Laboratory Investigations

Felypressin-induced reduction in coronary blood flow and myocardial tissue oxygen tension during anesthesia in dogs

Hideharu Agata DDS PhD,
Tatsuya Ichinohe DDS PhD,
Yuzuru Kaneko DDS PhD

Purpose: To determine whether felypressin reduced myocardial tissue oxygen tension (PmO_2).

Methods: Seven open-chest dogs were studied under nitrous oxide and isoflurane anesthesia. Hemodynamic variables including heart rate (HR), blood pressure (BP), mean pulmonary arterial pressure (MPAP), PmO_2 and coronary blood flow (CBF) were continuously recorded. After baseline measurements, felypressin was infused at 0.15, 0.3, 0.6 and 1.0 $IU \cdot hr^{-1}$ in a successive manner. Hemodynamic variables were evaluated at 3, 6, 9 min after the start of each infusion.

Results: Felypressin caused reductions in CBF and inner layer PmO_2 (int-PmO_2). Decreases in CBF (-23%, $P < 0.05$) and int-PmO_2 (-8%, $P < 0.05$) observed at low dose (0.15$IU \cdot hr^{-1}$) were not accompanied by changes in BP and HR. Negative correlations between cumulative doses of Felypressin ($mIU \cdot kg^{-1}$) and CBF (% change from base line) ($r=-0.69$, $P < 0.05$) or int-PmO_2 (% change from base line) ($r=-0.48$, $P < 0.05$) were observed.

Conclusion: Felypressin reduced PmO_2 along with minimal changes in HR and BP.

Objectif : Vérifier si la félypressine réduit la pression de l'oxygène du myocarde (PmO_2).

Méthode : Sept chiens ont été étudiés à thorax ouvert sous anesthésie au protoxyde d'azote et à l'isoflurane. Les variables hémodynamiques évaluées continûment étaient la fréquence cardiaque (FC), la tension artérielle (TA), la tension pulmonaire moyenne (TPM), la pression de l'oxygène du myocarde (PmO_2) et le débit sanguin coronarien (DSC). Les mesures de base prises, la félypressine est perfusée selon des concentrations successives de 0,15 - 0,3 - 0,6 et de 1,0 $UI \cdot hr^{-1}$. Les variables hémodynamiques sont évaluées à 3, 6, 9 min suivant le début de chaque perfusion.

Résultats : La félypressine a causé des réductions du DSC et de la PmO_2 de la couche interne (PmO_2-int). Des baisses du DSC (-23 %, $P < 0,05$) et de la PmO_2-int (-8 %, $P < 0,05$) ont été observées pour des faibles doses ($0,15 \cdot hr^{-1}$) et n'étaient pas accompagnées de changements de TA ni de FC. On a cependant observé des corrélations négatives entre les doses cumulatives de félypressine ($mUI \cdot kg^{-1}$) et le DSC (% de changement de la donnée de base) ($r=-0,69$, $P < 0,05$) ou la PmO_2-int. (% de changement de la donnée de base) ($r=-0,48$, $P < 0,05$).

Conclusion : La félypressine a réduit la PmO_2 tout en produisant des changements minimaux de FC et de TA.

From the Department of Dental Anesthesiology, Tokyo Dental College, 1-2-2, Masago, Mihamaku, Chiba city, 261, Japan.
Address correspondence to: Dr. Hideharu Agata, Phone: 81-43-270-3970; Fax: 81-43-270-3971.
Accepted for publication June 11, 1999

FELYPRESSIN is a synthetic hormone with a structure similar to that of arginine vasopressin (AVP). Felypressin is added to a local anesthetic solution in a concentration of 0.03 IU·ml^{-1} to enhance the local anesthetic effect and to reduce bleeding. Many clinicians use propitcaine -felypressin mixture, for dental use, as a first-choice for the management of patients with cardiovascular diseases because felypressin is considered to have fewer hemodynamic effects than epinephrine.[1] However, there are some reports of myocardial ischemia induced by felypressin, as well as by AVP, when administered in clinical doses.[2-5]

Kitagawa observed inhibition of cardiac function and a reduction in coronary blood flow (CBF) in felypressin- infused dogs and reported that these changes were not so marked as to impair the balance between myocardial oxygen supply and demand.[6] However, the study did not include measurements of myocardial oxygen tension (PmO_2) and other variables as indices to allow direct assessment of the balance between myocardial oxygen supply and demand. In addition, myocardial oxygen consumption was evaluated from rate-pressure product (RPP) which may not necessarily reflect myocardial oxygen consumption.[7] The AVP-induced inhibition of cardiac function is secondary to myocardial ischemia caused by CBF reduction and/or changes in sympathetic nervous activity.[5,8] If felypressin inhibits cardiac function by a mechanism similar to that of AVP, imbalance between myocardial oxygen supply and demand may occur in association with an apparent reduction in cardiac function. Thus, observation of changes in PmO_2 appears to be one of the best means of assessing the balance between myocardial oxygen supply and demand during administration of felypressin. No studies have investigated PmO_2 changes during felypressin infusion.

To confirm whether felypressin affects PmO_2, we examined PmO_2, CBF and other hemodynamic variables in dogs anesthetized with isoflurane (iso) and nitrous oxide (N_2O).

Methods

After approval by our Animal Care and Use Committee, seven mongrel dogs of either sex (weight range, 14-20 kg) were studied. All animals were allowed food and water *ad libitum* until the morning of the experiment. After an 18-gauge Teflon catheter was inserted into the left cephalic vein, anesthesia was induced with 10 mg·kg^{-1} thiopental *iv*. A 30 French size endotracheal tube was inserted into the trachea. After infusion of lactated Ringer's solution was started at 10 ml·kg^{-1}·hr^{-1}, the dog was given vecuronium and the lungs were mechanically ventilated. Anesthesia was maintained with a mixture of oxygen (2 l·min^{-1}), N_2O (2 l·min^{-1}) and isoflurane (end-tidal concentration (ETiso) 1-2%). Before skin incision, lidocaine was infiltrated into the surgical field. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were monitored continuously with a pressure transducer (P23ID; Gould, Oxnard, CA, USA) through an 18-gauge Teflon indwelling catheter in the right femoral artery. Mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), and central venous pressure (CVP) were continuously monitored with a transducer and a 7-French gauge thermodilution catheter (TC-704; Nihon Kohden, Tokyo, Japan) inserted via the left external jugular vein, the tip of which was positioned in a branch of the pulmonary artery. Heart rate (HR) was counted from pressure pulse wave. Cardiac output (CO) was measured, by thermodilution, with a hemodynamic profile computer (SP 1445; Spectramed). Following left thoracotomy in the fifth intercostal space, CBF was measured with an ultrasound flowmeter (T108; Transonic, Ithaca, NY, USA). The flow probe was positioned approximately 5 mm from the origin of the isolated left anterior descending artery (LAD). The PmO_2 was measured with a PO_2 monitor (PO_2-100DW; Inter Medical, Tokyo). Two plate-fixed polarographic needle electrodes (POE-40 PDS; Inter Medical, Tokyo) were set in the LAD-perfused area; one electrode was inserted in the myocardium to a depth approximately 2 mm from the epicardium to measure outer layer PmO_2 (ext-PmO_2), and the other was inserted to a depth approximately 7.5 mm from the epicardium to measure inner layer PmO_2 (int-PmO_2). Hemodynamic variables were continuously recorded with a polygraph (Polygraph series 360; NEC San-ei, Tokyo). Total peripheral resistance (TPR) was calculated by the following equation;

TPR = (MAP - CVP)·79.92·CO^{-1}. The ECG was continuously monitored throughout this study.

After experimental preparation, the ETiso was decreased to 1% and kept at this level for at least 60 min to stabilize hemodynamic variables. During the experiments, the ETiso and inhalation concentrations of N_2O were maintained at 1% and 50%, respectively, with $PaCO_2$ kept at 38 - 40 mmHg. The mean PaO_2 was 113 (90-130) mmHg. The concentrations of isoflurane and nitrous oxide were continuously monitored with an anesthetic gas monitor (Capnomac; Datex, Helsinki, Finland). Blood gas analysis was performed with a pH-blood gas electrolyte analyzer (Stat profile 5; Nova Biomedical, Boston, MA, USA). Body temperature was maintained at 36-38°C by the use of a heat lamp.

After hemodynamic stability was established, baseline values were obtained for each variable. Then, 0.01IU·ml^{-1} felypressin in physiological saline solution was infused at 0.15, 0.3, 0.6 and 1.0 IU·hr^{-1} in a successive manner: felypressin was diluted to the final concentration of 0.01 IU·ml^{-1} with physiological saline solution. Each infusion lasted for nine minutes, during which all variables were determined at 3, 6 and 9 min after the start of the infusion. There was an interval of at least one hour between each infusion to allow recovery of hemodynamic variables to baseline.

TABLE Effects of felypressin on hemodynamic parameters

	0.15IU·hr^{-1}				*0.3IU·hr^{-1}*			
	baseline	*3 min*	*6 min*	*9 min*	*baseline*	*3 min*	*6 min*	*9 min*
HR (bpm)	118.6 ± 17.0	116.7 ± 16.0	115.3 ± 17.2	115.0 ± 17.3	120.3 ± 17.0	119.3 ± 16.9	118.3 ± 19.5	115.6 ± 18.5*
SBP (mmHg)	132.7 ± 14.4	134.4 ± 17.5	132.6 ± 17.9	132.9 ± 18.1	134.0 ± 18.5	135.1 ± 19.2	136.7 ± 19.8	135.1 ± 17.1
DBP (mmHg)	84.0 ± 13.4	85.1 ± 12.6	85.1 ± 11.7	85.7 ± 11.9	84.1 ± 14.9	88.1 ± 15.2*	90.0 ± 16.2*	90.6 ± 14.9*
MAP (mmHg)	100.9 ± 12.8	101.6 ± 13.3	100.4 ± 14.5	101.1 ± 13.4	101.1 ± 15.9	103.6 ± 15.6	106.4 ± 16.7	104.9 ± 14.3
CO (L·min^{-1})	2.6 ± 0.3	2.5 ± 0.4	2.4 ± 0.4	2.3 ± 0.3	2.5 ± 0.3	2.2 ± 0.3*	2.1 ± 0.2*	2.2 ± 0.2*
TPR (dyne·sec·cm^{-5})	2754 ± 496	2985 ± 697	2978 ± 648	3167 ± 677	2891 ± 387	3264 ± 560*	3558 ± 561*	3418 ± 659*
MPAP (mmHg)	13.6 ± 3.5	13.8 ± 3.8	13.9 ± 3.6	14.6 ± 3.9	15.1 ± 4.0	14.5 ± 4.4	14.2 ± 4.7	13.8 ± 4.9
PCWP (mmHg)	9.3 ± 2.9	9.7 ± 3.6	9.4 ± 3.2	10.3 ± 4.0	10.6 ± 3.1	9.7 ± 4.5	10.0 ± 5.2	10.4 ± 5.6
CBF (mL·min^{-1})	26.6 ± 16.7	24.3 ± 16.5*	22.8 ± 17.0*	20.5 ± 13.8*	28.0 ± 16.7	22.6 ± 14.4*	19.3 ± 10.5*	17.8 ± 8.9*
int PmO_2 (mmHg)	44.7 ± 11.2	43.3 ± 9.6	42.6 ± 9.7*	40.7 ± 8.8*	43.9 ± 11.0	42.1 ± 9.8	40.4 ± 10.1*	38.9 ± 9.9*
ext PmO_2 (mmHg)	39.1 ± 9.5	39.1 ± 9.8	39.2 ± 9.6	38.5 ± 8.3	39.0 ± 8.6	37.2 ± 4.7	38.7 ± 5.5	39.3 ± 6.4
	0.6IU·hr^{-1}				*1.0IU·hr^{-1}*			
	baseline	*3 min*	*6 min*	*9 min*	*baseline*	*3 min*	*6 min*	*9 min*
HR (bpm)	121.0 ± 17.6	117.4 ± 16.6*	115.0 ± 16.5*	113.9 ± 16.5*	117.3 ± 16.4	114.6 ± 18.9*	112.4 ± 18.7*	110.9 ± 18.9*
SBP (mmHg)	134.9 ± 20.3	137.1 ± 19.9	139.7 ± 22.2*	139.9 ± 22.4*	137.1 ± 19.2	139.3 ± 19.5	139.9 ± 19.7*	140.3 ± 18.2*
DBP (mmHg)	85.4 ± 17.2	92.0 ± 16.6*	95.6 ± 17.7*	96.3 ± 19.0*	87.6 ± 17.8	96.0 ± 18.9*	96.0 ± 17.6*	98.1 ± 18.3*
MAP (mmHg)	102.3 ± 18.2	108.1 ± 17.0	109.3 ± 18.3*	110.9 ± 19.5*	104.1 ± 16.1	109.4 ± 16.1*	110.6 ± 16.2*	111.4 ± 16.7*
CO (L·min^{-1})	2.4 ± 0.5	2.1 ± 0.4*	2.0 ± 0.4*	2.0 ± 0.3*	2.3 ± 0.4	1.9 ± 0.4*	1.9 ± 0.5*	1.8 ± 0.3*
TPR (dyne·sec·cm^{-5})	2986 ± 585	3657 ± 489*	3837 ± 533*	3968 ± 794*	3236 ± 531	4078 ± 545*	4281 ± 753*	4340 ± 836*
MPAP (mmHg)	17.1 ± 4.4	16.2 ± 4.0	15.8 ± 4.3	16.0 ± 4.4	17.1 ± 4.2	16.7 ± 4.0	16.1 ± 4.5	16.2 ± 4.9
PCWP (mmHg)	10.4 ± 4.0	10.3 ± 4.2	10.9 ± 4.7	11.7 ± 3.7	11.7 ± 3.5	10.9 ± 4.3	11.0 ± 4.0	11.0 ± 5.0
CBF (mL·min^{-1})	29.0 ± 18.1	18.5 ± 8.8*	15.9 ± 7.0*	14.8 ± 5.8*	24.2 ± 13.9	14.0 ± 6.1*	11.3 ± 3.5*	10.6 ± 2.8*
int PmO_2 (mmHg)	42.1 ± 12.0	39.9 ± 11.5*	37.6 ± 10.9*	36.7 ± 10.9*	40.3 ± 11.3	38.3 ± 10.7*	35.3 ± 10.2*	32.9 + 10.1*
ext PmO_2 (mmHg)	38.2 ± 7.0	38.6 ± 7.2	38.7 ± 7.6	38.0 ± 7.3	37.0 ± 7.1	36.5 ± 6.6	34.3 ± -6.1*	32.4 ± 5.0*

Values are mean ± SD

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial blood pressure; CO = Cardiac output; TPR = total peripheral resistance; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; CBF = coronary blood flow; int PMO_2 = inner layer myocardial tissue oxygen tension; ext PmO_2 = outer layer myocardial tissue oxygen tension.

* $P < 0.05$ *vs* baseline

Statistical analysis

Data are presented as mean ± SD. For data processing, one-way repeated measurements ANOVA followed by the Student-Newman-Keuls test for multiple comparisons and linear-regression and Pearson's correlation coefficients were applied. A P value < 0.05 was considered significant.

Results

All observed variables returns toward control values after each felypressin infusion. The baseline values of each variable at each infusion rate were not statistically significant.

The HR and CO showed dose-dependent decreases, which appeared earlier with increasing rates of administration. None of these variable was changed at the lowest infusion rate (Table).

Blood pressure (BP) and TPR showed dose-dependent increases, which appeared earlier with increasing rates of administration. Changes in these variables were not noted at the lowest infusion rate. Changes in DBP and MAP appeared at lower doses than those in SBP, and the magnitude of increases in DBP and MAP were greater than that of SBP.

The MPAP and PCWP were not affected at any infusion rate.

The CBF, int-PmO_2 and ext-PmO_2 decreased in a dose-dependent manner. Reductions in CBF and int-PmO_2 were observed even at low doses which did not affect other variables. Negative correlations between cumulative dose of felypressin per body weight at the time points for measurement ($mIU \cdot kg^{-1}$) and CBF (%change from base line) (r=-0.69, $P < 0.05$) or int-PmO_2 (%change from base line) (r=-0.48, $P < 0.05$) were observed (Figures 1, 2).

There were no ST changes throughout this study.

Discussion

In this study, felypressin caused reductions in CBF and int-PmO_2. The decreases observed at low dose (0.15 $IU \cdot hr^{-1}$) were not accompanied by changes in BP and HR (Figure 3). These results suggest that felypressin may cause myocardial ischemia without changes in BP and HR. The fact that the baseline values of each variable at each infusion rate were similar suggests the changes observed in this study were not time induced.

Felypressin is commonly used, though less frequently than epinephrine, in dentistry and, especially, in the management of patients with concurrent cardiovascular diseases in Japan and Europe because of the minimal hemodynamic effects. In contrast, felypressin, in extremely high doses (10-100 times higher than the conventional clinical doses), caused marked increases

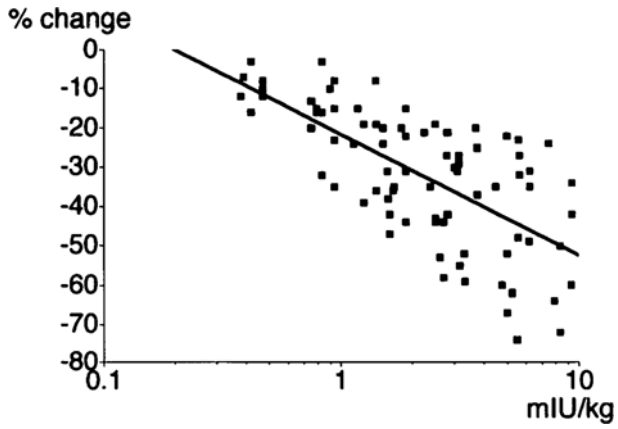

FIGURE 1 Negative correlation between cumulative doses of felypressin ($mIU \cdot kg^{-1}$), calculated from cumulative dose of felypressin at the time of measurement divided by each animal's body weight, and the percent changes from the baseline in coronary blood flow (CBF) (r=-0.69, $P < 0.05$). The abscissa shows felypressin dose ($mIU \cdot kg^{-1}$). The ordinate shows percent change in CBF.

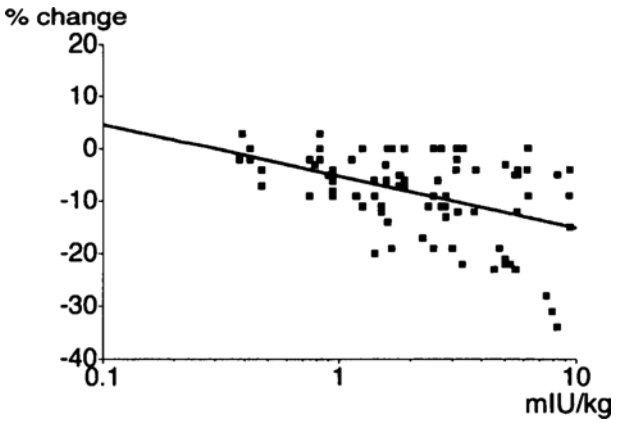

FIGURE 2 Negative correlation between cumulative doses of felypressin ($mIU \cdot kg^{-1}$), calculated from cumulative dose of felypressin at the time of measurement divided by each animal's body weight, and the percent changes from the baseline in inner layer myocardial oxygen tension (int-PmO_2) (r=-0.48, $P < 0.05$). The abscissa shows felypressin dose ($mIU \cdot kg^{-1}$). The ordinate shows percent change in int-PmO_2.

both in SBP and in DBP as well as impairment of myocardial oxygen supply/demand balance.[9,10]

Kitagawa examined cardiac function during continuous infusion of low doses of felypressin, at to 1.5, 4.5, 10.5 and 22.5 m $IU \cdot kg^{-1}$ over 120 min, respectively. Felypressin decreased HR, which was attributed to

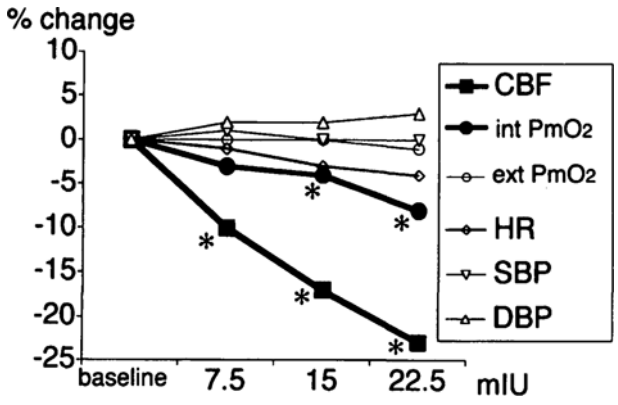

FIGURE 3 Administration of felypressin produced reductions in coronary blood flow (■, CBF) and inner layer myocardial tissue oxygen (●, int-PmO2). The abscissa shows cumulative doses of felypressin during felypressin infusion at 0.15 IU·hr^{-1}. The ordinate shows percent changes in CBF, int-PmO_2, outer layer myocardial tissue oxygen tension (○, ext-PmO_2), systolic blood pressure (▽, SBP), diastolic blood pressure (△, DBP) and heart rate (◇, HR) from the baseline. Low dose felypressin produced significant reductions in CBF and int-PmO_2 with no apparent changes in SBP, DBP and HR. *$P < 0.05$ *vs* baseline.

baroreceptor reflex without myocardial ischemia.[6] Although AVP may enhance the sensitivity of baroreceptor reflex,[8] other interpretations of AVP-induced cardiac depression have been suggested such as decreases in HR and CO, myocardial ischemia secondary to reduction in CBF,[8] a neurally mediated effect[11] or a direct cardiac depressive effect.[12] Recently, Graf *et al.* showed that AVP caused indirect myocardial depression by coronary constriction and myocardial ischemia.[13]

Myocardial oxygen tension is dependent on the balance between myocardial oxygen supply and oxygen consumption. Although PmO_2 is less indicative than myocardial tissue carbon dioxide of severe myocardial ischemia with histological changes, it is considered to be a more sensitive index of early ischemia.[14]

In this study, a reduction in PmO_2 was observed during felypressin infusion, especially in the inner layer, probably because this site is more liable to ischemia than is the outer layer.[15] Other mechanisms may also be considered. Felypressin induces contraction of vascular smooth muscle cells by binding to vasopressin receptor subtype-V1a(V1a).[1] Arginine vasopressin is involved in the release of endothelin-1 (ET-1) via an interaction with V1a in endothelial cells.[16] Endothelin-1 is a potent, long-acting vasoconstrictor peptide derived from the endothelium, which constricts vascular smooth muscle. If felypressin affects the release of the peptide as with AVP, ET-1 can be regarded as a factor involved in the coronary vasoconstriction by felypressin. It is reported that more ET-1selective endothelin receptor subtype ET_A exist in distal resistance coronary vessels than in relatively large, proximal, coronary blood vessels;[17] this different distribution may also be related to int-PmO_2 reduction. Accordingly, felypressin may produce a dose-dependent coronary vasoconstriction and impair the balance between oxygen supply and demand in the inner layer of the myocardium even in the absence of changes in BP and HR.

The plasma half life of AVP is approximately 17-35 min.[5] If felypressin has a plasma half-life similar to that of AVP, the effects of previous dosing should be minimal at each change of infusion in this study. The mean total doses at the end of each infusion were 1.35, 2.7, 5.4 and 9.0 mIU·kg^{-1}, which correspond to 1.5, 3, 6 and 10 units for a patient weighing 60 kg, as the local anesthetic cartridge (54mg propitocaine hydrochloride and 54 mIU felypressin contained in 1.8ml solution), respectively. These doses are within the range employed in oral surgery and are closer to usual clinical doses than those given in previous studies.

This study was not a chronic study, but an acute study under anesthesia. Since isoflurane has a potent coronary vasodilating action, it has been reported that the drug may cause coronary steal in the ischemic heart[18] and the addition of N_2O 50 % reduces the inner/outer layer blood flow ratio only in the ischemic region of the myocardium.[19] Thus, the interaction of felypressin and isoflurane or N_2O cannot be neglected. However, it is unlikely that the method of anesthesia used in this study exerted significant effects on the results because no changes in the method of anesthesia, the state of mechanical ventilation, or blood gas valueswere observed during a series of experiments (data not shown).

In clinical practice, routine monitoring of BP and HR may not provide information reflecting the state of myocardial oxygen supply/demand balance during felypressin administration. Ichinohe *et al.*[20] pointed out that continuous infusion of 5 ng·kg^{-1}·min^{-1} epinephrine alone produced dose-dependent changes in hemodynamic variables, which were not easily detected by routine monitoring of BP and HR during anesthesia. Combining these results, it is suggested that felypressin is not much safer than epinephrine in terms of myocardial ischemia.

In conclusion, felypressin decreased both CBF and int-PmO_2 . With increasing dosage, reductions in HR and CO, and increases in DBP, SBP and TPR were observed. The reductions in CBF and int-PmO_2 at low doses were not associated with changes in BP and HR.

Acknowledgments

The felypressin for this study was supplied by ASTRA JAPAN Co., Osaka, Japan. The author would like to greatly thank Dr. Masataka Kasahara, Department of Dental Anesthesiology, Tokyo Dental College, for his technical support.

References

1 *Yagiela JA.* Vasoconstrictor agents for local anesthesia. Anesth Prog 1995; 42: 116–20.
2 *El-Din ASMAK, Mostafa SM.* Severe hypertension during anaesthesia for dacryocystorhinostmy. Anaesthesia 1985; 40: 787–9.
3 *Himuro H, Aono K, Honda T, Nakajima T, Ohara G.* A case of coronary artery spasm during oral surgery under general anesthesia. Anesth Pain Control Dent 1992; 1: 215–8.
4 *Martin JD, Shenk LG.* Intraoperative myocardial infarction after paracervical vasopresssin infiltration. Anesth Analg 1994; 79: 1201–2.
5 *Jackson EK.* Vasopressin and other agents affecting the renal conservation of water. *In:* Hardman JG, Limbird LE (Eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed. New York: MacGraw-Hill, 1996: 715–31.
6 *Kitagawa E.* The effects of intravenously injected felypressin on cardiac function in dogs with intact or ischemic hearts. Anesth Prog 1995; 42: 154–5.
7 *Kissin I, Reves JG, Mardis M.* Is the rate-pressure product a misleading guide? (Letter) Anesthesiology 1980; 52: 373–4.
8 *Share L.* Role of vasopressin in cardiovascular regulation. Physiol Rev 1988; 68: 1248–84.
9 *Tsakiris A, Bühlmann A.* Experimentelle untersuchngen beim menschen über die wirkung von vasopressin auf die leberdurchblutung und den portalen druck. Helv Med Acta 1961; 28: 615–21.
10 *Saito T, Matsuzaki T, Wakisaka K, et al.* Problems and precautions in the application of octapressin. (Japanese) Masui 1966; 15: 1089–94.
11 *Hof RP.* Vasopressin induced myocardial depression is neurally mediated and not due to impaired coronary blood flow. Br J Pharmacol 1986; 87: 611–8.
12 *Tipayamontri U, Young DB, Nuwayhid BS, Scott RE.* Analysis of the cardiovascular effects of arginine vasopressin in conscious dogs. Hypertension 1987; 9: 371–8.
13 *Graf BM, Fischer B, Martin E, Bonsjak ZJ, Stowe DF.* Differential effects of arginine vasopressin on isolated guinea pig heart function during perfusion at constant flow and constant pressure. J Cardiovasc Pharmacol 1997; 29: 1–7.
14 *Yokoyama M, Maekawa K, Katada Y, et al.* Effects of graded coronary constriction on regional oxygen and carbon dioxide tensions in outer and inner layers of the canine myocardium. Jpn Circ J 1978; 42: 701–9.
15 *Guyaton AC, Hall JE.* Muscle blood flow and cardiac output during exercise; the coronary circulation and ischemic heart disease. *In:* Guyaton AC, Hall JE (Eds.). Text Book of Medical Physiology. Philadelphia: W.B. Saunders Company, 1996: 253–63.
16 *Kohno M, Horio T, Ikeda M, et al.* Natriuretic peptides inhibit mesangial cell production of endothelin induced by arginine vasopressin. Am J Physiol 1993; 264: F678–83.
17 *Godfraind T.* Evidence for heterogeneity of endothelin receptor distribution in human coronary artery. Br J Pharmacol 1993; 110: 1201–5.
18 *Priebe H-J.* Isoflurane and coronary hemodynamics. Anesthesiology 1989; 71: 960–76.
19 *Nathan HJ.* Nitrous oxide worsens myocardial ischemia in isoflurane-anesthetized dogs. Anesthesiology 1988; 68: 407–15.
20 *Ichinohe T, Kaneko Y, Nakakuki T.* The effect of epinephrine on circulation and respiration - a study on epinephrine infusion technique. Dentistry in Japan 1991; 28: 161–5.