Laboratory Investigations

Adenosine and amrinone reverse felypressin-induced depression of myocardial tissue oxygen tension in dogs

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Purpose: To determine whether continuous infusion of adenosine triphosphate (ATP), nitroglycerin (NTG) or amrinone (AM) would ameliorate the reductions in coronary blood flow (CBF) and myocardial oxygen tension (PmO_2) induced by felypressin.

Methods: Seven open-chest dogs were studied under urethane and alpha-chloralose anesthesia. Hemodynamic variables including heart rate (HR), systolic blood pressure, diastolic blood pressure (DBP), mean pulmonary artery pressure, pulmonary capillary wedge pressure, CBF (ultrasound flowmetry), PmO_2 (polarography) and cardiac output (thermodilution method) were recorded. Felypressin was infused in a loading dose of $6 \text{ mL} \cdot \text{kg}^{-1}$ for five minutes and then continued at $0.2 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. After 30 min felypressin infusion, each agent was administered for 15 min to evaluate hemodynamic changes. Infusions were 100 and $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for ATP, 2.5 and $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for NTG, and 10 and $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for AM.

Results: After felypressin DBP increased by 17 ± 5 (mean $\pm$ SD) %; CBF decreased by 49 ± 9 %; CI decreased by 40 ± 13 %; HR decreased by 29 ± 11 %; PmO_2 in the inner layer decreased by 21 ± 7 %. The CI and CBF returned to baseline after ATP 100 and $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, AM 10 and $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, but not after NTG. The PmO_2 in the inner layer returned to the baseline value by any infusion except for NTG $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

Conclusion: Adenosine and amrinone, but not nitroglycerin reverses the adverse cardiovascular effects of felypressin.

Objectif : Vérifier si une perfusion continue d'adénosine triphosphate (ATP), de nitroglycérine (NTG) ou d'amrinone (AM) améliore la réduction du débit coronarien (DC) et de la pression partielle en oxygène myocardique (PmO_2) induits par la félypressine.

Méthode : Sept chiens sous anesthésie avec uréthane et alpha-chloralose ont été étudiés à thorax ouvert. On a mesuré les variables hémodynamiques suivantes : la fréquence cardiaque (FC), la tension artérielle systolique (TAS), la tension artérielle diastolique (TAD), la tension artérielle pulmonaire moyenne, la tension capillaire pulmonaire, le DC (par ultrasonographie Doppler), la PmO_2 (par polarographie) et le débit cardiaque en qualité d'index cardiaque IC (par thermodilution). La félypressine a été injectée en dose de charge de $6 \text{ mL} \cdot \text{kg}^{-1}$ pendant cinq minutes, puis par une perfusion de $0,2 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Après 30 min, on a administré, pendant 15 min, une des perfusions de 100 et $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ d'ATP, $2,5$ et $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ de NTG et 10 et $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ d'AM et on a évalué les changements hémodynamiques.

Résultats : Après l'administration de félypressine, la TAD a augmenté de 17 ± 5 (moyenne $\pm$ écart type) %; le DC a diminué de 49 ± 9 %; l'IC a baissé de 40 ± 13 %; la FC a baissé de 29 ± 11 %; la PmO_2 a baissé de 21 ± 7 % dans la couche interne. L'IC et le DC sont revenus aux mesures de base après l'administration de 100 et $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ d'ATP, 10 et $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ d'AM, mais non après la NTG. La PmO_2 de la couche interne est revenue aux valeurs de base après toutes les perfusions, sauf après $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ de NTG.

Conclusion : L'adénosine et l'amrinone, mais non la nitroglycérine, ont renversé les effets cardiovasculaires indésirables de la félypressine.

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FELYPRESSIN,¹ a synthetic analogue of vasopressin, is used as a vasoconstrictor in combination with local anesthetics in dentistry. Causing less hemodynamic effects than epinephrine,² the agent is frequently used in patients with concurrent cardiovascular disorders. However, much of its pharmacological activities is unknown, and there are reports of myocardial ischemia induced by conventional clinical doses.³⁻⁶

Kitagawa⁷ observed inhibition of cardiac function and a reduction in coronary blood flow (CBF) in dogs given felypressin in relatively low doses. Agata *et al.*⁸ reported that, in dogs, clinical doses of felypressin caused decreases of both CBF and myocardial tissue oxygen tension in the inner layer (int-PmO₂), suggesting impairment of the myocardial oxygen supply/demand balance. Although studies of pressor responses to high-dose felypressin have been reported,^{9,10} the hemodynamic effects of clinical doses are less well documented and much remains to be clarified. Since felypressin is widely used clinically, practical information on the prevention and treatment of its side effects is of importance.

Provided the felypressin-induced decrease in CBF is responsible for the reduction of PmO₂, improvement in CBF would be important. Thus, the current study was designed to determine whether continuous infusion of coronary vasodilators, adenosine triphosphate (ATP), nitroglycerin (NTG) or amrinone (AM) ameliorate the hemodynamic effects of felypressin on CBF and PmO₂ in thoracotomized dogs under anesthesia with urethane and alpha-chloralose.

Methods

After approval by our Animal Care and Use Committee, 10 Labrador-Beagle hybrid dogs (NRB; Nihon Nohsan Kohgyo, Yokohama, Japan) were studied. After an 18-gauge Teflon catheter was inserted into the left cephalic vein, anesthesia was induced with 15 mg·kg⁻¹ thiopental *iv*. A 30 French size endotracheal tube was inserted into the trachea. Anesthesia was maintained with a mixture of oxygen, air and isoflurane (end-tidal concentration 1-2%). Lactated Ringer's solution was infused at a rate of 10 ml·kg⁻¹·hr⁻¹. After administration of vecuronium, the lungs were mechanically ventilated. Eighteen gauge Teflon indwelling catheters were inserted into the right femoral artery, right femoral vein, and right cephalic vein, respectively, for measurement of arterial pressure and for infusion of drugs. A 7-French thermodilution catheter (TC-704; Nihon Kohden, Tokyo, Japan) was also inserted via the right external jugular vein, the tip of which was positioned in the branch of

the pulmonary artery. Following left thoracotomy in the fifth intercostal space, a flow probe (Type 3SB) of an ultrasound flowmeter (T108; Transonic, Ithaca, NY, USA) was placed approximately 5 mm from the origin of the isolated left anterior descending artery (LAD) for measurement of CBF. Two plate-fixed polarographic needle electrodes (POE-40 PDS; Inter Medical, Tokyo, Japan) were set in the LAD-perfused area; one electrode was inserted into the myocardium to a depth of approximately 2 mm from the epicardium to measure PmO₂ in the outer layer (ext-PmO₂) and the other was inserted to a depth of approximately 7.5 mm from the epicardium to measure int-PmO₂.

Following completion of preparations for the experiments, inhalation of isoflurane was discontinued and the animal was supplied with an air-oxygen gas mixture (fractional concentration of oxygen in inspired gas, 40%). Anesthesia was maintained by continuous infusion of urethane and alpha-chloralose through the right femoral vein at rates of 160 mg·kg⁻¹·hr⁻¹ and 16 mg·kg⁻¹·hr⁻¹, respectively. Muscle relaxation was achieved with vecuronium as required. The lungs were mechanically ventilated to maintain arterial carbon dioxide tension at 35-40 mmHg. Blood gas analysis was performed with a pH-blood gas electrolyte analyzer (Stat profile 5; Nova Biomedical, Boston, MA, USA). Body temperature was maintained within a range of 36-38°C by the use of a heat lamp.

Hemodynamic parameters were continuously recorded with a polygraph (Polygraph series 360; NEC San-ei, Tokyo, Japan). Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean pulmonary artery pressure (MPAP) and pulmonary capillary wedge pressure (PCWP) were measured continuously with a pressure transducer (P23ID; Gould, Oxnard, CA, USA). Heart rate (HR) was counted from pressure pulse wave. Coronary blood flow was measured with an ultrasound flowmeter. Myocardial oxygen tension was measured with a PmO₂ monitor (PO₂-100 DW; Inter Medical, Tokyo, Japan). Cardiac output was measured by the thermodilution method, which involved infusing 10 ml glucose 5% solution at 0°C through the proximal lumen of the thermodilution catheter and by means of a hemodynamic profile computer (SP 1445; Spectramed, Oxnard, CA, USA); the results were indicated as the cardiac index (CI).

Figure 1 shows the study protocol. The baseline measurements were obtained when hemodynamic stability was established one hour or more after completion of surgical preparation. Felypressin was administered through the left cephalic vein first at a loading dose of 6 mIU·kg⁻¹ for five minutes and then infused at a rate of 0.2 mIU·kg⁻¹·min⁻¹ continuously

FIGURE 1 Study protocol: = time of measurement. Felypressin was infused first in a loading dose of $6 \text{ mIU} \cdot \text{kg}^{-1}$ for five minutes and then at a rate of $0.2 \text{ mIU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ continuously during the experiments. Following a 30 min infusion of felypressin, each agent was administered concurrently for 15 min to evaluate changes in hemodynamic parameters. The rates and dosages of intravenous infusion were 100 and $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for adenosine triphosphate (ATP100, ATP200), 2.5 and $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for nitroglycerin (NTG2.5, NTG5), and 10 and $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for amrinone (AM10, AM20). The infusions of felypressin were stopped after all assessments were made. The measurements, no less than two hours after discontinuation of all infusions and when hemodynamic stability was attained, were recorded as the end values.

during the experiments. Hemodynamic measurements obtained 30 min after the start of continuous felypressin infusion were used as control values (cont ATP 100).

Adenosine triphosphate was infused at $100 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ through the right cephalic vein. The hemodynamic measurements were evaluated 15 min after the start of the infusion. With a test drug-free interval of not less than 60 min, infusion of ATP was resumed at a rate of $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and measurements were evaluated after 15 min. Experiments were repeated with NTG at dosages of $2.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Amrinone was infused first at a loading dose of $1 \text{ mg} \cdot \text{kg}^{-1}$ over five minutes and then at a dose of $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 10 min. Hemodynamic measurements were evaluated 15 min after the start of the infusion. After an interval of five minutes, AM was then infused at a rate of $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 15 min and hemodynamic measurements taken.

The dose range of each drug was set on the basis of a preliminary study at a level which decreased DBP, which had been elevated by administration of felypressin, to the baseline value.

The infusions of felypressin were stopped after all assessments were made. The measurements, no less than two hours after discontinuation of all infusions and when hemodynamic stability was attained, were

FIGURE 2 Hemodynamic parameters during continuous infusion of felypressin. Felypressin produced changes ($P < 0.05$) in diastolic blood pressure (■, DBP), inner layer myocardial tissue oxygen tension (●, int-PmO₂), heart rate (□, HR), cardiac index (○, CI) and coronary blood flow (Δ, CBF). Outer layer myocardial tissue oxygen tension (●, ext-PmO₂) and systolic blood pressure (▲, SBP) were not affected. The DBP increased approximately 17 ± 5 (mean $\pm$ SD)%. The CBF, CI and int-PmO₂ decreased approximately 49 ± 9 , 40 ± 13 and $21 \pm 7\%$, respectively. Asterisk indicates statistical significance ($P < 0.05$) as compared with baseline.

recorded as the end values. Felypressin was supplied as a stock solution ($22.6 \text{ IU} \cdot \text{ml}^{-1}$) to be diluted in physiological saline.

Statistical analysis

Data are presented as mean $\pm$ SD. For data processing, one-way repeated measurements ANOVA followed by the Student-Newman-Keuls test for multiple comparisons was applied. A P value less than 0.05 was considered significant.

Results

Since three of ten dogs were excluded from data analysis because of technical problems, data from seven dogs were served for statistical analysis.

The PaO₂ was maintained at 100-120 mmHg throughout the study.

Felypressin infusion caused changes in DBP, int-PmO₂, HR, CI and CBF, but ext-PmO₂ and SBP were not affected. The DBP increased about $17 \pm 5\%$, whereas CBF, CI and int-PmO₂ decreased approximately 49 ± 9 , 40 ± 13 and $21 \pm 7\%$, respectively. There were no differences among the control values in DBP, CI, CBF and int-PmO₂ for ATP 100, ATP 200, NTG 2.5, NTG 5, AM 10 and AM 20 (Table, Figure 2).

TABLE Hemodynamic effects of coronary vasodilators (adenosine triphosphate (ATP), nitroglycerin (NTG) or amrinone (AM)) in dogs receiving continuous infusion of felypressin.

	<i>baseline</i>	<i>cont ATP100</i>	<i>ATP100</i>	<i>cont ATP200</i>	<i>ATP200</i>	<i>cont NTG2.5</i>	<i>NTG2.5</i>
HR (bpm)	142.6 ± 33.7	100.9 ± 20.5*	118.7 ± 29.6*	103.0 ± 22.4*	141.9 ± 35.4†	104.0 ± 20.4*	103.7 ± 21.9*
SBP (mmHg)	167.1 ± 15.3	179.3 ± 20.0	168.1 ± 15.2	173.3 ± 18.1	159.4 ± 13.6†	169.4 ± 13.7	160.9 ± 14.4†
DBP (mmHg)	106.7 ± 16.4	125.1 ± 16.9*	108.1 ± 21.4†	123.4 ± 18.5*	92.7 ± 15.6*†	120.9 ± 17.4*	110.6 ± 15.1†
MPAP (mmHg)	11.5 ± 3.2	11.0 ± 2.6	10.8 ± 3.1	11.9 ± 3.7	11.3 ± 2.6	11.3 ± 4.0	9.6 ± 3.3
PCWP (mmHg)	3.9 ± 1.9	5.0 ± 2.5	5.4 ± 2.6	5.4 ± 3.2	3.7 ± 1.8	5.4 ± 2.3	4.0 ± 1.3
CI (L·min ⁻¹ ·m ⁻²)	4.3 ± 1.4	2.6 ± 0.9*	3.5 ± 1.3†	2.7 ± 0.8*	4.7 ± 1.7†	2.7 ± 0.8*	2.7 ± 0.7*
CBF (mL·min ⁻¹)	21.0 ± 6.8	10.7 ± 3.3*	16.6 ± 6.6	10.1 ± 3.2*	31.0 ± 18.7*†	10.6 ± 3.6*	10.3 ± 3.5*
int PmO ₂ (mmHg)	39.9 ± 10.8	31.7 ± 8.2*	36.1 ± 8.5	29.0 ± 8.5*	38.1 ± 8.7	29.7 ± 8.5*	32.1 ± 7.8
ext PmO ₂ (mmHg)	32.9 ± 8.7	36.3 ± 9.1	35.9 ± 10.8	35.1 ± 11.3	32.4 ± 14.9	35.1 ± 12.5	35.7 ± 13.5
	<i>cont NTG5</i>	<i>NTG5</i>	<i>cont AM10</i>	<i>AM10</i>	<i>cont AM20</i>	<i>AM20</i>	<i>end</i>
HR (bpm)	100.4 ± 19.7*	103.9 ± 22.2*	103.6 ± 23.8*	111.3 ± 26.9*	103.6 ± 23.8*	109.9 ± 29.5*	127.1 ± 26.7†
SBP (mmHg)	164.9 ± 15.8†	155.3 ± 13.3†	164.7 ± 12.7	161.0 ± 17.0†	164.7 ± 12.7	158.1 ± 14.4†	149.6 ± 29.1†
DBP (mmHg)	120.7 ± 15.6*	108.3 ± 14.1†	119.9 ± 15.5*	99.6 ± 15.4†	119.9 ± 15.5*	99.3 ± 14.2†	100.3 ± 18.1†
MPAP (mmHg)	12.3 ± 3.6	8.7 ± 3.5	12.1 ± 3.4	8.3 ± 2.7	12.1 ± 3.4	8.4 ± 2.7	10.3 ± 4.1
PCWP (mmHg)	4.9 ± 2.2	3.3 ± 2.0	6.3 ± 2.6	3.1 ± 1.8	6.3 ± 2.6	3.3 ± 1.8	4.6 ± 1.9
CI (L·min ⁻¹ ·m ⁻²)	2.8 ± 0.7*	2.9 ± 0.7*	2.8 ± 0.8*	3.7 ± 1.3†	2.8 ± 0.8*	3.8 ± 1.3†	3.9 ± 1.3†
CBF (mL·min ⁻¹)	10.3 ± 3.1*	10.4 ± 3.0*	9.6 ± 2.6*	15.7 ± 5.1	9.6 ± 2.6*	15.3 ± 7.2	14.9 ± 6.4
int PmO ₂ (mmHg)	30.7 ± 8.1*	31.7 ± 7.1*	28.6 ± 8.0*	38.6 ± 14.5	28.6 ± 8.0*	39.6 ± 13.1	37.7 ± 14.2
ext PmO ₂ (mmHg)	36.1 ± 13.1	35.1 ± 15.1	33.9 ± 14.9	33.6 ± 16.0	33.9 ± 14.9	34.6 ± 13.5	31.9 ± 17.8

Values are mean ± SD

HR= heart rate; SBP= systolic blood pressure; DBP= diastolic blood pressure; MPAP= mean pulmonary artery pressure; PCWP= pulmonary capillary wedge pressure; CI= cardiac index; CBF= coronary blood flow; int PmO₂= inner layer myocardial tissue oxygen tension; ext PmO₂= outer layer myocardial tissue oxygen tension. cont= control values for each measurements.

*: $P < 0.05$ from baseline; †: $P < 0.05$ from cont ATP100.

The baseline values of the hemodynamic parameters did not differ from the end values. The DBP, increased by felypressin, returned to the baseline value by infusion of each drug. However, infusion of ATP 200 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ resulted in a decrease in DBP below the baseline value. The CI, decreased through the administration of felypressin, returned to the baseline value with the infusion of ATP 100 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, ATP 200 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, AM 10 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and AM 20

$\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, while infusion of NTG 2.5 or 5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ failed to bring about recovery to baseline values. The CBF, decreased with felypressin, returned to the baseline value by infusion of ATP 100 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, AM 10 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and AM 20 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Infusion of ATP 200 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ resulted in an increase in CBF above the baseline value. Infusion of NTG 2.5 or 5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ failed to achieve recovery of CBF. The int-PmO₂ returned to the

baseline value with infusion of ATP $100 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, ATP $200 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, NTG $2.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, AM $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and AM $20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Infusion of NTG $5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ failed to effect recovery to the baseline value. The SBP, MPAP, PCWP, and ext-PmO₂ did not deviate from baseline values until the end of the experiments. The HR returned to the baseline value by infusion of ATP $200 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ but was unchanged by infusion of the other agents.

Discussion

In this study, DBP, which was increased by intravenous felypressin, returned to the baseline value by infusion of ATP at the lower dosage and NTG and AM at both the lower and higher dosages, although ATP infusion at $200 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ decreased DBP below the baseline value. The CI, CBF and int-PmO₂, decreased by felypressin, returned to the baseline values by infusion of ATP and AM. Nitroglycerin infusion at $2.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ provided a slight improvement of int-PmO₂.

Kitagawa⁷ tried intravenous infusion of felypressin in relatively low doses (0.05, 0.1, 0.2 and $0.4 \text{ mIU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for 30 min) in thoracotomized dogs under anesthesia with urethane and alpha-chloralose. Although inhibition in cardiac function and a reduction in CBF were observed during infusion, changes in these parameters were not so great as to indicate impairment of the myocardial oxygen supply and demand balance. However, his study did not include measurement of PmO₂¹¹ as an index allowing direct assessment of the balance between myocardial oxygen supply and demand. The author calculated myocardial oxygen consumption from the rate-pressure product and other hemodynamic parameters. Agata *et al.*⁸ administered felypressin *iv* in the low dose of 22.5 mIU (equivalent to Citanest™-Octapressin™ Dental Cartridge 0.75 ml) to thoracotomized dogs under isoflurane anesthesia and observed reductions in CBF and int-PmO₂ which were not accompanied by changes in blood pressure (BP) or HR. Based on these findings, they suggested that felypressin may impair the myocardial oxygen supply and demand balance in the internal layer even without changes in BP or HR by causing a dose-dependent contraction of the coronary vessels.

Felypressin has a vasoconstricting potency five times greater than that of vasopressin (VP).¹ Coronary vasoconstriction occurs through the binding of the agent to V1 receptors in the same manner as VP.² In this study, felypressin decreased CBF by approximately 49% from baseline and maintained that level during infusion. A 40-60% decrease in CBF would cause a 90% or more reduction in the diameter of the vessel,¹²

indicating the development of significant impairment of the myocardial oxygen supply and demand balance.

In the experimental model used in the study, the CI, CBF and int-PmO₂ returned to the felypressin-induced low values after infusion of each drug was completed and no differences in any of the parameters were found among the control values for any of the drugs studied. In addition, each hemodynamic parameter returned to the baseline value after completion of felypressin infusion. Thus, the experimental model, in which occurs a stable period between the infusions of different drugs, is valid for investigating the hemodynamic effect of a series of agents.

In the body, most ATP is converted to adenosine (ADO). The major actions of ADO are 1) vasodilation and afterload reduction through a decrease of peripheral resistance, 2) increase of both cardiac output and stroke volume without inducing tachycardia and 3) increase of CBF and decrease of cardiac oxygen consumption.¹³ These hemodynamic effects appear to be mediated by ADO receptors,^{14,15} with the major ADO receptors designated as A1 and A2. A1 receptors mainly mediate inhibition of norepinephrine release,¹⁶ inhibition of excessive myocardial contraction induced by beta-stimulation^{17,18} and delay of stimulation conduction velocity,¹⁴ all actions which reduce myocardial oxygen demand. A2 receptors mainly mediate smooth muscle relaxation,^{19,20} inhibition of platelet aggregation²¹ and inhibition of neutrophilic free radicals,²² which result in an increase of CBF and oxygen supply. In this study, the CI and CBF returned to baseline values with subsequent recovery of int-PmO₂. These results can be attributed to the increased oxygen supply due to the increase in CBF and the decreased oxygen demand due to the reduction of afterload.

Saito *et al.*¹⁰ studied the effects of felypressin $0.2 \text{ IU}\cdot\text{kg}^{-1}$ in two dogs pretreated with $0.5 \text{ mg}\cdot\text{kg}^{-1}$ dipyridamole after thoracotomy under secobarbital anesthesia; they reported that dipyridamole antagonized the felypressin-induced reduction of CBF. Dipyridamole inhibits ADO uptake by cells.²³ Thus, the antagonistic effect of dipyridamole on felypressin appears to be mediated by ADO. In this study, ADO ameliorated the adverse effects of felypressin.

Low-dose NTG decreases myocardial oxygen consumption by acting on capacitance vessels,²⁴ which may account for the slight improvement in int-PmO₂ produced by NTG infusion $2.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, although no improvement was observed in CBF. There were no significant differences in hemodynamic parameters at 15 min of infusion between NTG $2.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and $5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. The PCWP tended to be lower with the infusion of NTG $5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$

than with that of $2.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. It seemed that there were further decreases in the preload and in myocardial oxygen consumption. However, NTG $5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ did not bring about the recovery of int-PmO₂. The increase of int-PmO₂ observed with NTG $2.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ was only slight, which may be attributable to the lack of recovery of CBF.

The fundamental actions of NTG involve coronary vasodilation which induces an increase in oxygen supply.²⁵ In an experimental study of the interactions of VP and NTG, NTG was shown to improve CBF and cardiac output.²⁶ However, in this study, NTG failed to bring about the recovery of CBF, indicating that the dosage may be insufficient for the animal model. Since there are no published reports on the interaction between felypressin and NTG in terms of CBF and other parameters of cardiac function, this subject requires further study.

Amrinone is a phosphodiesterase inhibitor with cardiotonic and vasodilatory actions.^{27,28} Although AM increases the force of contraction of the cardiac muscle, it does not significantly affect HR, causing little increase in myocardial oxygen consumption.²⁹ Jentzer *et al.*²⁹ have suggested that AM, by reducing preload, causes a reduction in wall tension, a decrease in myocardial oxygen consumption, and improvements in myocardial blood flow and in the oxygen supply and demand balance in ischemic regions of the myocardium. In this study, the CI and CBF recovered with the consequent recovery of int-PmO₂. This response may be generated by the effects of AM, comprising an improvement in felypressin-induced cardiac depression through a direct cardiotonic action, reduction of oxygen demand by decreasing both preload and afterload, and increase in oxygen through an increase in CBF. In this study, AM was infused first at $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and then at $20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ with a short interval of five minutes in view of the long half-life for plasma elimination.^{30,31}

Adenosine triphosphate and AM were effective in reversing the reductions in CBF, CI and int-PmO₂ induced by felypressin. Although ATP appears to have the advantage of allowing fine adjustments in dosage, it sometimes induces chest pain³² and may be problematic for use in conscious patients. Amrinone appears to provide the favourable combination of cardiotonic effect, reduction of myocardial oxygen demand and increase in oxygen supply. While the increase in CBF was less remarkable with AM than with ATP, AM improved int-PmO₂ and thus appears to be preferable to ATP.

The animal model for the study, which showed a reduction of CBF with felypressin infusion, simulated

severe coronary artery stenosis. This state of pathology may cause myocardial necrosis depending upon the severity of the oxygen supply/demand imbalance and should be managed carefully in clinical situations. For effective management, the dose ranges of the agents studied were based on levels which would antagonize the increase in DBP, a characteristic and clinically detectable effect of felypressin.⁸ At the dosages used, ATP and AM were effective and appear to be promising for treatment or prevention of the hemodynamic adverse reactions associated with felypressin.

In conclusion, the cardiac and hemodynamic effects of ATP, NTG and AM were studied in anesthetized, thoracotomized dogs receiving continuous infusion of felypressin at a low concentration. Adenosine triphosphate and AM were effective in ameliorating the adverse effects of felypressin. Nitroglycerin $2.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ produced a slight improvement in int-PmO₂. The appropriate dosage of NTG remains to be defined. Adenosine triphosphate and AM are promising as measures for treating or preventing the adverse hemodynamic effects of felypressin.

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