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Comparative hemodynamic effects of hypotension induced by diadenosine tetraphosphate (AP_4A) and ATP in dogs

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Abstract: ATP and diadenosine tetraphosphate (AP_4A) have been shown to produce vasodilation mediated by P_1- and P_2-purinoceptor, respectively. The differing mechanisms involved in this vasodilating activity may induce different systemic hemodynamic changes. We compared the hemodynamic effects of AP_4A-induced hypotension with those induced by ATP. Fourteen mongrel dogs were anesthetized with 0.87% halothane in oxygen (1 MAC). After the baseline period, mean arterial pressure was reduced to 60 mmHg for 60 min by the infusion of AP_4A or ATP. The ATP- and AP_4A-induced hypotension resulted in a maximum reduction in systemic vascular resistance of 43% and 46%, respectively ($P < 0.01$), associated with a significant increase in stroke volume index. With ATP, a 20% of maximum increase ($P < 0.05$) in cardiac index (CI) was observed during the induced hypotension. In contrast, AP_4A-induced hypotension did not result in any changes in CI throughout the observation period. The varying results concerning CI during the ATP- and AP_4A-induced hypotension were probably due to differences in ventricular filling pressure, since AP_4A-induced hypotension was associated with decreases ($P < 0.01$) in both right atrial and pulmonary capillary wedge pressures, whereas neither of these variables significantly changed with ATP. The hypotension induced by either ATP or AP_4A was associated with a significant decrease in heart rate (HR). However, both the magnitude and duration of decreases in HR due to ATP-induced hypotension were more pronounced than those seen with AP_4A. In conclusion, while both drugs were equally capable of inducing hypotension, our results suggest that AP_4A was more suitable for induced hypotension because of its potent vasodilatory action with venodilation and less negative chronotropic action.

Key words: Diadenosine tetraphosphate (AP_4A), ATP, Induced hypotension, Systemic hemodynamics

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Introduction

Diadenosine tetraphosphate (AP_4A) is an adenosine nucleotide which is present in the dense granules of human platelets [1]. Extracellular functions of AP_4A may be involved in physiological processes such as platelet aggregation, histamine release from mast cells, regulation of vascular tone, and various leucocyte functions [2]. These biological activities of AP_4A are mediated via purinoceptors which are classified into P_1- and P_2-purinoceptors based on the relative potencies of agonists and antagonists [3]. Further, receptor-binding studies using biological and pharmacological methods have led to a proposed subdivision of P_1-purinoceptors into A_1- and A_2-receptors [4] and subdivision of P_2-purinoceptors into P_{2x}- and P_{2y}-receptors [5]. In general, P_1-purinoceptors mediate the effects of adenosine and adenosine monophosphate (AMP), whereas they do not mediate the effects of adenosine diphosphate (ADP) and ATP. P_2-purinoceptors mediate response to ADP and ATP, whereas adenosine and AMP do not act via P_2-purinoceptors.

ATP is rapidly degraded to adenosine by ATP-pyrophosphohydrolase as well as by ectoenzymes (ATPase, ADPase, and AMPase) located on the surface of blood cells and the vascular endothelium [6]. Adenosine is inactivated to inosine in a reaction catalyzed by adenosine deaminase or is taken up by the cells. It is assumed that the hypotensive action of ATP is related to the arterial concentration of adenosine [7]. Accordingly, the vasodilatory effects of ATP are caused by the action of adenosine, mediated via the A_2-receptor. In contrast to mononucleotides such ATP, ADP, and AMP, AP_4A is not degraded by ectoenzymes of the blood cells. AP_4A is converted to AMP and ATP by AP_4Aase in the plasma [8]. In addition, the degradation of AP_4A is inhibited by the blood concentrations of ATP, ADP, and AMP, which are elicited by the degradation of AP_4A [9]. Thus it is suggested that AP_4A is a

long-lived signal molecule in the blood vessel [8]. It is suggested that the endothelium-dependent vasodilator effect of AP_4A is mediated by endothelial P_{2y}-purinoceptors [10]. The vasodilator effects of AP_4A may be caused by the actions of the uncleaved parent AP_4A and ATP mediated via P_{2y}-receptor, as well as by the actions of either AMP or adenosine produced by the breakdown product of AP_4A acting via the A_2-receptor.

It is possible that different mechanisms of vasodilating activity are induced by ATP and AP_4A, thus resulting in different changes in systemic hemodynamics. Therefore, the objectives of this study were to compare the hemodynamic effects of AP_4A-induced hypotension with those of ATP, which is a well known vasodilator.

Materials and methods

Instrumentation

All experimental procedures and the protocols for this study were approved by the Animal Experiment Ethics Committee of Showa University Fujigaoka Hospital. Fourteen mongrel dogs weighing 12–21 kg (16.1 ± 2.9 kg, mean ± SD) were studied. Anesthesia was induced with sodium pentobarbital (25 $mg \cdot kg^{-1}$) intravenously. After tracheal intubation, the animals were mechanically ventilated with a Harvard ventilator to maintain normocapnia. Anesthesia was maintained with 1.0 minimum alveolar concentration (MAC) halothane (0.87%), delivered through an Ohmeda Vaporizer (BOC Health Care, Wilddlesham, UK) using oxygen as a carrier gas at a flow rate of 3–5 $l \cdot min^{-1}$ throughout the observation period. End-tidal halothane and CO_2 concentrations were measured continuously by an infrared analyzer (Capnomac Ultima, Datex, Helsinki, Finland).

Cannulae were placed by a cutdown into the left femoral artery for continuous systemic blood pressure (SBP) monitoring and blood sampling, and into the right femoral vein for drug administration. Normal saline was infused at a rate of 7 $ml \cdot kg^{-1} \cdot h^{-1}$ together with the infusion of the hypotensive drugs.

A 7F flow-directed pulmonary catheter (Swan-Ganz thermodilution catheter, Baxter Health Care, Irvine, CA, USA) was advanced into a pulmonary artery via cutdown of the right external jugular vein and positioned by means of pressure monitoring in a branch of the pulmonary artery for the measurements of right atrial pressure (RAP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO). CO was measured in triplicate by a thermodilution technique; we used a cardiac output computer (MTC6210, Nihon Kohden, Tokyo, Japan) and injected 5 ml ice-cold, temperature-monitored, normal saline into the right atrium at end-expiration. Cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were calculated by standard formulae. Mean arterial pressure (MAP) was determined by electronic averaging. Heart rate (HR), calculated from lead II of the electrocardiogram (ECG) using a cardiotachometer (AT601G, Nihon Kohden), was continuously monitored. Body temperature, monitored by a thermistor attached to the pulmonary artery catheter, was maintained at 37.0 ± 1.0°C with electric heating pads and lamps. Each pressure monitoring catheter was connected to a pressure transducer (Uniflow, Baxter Health Care). SBP and ECG were monitored continuously on a polygraph (RM6200, Nihon Kohden) and recorded with an eight-channel recorder (VM-640G, Nihon Kohden).

Experimental protocol

The 14 dogs were divided into two groups: The AP_4A group (n = 8) received a 1% solution of AP_4A (AP_4A dissolved in normal saline). The ATP group (n = 6) received a 3% solution of ATP (ATP dissolved in normal saline).

After the completion of surgical preparations, the animals were observed for approximately 60 min to allow hemodynamic variables (SBP, MPAP, and HR) to stabilize. Measurements of baseline values were obtained before infusion of the hypotensive drugs began. After baseline measurements had been made, MAP was reduced to 60 mmHg for a 60-min hypotensive period by the infusion of AP_4A or ATP. The AP_4A and ATP solutions were infused into the left femoral vein with an infusion pump (STG-521, Terumo, Tokyo, Japan). Measurements of hemodynamic variables were taken 30 and 60 min after the induction of hypotension, and 10 and 30 min after the termination of drug infusion.

Statistical analysis

Values are expressed as mean ± SD. Intragroup differences were analyzed by two-way analysis of variance from repeated measurements of the same variables followed by Dunnett's test when appropriate. Intergroup differences were analyzed by Student's unpaired t-test if the F-test was significant. A probability value less than 0.05 was considered statistically significant.

Results

There were no significant differences in baseline values of systemic hemodynamics including MAP, CI, SVI,

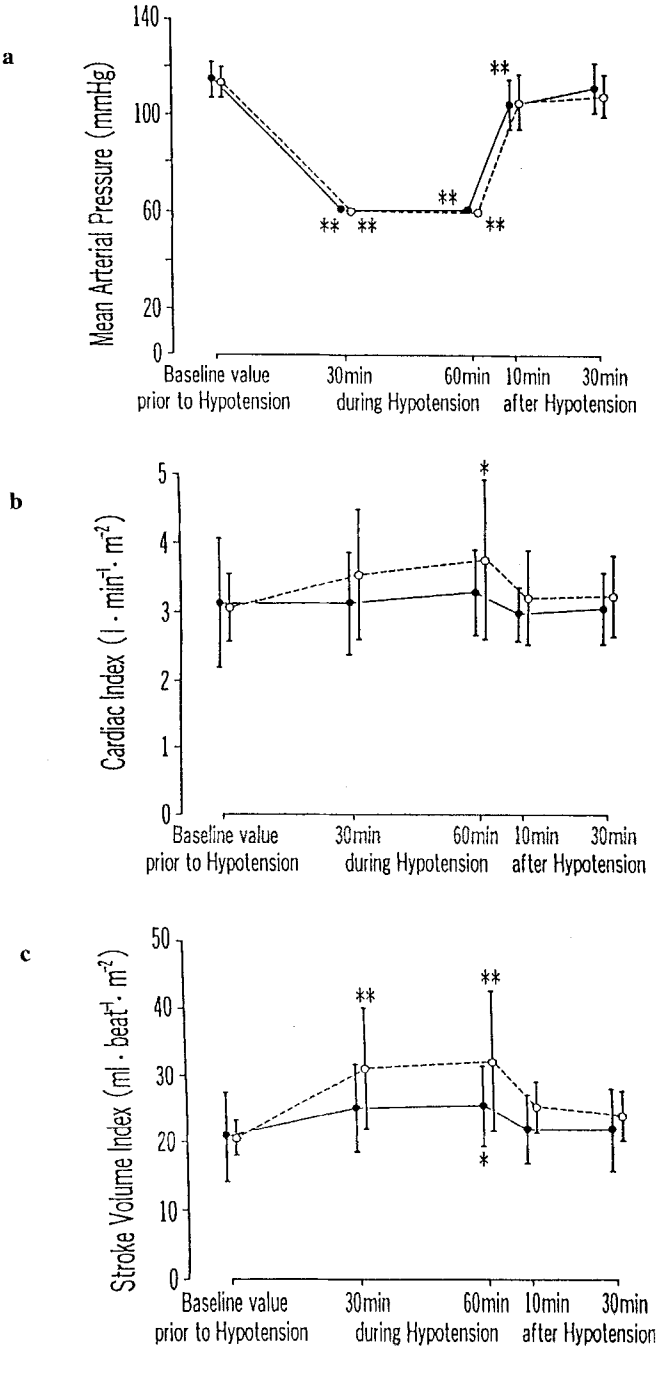

Fig. 1. Effect of diadenosine tetraphosphate (AP_4A)-($n = 8$, *solid circles*) and ATP ($n = 6$, *open circles*)-induced hypotension on mean arterial pressure (**a**), cardiac index (**b**), and stroke volume index (**c**) in halothane-anesthetized dogs. $^*P < 0.05$, $^{**}P < 0.01$ significantly different from baseline values. Values are mean ± SD

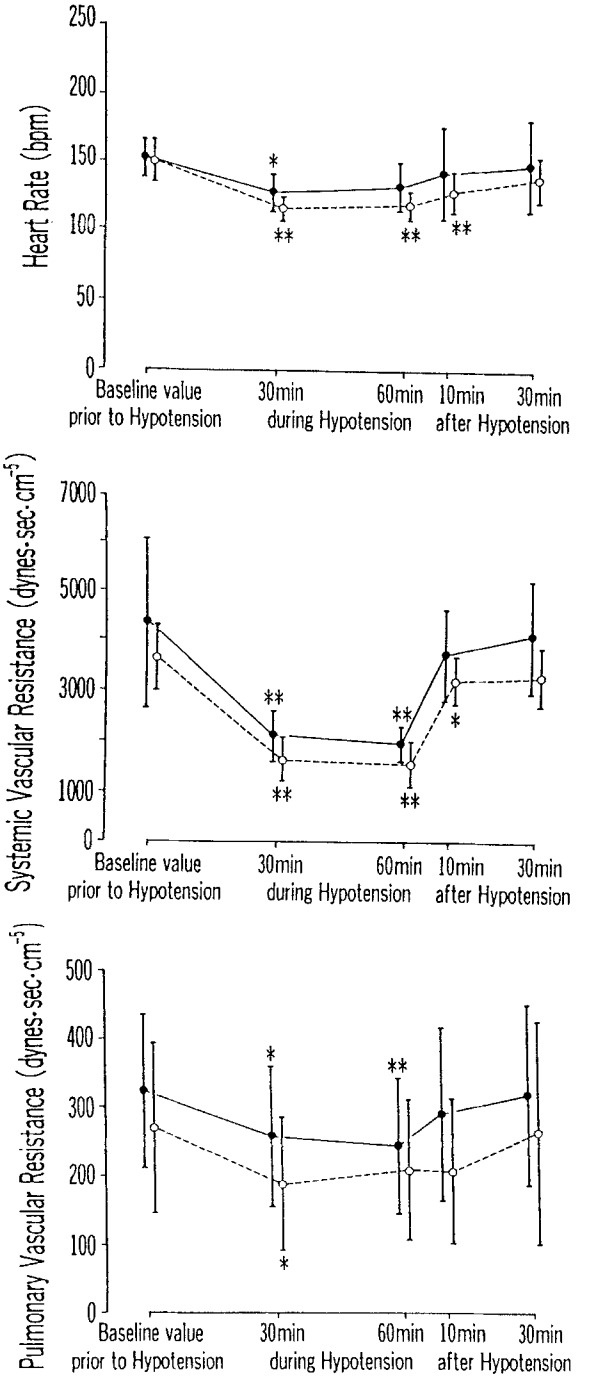

Fig. 2. Effect of AP_4A-($n = 8$, *solid circles*) and ATP ($n = 6$, *open circles*)-induced hypotension on heart rate (**a**), systemic vascular resistance (**b**), and pulmonary vascular resistance (**c**) in halothane-anesthetized dogs. $^*P < 0.05$, $^{**}P < 0.01$ significantly different from baseline values. Values are mean ± SD

HR, SVR, PVR, RAP, MPAP, and PCWP between the AP_4A and ATP groups. The mean doses of AP_4A and ATP required to maintain MAP at 60 mmHg for a 60-min hypotensive period were 156 ± 118 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 1445 ± 1010 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively.

Both AP_4A and ATP infusion produced stable hypotension during the 60-min observation period. The MAP of 60 mmHg was significantly lower than the baseline values of 115 ± 7 mmHg and 113 ± 6 mmHg in the AP_4A- and ATP-induced hypotensions, respec-

tively. Within 30 min after the termination of drug infusion, MAP tended to recover promptly to near-baseline values. (Fig. 1a). Hypotension induced by ATP was associated with an increase in CI, from baseline values of 3.0 ± 0.5 $l \cdot min^{-1} \cdot m^{-2}$ to 3.8 ± 1.1 ($P < 0.05$) $l \cdot min^{-1} \cdot m^{-2}$ at 60 min during induced hypotension, then recovered to near-baseline values after the termination of hypotension (Fig. 1b). SVI increased from baseline values of 20 ± 3 $ml \cdot beat^{-1} \cdot m^{-2}$ to a maximum of 32 ± 11 $ml \cdot beat^{-1} \cdot m^{-2}$ at 60 min of the hypotensive period ($P < 0.01$), and then promptly recovered to near-baseline values after the termination of infusion in the ATP group (Fig. 1c). In contrast, AP_4A-induced hypotension resulted in no significant change in CI throughout the course of observation, although SVI increased significantly at 60 min of the hypotensive period and then promptly recovered to near-baseline values by 10 min after the termination of infusion (Fig. 1b,c).

HR in the ATP group decreased from baseline values of 150 ± 16 bpm to 116 ± 9 ($P < 0.01$) bpm at 30 min and 119 ± 10 ($P < 0.01$) bpm at 60 min, after the induction of hypotension and remained decreased at 10 min after the termination of ATP. HR in the AP_4A group decreased from baseline values of 152 ± 14 bpm to 128 ± 14 ($P < 0.05$) bpm at 30 min of the induced hypotensive period and thereafter recovered to a level not significantly different from baseline values (Fig. 2a). SVR in the ATP group declined from baseline values of 3648 ± 657 $dynes \cdot s \cdot cm^{-5}$ to a nadir of 1583 ± 452 ($P < 0.01$) $dynes \cdot s \cdot cm^{-5}$ at 60 min of the induced hypotensive period, followed by a significant reduction below the baseline values at 10 min after the termination of ATP. In the AP_4A group, SVR declined from baseline values of 4360 ± 1703 $dynes \cdot s \cdot cm^{-5}$ to a nadir of 1992 ± 355 ($P < 0.01$) $dynes \cdot s \cdot cm^{-5}$ at 60 min of the hypotensive period, but it recovered to a level not significantly different from baseline values within 10 min after AP_4A infusion was discontinued (Fig. 2b). PVR in the ATP group declined from baseline values of 270 ± 124 $dynes \cdot s \cdot cm^{-5}$ to 188 ± 96 ($P < 0.05$) $dynes \cdot s \cdot cm^{-5}$ at 30 min of the hypotensive period. PVR in the AP_4A group declined from baseline values of 322 ± 111 $dynes \cdot s \cdot cm^{-5}$ to 257 ± 102 ($P < 0.05$) $dynes \cdot s \cdot cm^{-5}$ at 30 min and 243 ± 98 ($P < 0.01$) $dynes \cdot s \cdot cm^{-5}$ at 60 min into the period of induced hypotension (Fig. 2c).

RAP in the ATP group remained unchanged throughout the course of observation. RAP in the AP_4A group significantly decreased at 30 min and 60 min after the induction of hypotension, followed by a significant decrease after the termination of induced hypotension. RAP was significantly lower in the AP_4A group when compared with that of the ATP group at 60 min in the induced hypotensive period (Fig. 3a). MPAP in the ATP group significantly decreased at 30 min of the hypotensive period. MPAP in the AP_4A group significantly decreased at 30 min and 60 min of the induced hypotension (Fig. 3b). PCWP in the ATP group remained unchanged throughout the course of observation. PCWP in the AP_4A group significantly decreased at 30 min and 60 min of the induced hypotension. PCWP

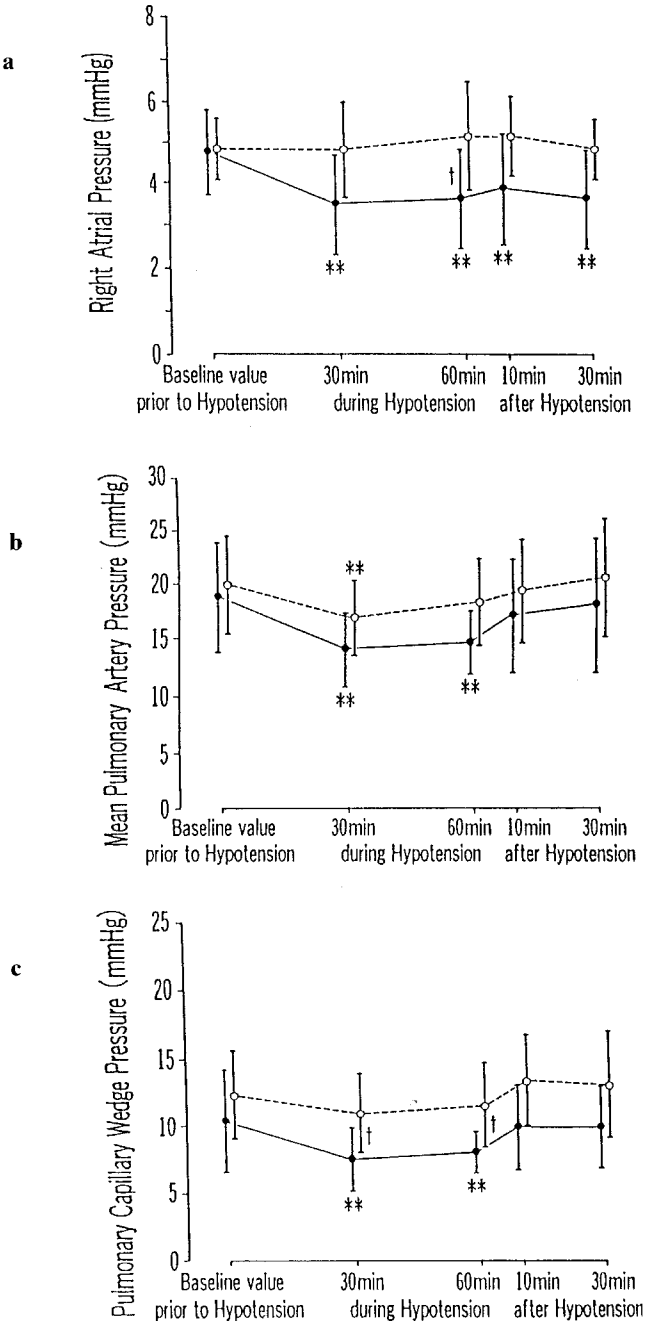

Fig. 3. Effect of AP_4A-($n = 8$, *solid circles*) and ATP ($n = 6$, *open circles*)-induced hypotension on right atrial pressure (**a**), mean pulmonary artery pressure (**b**), and pulmonary capillary wedge pressure (**c**) in halothane-anesthetized dogs. $^{**}P < 0.01$ significantly different from baseline values. $^{+}P < 0.05$ significantly different compared with both AP_4A and ATP (these values were compared at predetermined identical times). Values are mean ± SD

was significantly lower in the AP_4A group when compared with that in the ATP group at 30 and 60 min of the hypotensive period (Fig. 3c).

Discussion

The results of the present study demonstrated that hypotension induced by either ATP or AP_4A was attributable to the significant reduction in SVR, and that ATP-induced hypotension was accompanied by a significant increase in CI, whereas AP_4A-induced hypotension was not. AP_4A-induced hypotension was associated with significant decreases in both RAP and PCWP, while neither of these variables significantly changed with ATP. This may reflect differences in the site of vasodilatory action within the arterial and venous vascular beds. These results suggest that ATP behaves as an arteriolar vasodilator but that AP_4A is a vasodilator of both arteriolar and venous systems. The difference in CI between ATP and AP_4A may therefore be attributed to the different effects of two drugs on venous return.

The venous pressures during ATP-induced hypotension were consistent with those reported in earlier studies which reported that with ATP[11–13]- and adenosine[14–20]-induced hypotension there were either no changes or a slight increase in RAP, MPAP, and PCWP. The results of the studies using nitroprusside (SNP), nitroglycerin (TNG), and ATP-induced hypotension by Hoka et al. [21] demonstrated that a redistribution of cardiac output from the splanchnic vascular bed to the extrasplanchnic vascular bed could result in an increase in venous return, suggesting that dilatation of the capacitance vessels occurred during SNP- and TNG-induced hypotension, but did not occur during ATP-induced hypotension. Ventricular filling pressures remained unchanged during ATP-induced hypotension. Consequently, the increased CI with ATP may be explained by the increase in SVI due to the reduction of afterload and by the maintenance of venous return in spite of a decrease in HR.

With respect to the limited effect of adenosine or ATP on venous pressure, it has been explained that the weak effect of adenosine or ATP on venous vascular tone may be due to the rapid degradation of adenine nucleosides in the blood stream; indeed, adenosine is completely metabolized on passage through the pulmonary circulation [22]. It has also been reported that the concentrations of adenosine in venous blood are consistently lower when compared with those of the arterial blood [19]. Therefore, it may be possible that the low concentrations of adenosine or adenosine metabolites were not able to stimulate the purinergic receptors of the veins effectively, as adenine nucleosides at adequate concentrations have been demonstrated to cause the relaxation of isolated canine saphenous veins [23]. Presumably, a considerable amount of AP_4A remains intact during transpulmonary passage in the circulation, and the uncleaved compound may reach the venous vascular bed. The venodilatory activity of AP_4A-induced hypotension may be mediated by intact compounds or the breakdown products of AP_4A acting on P_{2y}-purinoceptors or A_2-receptors of the venous endothelium. Another explanation for the present findings may be that the different responses related to ATP and AP_4A on the venous vascular tone may be caused by the varying sensitivity and density of the P_1-receptors or P_2-receptors in the venous endothelium.

The results of the present study showed that hypotension induced by either ATP or AP_4A was associated with a significant decrease in HR. However, the magnitude of decrease in HR produced by ATP was greater than that seen with AP_4A. It is well accepted that the decrease in HR elicited by adenine compounds may be due to a direct inhibitory effect on the sinus node [24] and an inhibition of cardiac sympathetic neurotransmission [25]. Owing to the small dosage of AP_4A, which was 1/10 that of ATP, the adenosine concentration during AP_4A infusion may increase only slightly when compared with ATP. The negative chronotropic effects of adenosine may be mediated by A_1-receptor activation [26]. However, in the literature the chronotropic response to adenine compounds is complex: HR was increased [11,15], decreased [18,19], or not changed [12–14,16,17,20] significantly during ATP- or adenosine-induced hypotension. These inconsistent results may be due to experimental conditions such as dosage of adenosine or ATP, anesthetics used, and the magnitude of hypotension.

In the present study, ATP- and AP_4A-induced hypotension resulted in a significant reduction in PVR, indicating pulmonary vasodilation produced by ATP and AP_4A. McCormack et al. [27] suggested that the pulmonary vasodilator effects of adenosine are mediated through A_2-receptor and that adenosine may function as a regulator of pulmonary vascular tone. More recently, Hasséssian and Burnstock [28] have reported that nitric oxide release evoked by purinoceptor agonists attenuates the increase in pulmonary vascular pressure, suggesting that P_{2y}-purinoceptor stimulation evokes the release of nitric oxide to produce vasodilation. The dramatic effects of AP_4A-induced hypotension on PVR suggest that AP_4A produces pulmonary vasodilation by the cumulative effects of both A_2-receptor and P_{2y}-purinoceptors.

In conclusion, ATP and AP_4A at appropriate infusion rates are equally effective in decreasing afterload during induced hypotension but produce different effects on CI. The difference in CI between ATP and AP_4A

may be attributed to different effects of the two drugs on venous return. Further, AP_4A-induced hypotension is suggested to be more effective with respect to its potent vasodilatory action and reduced negative chronotropic action during the period of profound induced hypotension. Further studies are needed to evaluate whether this drug can be used effectively in clinical practice.

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