



Effects of vasopressin administration in the oral cavity on cardiac function and hemodynamics in rats

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Background: The vasoconstrictive effect of epinephrine in local anesthetics affects the heart, which leads to hesitation among dentists in injecting local anesthetics into patients with cardiovascular disease. Due to its vasoconstrictive effects, the present study investigated the effects of vasopressin administration on cardiac function in rats.

Methods: Experiment 1 aimed to determine the vasopressin concentration that could affect cardiac function. An arterial catheter was inserted into the male Wistar rats. Next, 0.03, 0.3, and 3.0 U/mL arginine vasopressin (AVP) (0.03V, 0.3V, and 3.0V) was injected into the tongue, and the blood pressure was measured. The control group received normal saline only. In Experiment 2, following anesthesia infiltration, a pressure-volume catheter was placed in the left ventricle. Baseline values of end-systolic elastance, end-diastolic volume, end-systolic pressure, stroke work, stroke volume, and end-systolic elastance were recorded. Next, normal saline and 3.0V AVP were injected into the tongue to measure their effect on hemodynamic and cardiac function.

Results: After 3.0V administration, systolic blood pressures at 10 and 15 min were higher than those of the control group; they increased at 10 min compared with those at baseline. The diastolic blood pressures at 5–15 min were higher than those of the control group; they increased at 5 and 10 min compared with those at baseline. The preload decreased at 5 and 10 min compared to that at baseline. However, the afterload increased from 5 to 15 min compared with that of the control group; it increased at 10 min compared with that at baseline. Stroke volume decreased at 10 and 15 min compared with that of the control group; it decreased from 5 to 15 min compared with that at baseline. Stroke work decreased from 5 to 15 min compared with that of the control group; it decreased from 5 to 15 min compared with that at baseline.

Conclusion: Our results showed that 3.0 U/mL concentration of vasopressin resulted in increased blood pressure, decreased stroke volume and stroke work, decreased preload and increased afterload, without any effect on myocardial contractility.

Keywords: Cardiac Catheters; Cardiac Volume; Cardiovascular System; Hemodynamics; Vasopressins; Ventricular Pressure.



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INTRODUCTION

Epinephrine is added to local anesthetic agents to achieve local vascular constriction, thereby increasing the anesthetic effect, prolonging the duration of action, controlling bleeding, and preventing toxicity [1,2]. Local

anesthetics with epinephrine increase blood pressure by acting on alpha-1 receptors, resulting in peripheral blood vessel constriction. However, epinephrine also acts on beta-1 receptors, leading to an increase in myocardial contractility and heart rate. This, in turn, increases myocardial oxygen consumption and may cause myocardial ischemia and arrhythmia [3]. A dose limit of

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$\leq 20 \mu\text{g}$ is used in patients with serious cardiovascular disease and those receiving nonselective beta-blockers [4]. This requires a local anesthetic that does not affect the circulatory organs and allows for safe dental treatment in older adults. Furthermore, epinephrine emphasizes the cardiac effects of thyroid hormones. Thus, patients with hyperthyroidism require careful cardiovascular monitoring, considering the changes in their cardiac function following epinephrine administration [5,6]. Therefore, a safer vasoconstrictor is required as an alternative to epinephrine to provide adequate local anesthesia for a wider range of patients.

Arginine vasopressin (AVP) is secreted by the pars nervosa of the posterior hypophysis and acts on vasopressin 1a (V1a) receptors on vascular smooth muscle cells to constrict peripheral vessels. AVP is used to increase blood pressure in shock, as a hemostatic agent for bleeding esophageal varices, and to decrease bleeding during myomectomy by enucleation [7-11]. Felypressin is synthesized by replacing the tyrosine in AVP with phenylalanine. This synthetic polypeptide has vasoconstrictive effects similar to those of AVP; however, it does not exhibit β -activity. Therefore, it exerts fewer effects on the circulatory system than epinephrine [12]. Prilocaine with felypressin is used in dentistry as a safer local anesthetic for patients with circulatory disease [3]. However, the anesthetic effect of prilocaine with felypressin is weaker than that of epinephrine-containing anesthetics. Therefore, we aimed to investigate the anesthetic effects of lidocaine with AVP. Local anesthetics containing AVP may increase the anesthetic effect, prolong the duration of action, control bleeding, and prevent toxicity without affecting hemodynamics, particularly cardiac function [13,14]. Conversely, Fujimori et al. [15] reported increased blood pressure and decreased pulse rate following AVP injection into the oral cavity of rats. In addition, Walker et al. [16] demonstrated that AVP stimulates cardiac function via V1a receptors. Considering that AVP-containing local anesthetics are indicated for patients with circulatory diseases, a better understanding of the effects of AVP on cardiac function

is required. To date, no studies have investigated the cardiac effects of AVP administration in the oral cavity. Katagiri et al. [17] reported that the vasoconstrictive effect of 3.0 U/mL AVP administration was equivalent to that of epinephrine added to local dental anesthetics. Accordingly, the present study was performed to investigate the hemodynamic outcomes of AVP administration in a rat model. The null hypothesis was that AVP administration in the oral cavity would not affect the cardiac function.

METHODS

The study protocol was approved by the Animal Ethics Committee of our university (details blinded for peer review) and was conducted in accordance with the committee's regulations and guidelines under Animal Research: Reporting of in vivo Experiments. All efforts were made to minimize animal suffering, reduce the number of animals used, and utilize alternatives to in vivo techniques, if available.

1. Experiment 1: Determining AVP concentration

To determine the concentration of vasopressin that could affect cardiac function, felypressin was added to prilocaine in various concentrations and fluctuation in blood pressure was evaluated. The following four formulations were tested:

1. Normal saline (NS)
2. 0.03 U/mL AVP (0.03V); 9 μL of AVP (Pitressin[®], Daiichi Sankyo Co. Ltd., Tokyo, Japan) + 5991 μL NS
3. 0.3 U/mL AVP (0.3V); 90 μL of Pitressin[®] + 5910 μL NS
4. 3.0 U/mL AVP (3.0V); 900 μL of Pitressin[®] + 5100 μL NS

2. Procedure

Four 10–12-week-old male Wistar rats were assigned to each group. We administered 50 mg/kg of pentobarbital

(Somnopentyl[®], Kyoritsu Pharmaceutical Corporation, Tokyo, Japan) intraperitoneally and injected 2% lidocaine (lidocaine injection 2%, Maruishi Pharmaceutical Co. Ltd., Osaka, Japan) into the right inguinal region for infiltration anesthesia. Next, the right femoral vein was exposed and a 22-gauge venous indwelling needle (Surflo; Terumo, Tokyo, Japan) was placed for intravenous catheterization. Propofol (1% propofol injection; Maruishi Pharmaceutical Co. Ltd, Tokyo, Japan) was administered at a rate of 15 mg/kg/h using a syringe pump for small animals (CFV-3200; Nihon Kohden, Tokyo, Japan). The animals breathed spontaneously.

Subsequently, a 24-gauge venous indwelling needle (Surflo; Terumo) was placed in the right femoral artery following infiltration anesthesia and connected to an analysis software (Ponemah[®]; Data Sciences International, St. Paul, MN, USA) via a blood pressure transducer (DX360, Nippon Becton Dickinson Co. Ltd., Tokyo, Japan) filled with 5000 U/mL of heparinized (Heparin Sodium-N "AY"; Yoshindo Inc., Toyama, Japan) NS. The tongue was pulled outside the oral cavity using forceps to test the formulation injection (Fig. 1).

3. Blood pressure measurements

Following hemodynamic stabilization, baseline (B) systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at 0 min in each experiment. A 31-gauge needle (Ito micro syringe; Ito Corp., Tokyo, Japan) was used to inject 20 μ L of one of the aforementioned test formulations into the lingual muscle. The blood pressure was measured 5 min after administration.

4. Experiment 2: Cardiac function and hemodynamic measurements

Among the three concentrations of AVP administered in Experiment 1, blood pressure showed an increase with 3.0V. Therefore, 3.0V was used to compare the cardiovascular changes with NS.

5. Study animals and the insertion of catheters

Six 10–12-week-old male Wistar rats were assigned to

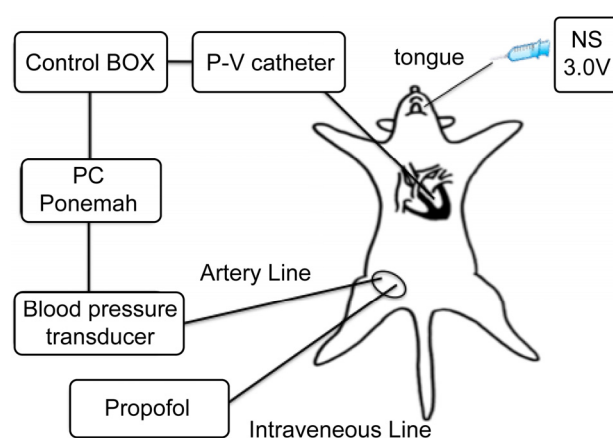


Fig. 1. Under sedation, NS or 3.0V is injected into the tongue of the rats to measure the blood pressure and cardiac function. NS, normal saline; 3.0V, 900 μ L of arginine vasopressin + 5100 μ L NS.

each group. Anesthesia and arterial catheter insertion were performed according to the methods described in Experiment 1. After infiltration anesthesia, a skin incision was made and a pressure volumetric catheter (FTH-1912B-8018, Transonic Scisense Inc., London, Ontario, Canada) was placed in the left ventricle via the right carotid artery. The catheter was then connected to a control box (FY097B; Transonic Scisense, Inc.). In addition, a 1-cm splitting incision was made at the bottom of the chondroxiphoid to measure end-systolic volume elastance (Ees).

The data measured by arterial and pressure-volume catheters were analyzed using biosignal acquisition and analysis software (Ponemah[®], Data Sciences International) [18,19] (Fig. 1).

6. Study drug and measurement of cardiac function and hemodynamics

Following hemodynamic stabilization, heart rate, left ventricular end-diastolic volume (Ved), left ventricular end-systolic pressure (Pes), stroke work (SW), and stroke volume (SV) were measured, followed by measurements of Ees through compression of the inferior vena cava. The other parameters were measured before Ees as the preload needed to be changed during the Ees measurements. These measurements were recorded as B values.

Subsequently, a 31-gauge needle was used to

Table 1. Blood pressure for various concentrations of AVP (n = 4)

	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
NS	129 ± 15	109 ± 15
0.03V [†]	139 ± 13	113 ± 29
0.3V [‡]	138 ± 12	112 ± 10
3.0V [§]	167 ± 16*	137 ± 12

One-way ANOVA and Dunnett t test were used as post hoc tests.

*Significant differences between NS

[†]9 μL of AVP + 5991 μL NS

[‡]90 μL of AVP + 5910 μL NS

[§]900 μL of AVP + 5100 μL NS

ANOVA, analysis of variance; AVP, arginine vasopressin; NS, normal saline.

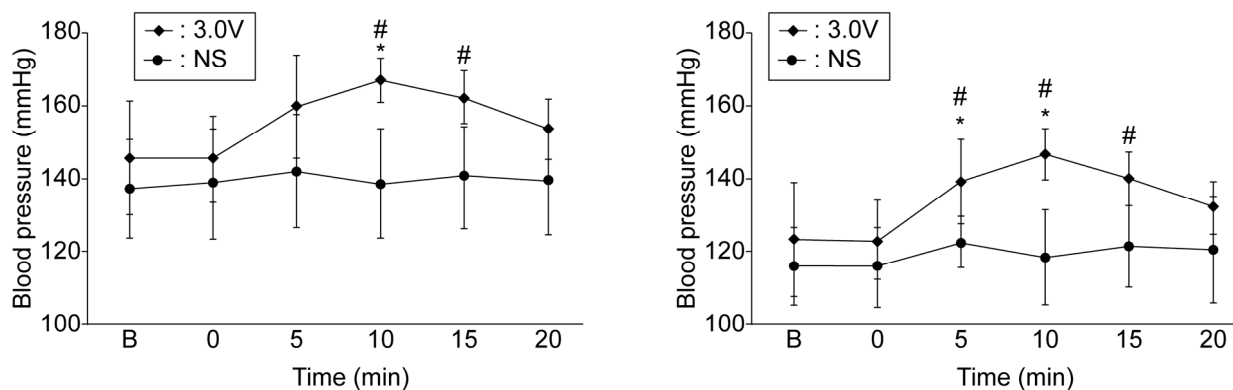


Fig. 2. Changes in SBP until 20 min after injection (n = 6) show significantly increased values in the 3.0V group compared to that of NS and that at B (Left). Changes in DBP until 20 min after injection (n = 6) show significantly increased values in the 3.0V group compared to that of NS and that at B (Right). *: significant difference from B. #: significant difference between the two groups. AVP, arginine vasopressin; B, baseline; DBP, diastolic blood pressure; SBP, systolic blood pressure; NS, normal saline; 3.0V, 900 μL of AVP + 5100 μL NS.

administer 20 μL of NS or 3.0V to the tongue. The first values were measured immediately after the injection. Following NS or 3.0V administration, the parameters of cardiac function and hemodynamics were measured at 5-min intervals for up to 20 min.

7. Statistical analyses

Measurements are indicated as mean ± standard deviation because the measured values showed normal distribution as per the Shapiro–Wilk test. Levene’s test was performed to calculate equal variance. One-way analysis of variance and Dunnett’s test, a post-hoc test, were conducted to compare the results of Experiment 1. For Experiment 2, a repeated-measures analysis of variance was performed for each time-point comparison. An unpaired t-test was performed for NS and 3.0V between-group comparisons. The statistical significance level was set at $P < 0.05$. The SPSS software was used

for all statistical analyses (IBM SPSS[®] Statistics ver. 25; IBM Corp., Armonk, NY, USA).

RESULTS

1. Experiment 1: Determining AVP concentration

Table 1 summarizes the changes in SBP and DBP. The test showed a significant effect on SBP ($F [3,12] = 5.383, P = 0.014$). Multiple comparisons revealed that the SBP after 3.0V administration was significantly higher than that after administration of the other three concentrations.

2. Experiment 2: Cardiac function and hemodynamic measurements

After administration of 3.0V, SBP was significantly increased in 10 minutes compared to before administration

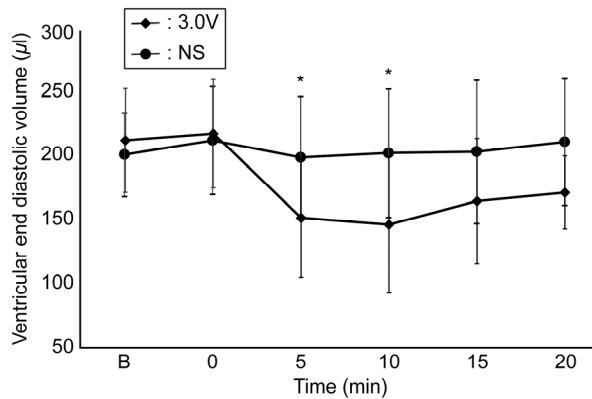


Fig. 3. Changes in Ved until 20 min after injection (n = 6) show significantly decreased values in the 3.0V group compared to that at B. *: significant difference from B. AVP, arginine vasopressin; B, baseline; NS, normal saline; Ved, left ventricular end-diastolic volume; 3.0V, 900 μL of AVP + 5100 μL NS.

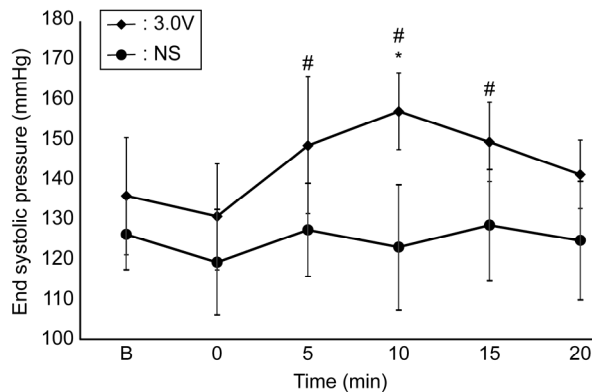


Fig. 4. Changes in the Pes until 20 min after injection (n = 6) show significant increase in the value of the 3.0V group compared to that after administering NS and that at B. *: significant difference from B. #: significant difference between two groups. AVP, arginine vasopressin; B, baseline; NS, normal saline; Pes, left ventricular end-diastolic pressure; 3.0V, 900 μL of AVP + 5100 μL NS.

($P = 0.004$). In addition, it increased significantly in 10 minutes and 15 minutes compared to NS ($P = 0.012, 0.012$) (Fig. 2). DBP significantly increased at 5 and 10 minutes compared to before administration ($P = 0.019, 0.013$). In addition, it increased significantly at 5, 10 and 15 minutes compared to NS ($P = 0.016, 0.004, 0.010$) (Fig. 2). Ved significantly decreased at 5 and 10 minutes compared to before administration ($P = 0.010, 0.005$) (Fig. 3). In Pes, it increased significantly in 10 minutes compared to before administration ($P = 0.030$). It also increased significantly at 5, 10 and 15 minutes compared to NS ($P = 0.022, 0.008, 0.020$) (Fig. 4). SV was significantly lower at 5,

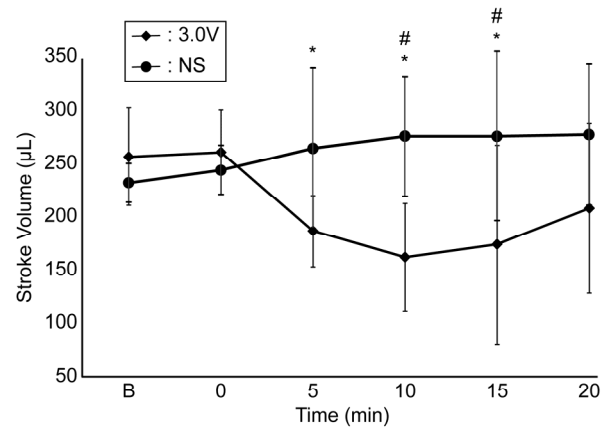


Fig. 5. Changes in the SV until 20 min after injection (n = 6) demonstrate significantly decreased SV in the 3.0V group compared to that after administering NS and that at B. *: significant difference from B. #: significant difference between two groups. AVP, arginine vasopressin; B, baseline; NS, normal saline; SV, stroke volume; 3.0V, 900 μL of AVP + 5100 μL NS.

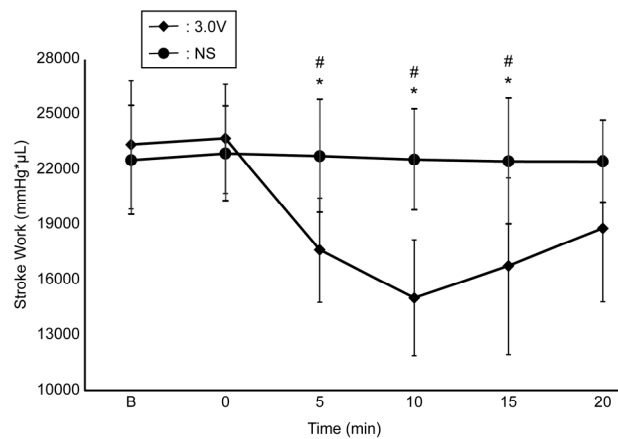


Fig. 6. Changes in the SW until 20 min of injection (n = 6) demonstrate significantly decreased SW in the 3.0V group compared to that after administering NS and that at B. *: significant difference from B. #: significant difference between two groups. AVP, arginine vasopressin; B, baseline; NS, normal saline; SW, stroke work; 3.0V, 900 μL of AVP + 5100 μL NS.

10 and 15 minutes compared to before administration ($P = 0.027, 0.002, 0.008$). It also decreased significantly at 10 and 15 minutes compared to NS ($P = 0.003, 0.037$) (Fig. 5). SW significantly decreased at 5, 10 and 15 minutes compared to before administration ($P = 0.012, 0.001, 0.004$). It also decreased significantly at 5, 10 and 15 minutes compared to NS ($P = 0.023, 0.002, 0.020$) (Fig. 6). No significant changes were observed in the heart rate and Ees measurements (data not shown).

DISCUSSION

Our findings demonstrated that intraoral administration of 20 μ L of 3.0 U/mL AVP increased blood pressure. However, we observed no change in Ees, which indicates myocardial contractility, resulting in a decrease in both SV and SW. Therefore, the hypothesis that intraoral AVP administration had no effect on cardiac function can be rejected.

SV is the volume of blood output by a single cardiac contraction, and it is calculated by subtracting the ventricular end-systolic volume, of which the Pes and Ees are indices, from the Ved. If Ees, which represents cardiac contractility, is constant, SV is small when the difference between Ved and Pes is small. In this study, while Ved decreased, Pes increased, and Ees showed no significant change. Therefore, the decrease in SV observed in this study was likely a result of the aforementioned changes in Ved, Pes, and Ees. In contrast, studies have shown that AVP promoted cardiac contractility [20,21].

Walker et al. [16] administered AVP and V1a receptor antagonists to a Langendorff-perfused isolated heart to measure left ventricular pressure. Perfusate AVP concentrations of 50–100 pg/mL increased the maximum rate of elevation of left ventricular pressure and maximum left ventricular pressure. Conversely, concentrations of 400–500 pg/mL decreased the levels of these parameters. Furthermore, these responses disappeared in the presence of V1a receptor antagonists. Therefore, the study demonstrated that AVP increased cardiac contractility via the V1a receptor up to a certain concentration. However, it decreased the cardiac contractility at higher concentrations. The appearance of two phases of cardiac contractility with high concentrations of AVP could be attributed to the following factors. The decreased myocardial oxygen supply due to coronary contractions related to high concentrations of AVP exceeded the effects of increased myocardial contractility via V1a receptors. Assuming that AVP 1 U is approximately equal to 2.5 μ g, the circulating blood volume of the rat is 20

mL, and all administered amounts of AVP reach the bloodstream, the AVP blood concentration in our study would be 75 x 100 pg/mL pg/mL [22,23]. There is no direct comparison of this in vivo concentration with the AVP concentration in the Langendorff perfusate reported by Walker et al. [16]. However, the lack of a significant change in the Ees with high concentrations of AVP may be explained by the cancellation of increasing myocardial contractility by decreasing coronary blood flow.

SW represents the energy expenditure of the ventricle while ejecting blood [24]. Therefore, an increase in SW indicates an increase in myocardial oxygen consumption and the risk of myocardial ischemia. Felypressin simultaneously constricts the coronary arteries and large vessels and causes myocardial ischemia [25,26]. However, considering our observations (i.e., a decrease in SW and the absence of tachycardia, which increases myocardial oxygen consumption), the risk of AVP administration-associated ischemic heart disease was considered low.

The decrease in SW was the result of a decrease in myocardial energy consumption because of the decrease in SV. The decrease in Ved in the present study represented a preload decrease and indicated venous vessel dilation. In contrast, the increase in Pes represented an afterload increase, suggesting a contraction in the arterial system. AVP administration has an antidiuretic effect that can increase the preload as the blood volume increases. The reason why AVP dilated the venous system and decreased preload remains unclear. However, as the expression of functional changes in the body generally take time due to hormones, it is possible that the measurement was performed before the antidiuretic effect of AVP was observed in this experiment. Felypressin primarily contracts the veins but can affect the arteries at higher concentrations [27]. Therefore, the administration of 3.0U possibly caused arterial contraction. The increases in SBP and DBP, despite the decrease in SV, were also considered to reflect arterial contraction.

The tip of the pressure-volume catheter used to assess cardiac function was equipped with two sets of electrodes and high-precision pressure sensors. We recorded

changes in the electric field between the electrodes to measure the ventricular volume. In addition, data from the pressure sensors were used to measure ventricular pressure. Numerous studies have reported the effectiveness of pressure-volume catheters in measuring cardiac function in small animals such as rats and mice [28,29]. Thus, it was selected as the most appropriate measurement method for this study.

This study has some limitations. In particular, the measurements were performed during administration of propofol, a potent vasodilator that could reduce the Ved and Pes [30]. This problem is unlikely to affect the interpretation of our results because NS and AVP were measured under the same conditions. However, the measurement conditions should be considered as these results were obtained under general anesthesia.

In conclusion, the administration of 20 μ L of 3.0V to the rat tongue decreased preload and increased afterload without affecting myocardial contractility, which resulted in increased blood pressure and decreased SV and SW. AVP is likely to be effective in patients with cardiovascular disease or those with contraindications for epinephrine administration. This necessitates further studies to investigate the effects of AVP on cardiac function and hemodynamics in spontaneously hypertensive rats. Furthermore, few reports have investigated the effects of adding AVP to local anesthetics [31], and further research is required to examine its clinical usefulness.

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AUTHOR CONTRIBUTIONS

Hayato Fukami: Data curation, Investigation, Resources, Software, Validation, Visualization, Writing - original draft

Katsuhisa Sunada: Conceptualization, (New Corresponding Author), Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - review & editing

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CONFLICT OF INTEREST: The authors have no conflicts of interest to declare.

ETHICS APPROVAL: Approval was obtained from the Animal Ethics Committee of Nippon Dental University, School of Life Dentistry, Tokyo (Approval no. 17-22).

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