1R levels in cardiac patients with respect to age groups.

## Discussion

The research offers a thorough examination of the levels of SP and NK1R in hypertensive and cardiac patients to clarify their possible significance in the pathophysiology of cardiovascular illnesses. It also explores demographic aspects and related risk factors among participants.

Among individuals with hypertension, the percentage of females was found to be much greater (73.3%). This implies that these neuropeptides and hypertension may be related. The age, gender, and risk factors of hypertension patients' demographic data provide a thorough picture of the research population. Given that women's mean age was much lower than men's mean age, it is possible that women are more likely than men to develop hypertension early in life. There was no discernible weight difference between hypertension individuals who were male or female. Among those with hypertension, smoking, family history, and a diet heavy in salt were the most common risk factors. These results are consistent with the body of research showing the contribution of genetic predisposition and lifestyle variables to hypertension. When compared to the control group, the levels of SP and NK1R in hypertension patients were considerably higher. The findings point to a possible link between SP/NK1R and hypertension. Although the SP levels of females were greater than those of men, there was no statistically significant difference. There was no discernible variation in NK1R levels by gender. Among hypertension patients, SP and NK1R levels did not significantly rely on age groups.

SP directly affects the immune system to modify hypertension situations, according to research.[34] In a study by Brattström and Seidenbecher, rats with hypertension showed higher blood pressure in response to increasing levels of SP. These results confirm the findings of elevated SP in hypertensive people made in the present investigation.[35] On the other hand, NK1R−/− mice showed elevated mean arterial blood pressure without a corresponding alteration in vascular reactivity, according to Moyes *et al*. According to these findings, NK1R may be involved in the brain's control of blood pressure.[36]

There was a noticeably greater percentage of men (68.6%) among cardiac patients. Although women's mean age was lower than men's, this difference was not statistically significant. Among cardiac patients, glycemic diet and family history were shown to be common risk factors. The levels of SP and NK1R in cardiac patients and the control group did not vary significantly. The findings point to a possible absence of correlation between cardiac diseases and SP/NK1R. Although there was a statistically insignificant difference, men had greater SP levels than females. There was no discernible variation in NK1R levels by gender.

Our study's findings are corroborated by a few additional investigations. According to Meléndez *et al*., SP may have a significant role in causing unfavorable myocardium remodeling by stimulating cardiac mast cells, which increases tumor necrosis factor-α and matrix metalloproteinases activation and causes the extracellular matrix to degrade.[37] Chottova Dvorakova *et al*. also showed that NK1R was localized in some smooth muscle cells and intracardiac neurons. Unidentified genes or factors implicated in the development of diabetic cardiomyopathy may trigger impaired transcription of the NK1R gene in the diabetic heart.[38]

The cross-sectional design and the relatively small sample size are two of this study's shortcomings. Larger cohorts and longitudinal studies may be beneficial in future studies to confirm and expand on the present results.

## Conclusions

The purpose of this research was to look at the levels of NK1R and SP in people who had been diagnosed with heart disease and hypertension. Significant variations in SP and NK1R levels were seen between the hypertensive patients and the control group in the research, indicating a possible link between these neuropeptides and hypertension. On the other hand, no significant variations in SP and NK1R levels were seen between the cardiac patients and the control group. Interesting trends were found in the demographic study, including a greater frequency of hypertension in women and a possible earlier beginning of hypertension in this population. The identification of risk factors for hypertension, such as smoking, family history, and dietary habits, is consistent with the body of research on the effects of genetics and lifestyle on cardiovascular health. These findings provide significant new information on the possible functions of these neuropeptides in CVDs.

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