Effect of Adenosine Triphosphate on Human Coronary Circulation

Nobuo Shiode, Masaya Kato, Kensho Nakayama, Koichi Shinohara, Junichi Kurokawa, Togo Yamagata, Hideo Matsuura and Goro Kajiyama

We investigated in humans the effects of adenosine triphosphate (ATP), administered by intracoronary bolus (4–16 μg) or intravenous infusion (25–200 μg/kg/min), on coronary and systemic hemodynamics and electrocardiogram (ECG) variables. All patients had normal epicardial coronary arteries. The maximal coronary blood flow velocity (CBFV) was determined with intracoronary bolus of papaverine. A 12 μg bolus of ATP (n=12) caused maximal coronary hyperemia similar to that caused by papaverine. Intracoronary boluses caused a small brief decrease in arterial pressure but no significant changes in HR or ECG variables. Intravenous infusion of ATP at 150 μg/kg/min (n=15) caused a decrease in the coronary resistance index similar to that caused by papaverine, but the rate of increase in CBFV by ATP was smaller than that caused by papaverine. No patients had a significant change in ECG variables, but some patients (40%) had a serious decrease in arterial pressure. These studies suggest that maximal coronary vasodilation can be achieved safely with intracoronary ATP administration and that intravenous infusions at 150 μg/kg/min cause near-maximal coronary hyperemia in most patients.

Key words: adenosine triphosphate (ATP), coronary flow reserve, papaverine

Introduction

Many studies of the coronary circulation, for measurement of coronary flow reserve, thallium-201 scintigraphy, and echocardiography, require the use of drugs that can safely and reliably produce maximal coronary hyperemia of brief duration. An ideal coronary vasodilator for these studies would rapidly produce maximal coronary hyperemia, would be quickly reversible, and would have neither adverse effects on systemic hemodynamics nor electrocardiographic variables.

Some drugs are currently used for producing maximal coronary hyperemia in humans. Intracoronary boluses of papaverine are available for producing maximal coronary hyperemia (1). But papaverine has some undesirable characteristics. First, the total dose that can be given is limited by its relatively slow systemic excretion (2), therefore, intravenous infusions can not be given without systemic hypotension. Secondly, intracoronary boluses of papaverine prolong the QT interval and can cause polymorphous ventricular tachycardia (3, 4). Intravenous dipyridamole produces maximal coronary hyperemia, but its prolonged effects preclude multiple measurements of coronary vasodilator reserve during the same study (4, 5). Even though the vasodilator effects can be attenuated by methylxanthine (6), prolonged ischemia has been reported (7, 8). Intracoronary boluses and intravenous infusions of adenosine cause maximal coronary hyperemia quite safely and effectively (9, 10), thus adenosine is widely used in Europe and the United States (11, 12).

Currently, adenosine triphosphate (ATP) is used in place of adenosine (13, 14), however, it is not well known in human coronary circulation whether ATP can produce maximal hyperemia safely and effectively. It has been reported that, intracoronary infusion of ATP in the canine coronary circulation causes maximal hyperemia similar to adenosine (15). On the other hand, large doses of ATP increases the refractory period of the atrioventricular nodes and can result in heart block in humans (16).

The purpose of this study was to examine the dose-response kinetics of intracoronary and intravenous ATP administration in humans.
Patients and Methods

Patients

Twelve patients (ATP intracoronary bolus) and 15 patients (ATP intravenous infusion) with normal coronary arteries undergoing coronary angiography for the diagnosis of chest pain syndrome were selected for this study. Four patients had hypercholesterolemia (serum total cholesterol values >220 mg/dl), one patient had hypercholesterolemia with a smoking history and two patients were smokers in the ATP intracoronary bolus group. Five patients had hypercholesterolemia, and two patients had a smoking history in the ATP intravenous infusion group. No patients had systemic hypertension or diabetes mellitus.

None of these patients had significant coronary vasospasm induced by acetylcholine provocation test. Left ventricular function was shown to be normal (ejection fraction >50%) by contrast ventriculography.

Written informed consent was obtained from all patients prior to the diagnostic angiogram, and all study methods were approved by the ethical committee of the First Department of Internal Medicine, Hiroshima University School of Medicine.

Study design

Patients were brought to the cardiac catheterization laboratory in a fasting state. Anti-anginal therapy was discontinued 48 hours prior to catheterization, except for the unrestricted use of sublingual nitroglycerin, which was withheld 1 hour prior to catheterization. But, no patient in this study had sublingual nitroglycerin 24 hours prior to catheterization. A variety of medications was given before and during catheterization (ergonovine, acetylcholine, intracoronary nitroglycerin, hydroxyzine, promethazine), but no patient received atropine. Diagnostic right and left heart catheterization and coronary angiography were performed through a standard percutaneous femoral approach. After vascular access had been obtained, 10,000 units of heparin was given intravenously. A 7F guide catheter was introduced into the left main coronary artery. A 0.014 inch guidewire was advanced through the guide catheter into the proximal segment of the left anterior descending coronary artery.

Catheterization protocol

After completion of the diagnostic catheterization, we waited for at least 10 minutes before beginning the study. A continuous intravenous infusion of very low-dose nitroglycerin (8 µg/min) was begun before the beginning of the ATP study to avoid catheter-induced coronary artery spasm and obviate flow-mediated vasodilation of the proximal coronary artery, which would influence the relation between changes in coronary flow velocity and coronary blood flow (1, 17, 18).

Intracoronary boluses of ATP. (n=12) (female 6, male 6, mean age: 62 ± 3 years old)

After measurements of coronary blood flow velocity at rest, 4 ml of 0.9% saline was injected into the coronary ostium and the resultant increase in coronary blood flow velocity was recorded. When coronary blood flow velocity returned to basal levels, sequentially greater boluses of ATP (4, 8, 12, 16 µg/4 ml 0.9% saline, Daiichi Pharmaceutical, Tokyo) were injected through the guiding catheter into the coronary ostium. Care was taken to inject at a rate that would not cause reflux of the ATP solution into the aorta. Coronary blood flow velocity, electrocardiogram, and arterial blood pressure were recorded until coronary blood flow velocity returned to basal levels.

Intravenous infusions of ATP. (n=15) (female 7, male 8, mean age: 61 ± 3 years old)

After coronary blood flow velocity returned to baseline, ATP (5.0 mg/ml) was infused into the left peripheral arm vein in seven different doses: 50, 75, 100, 125, 150, 175, and 200 µg/kg/min. In one patient infusion was stopped at 150 µg/kg/min because of severe hypotension. Infusions were performed with an infusion pump (CFV 3100, Nihon Koden, Japan). All infusions were continued for at least 2 minutes. Data were continuously recorded during infusions, and measurements were obtained during the last 15 seconds of the infusions.

Intracoronary papaverine.

After coronary blood flow velocity returned to the basal levels, 10 mg papaverine (10 mg/4 ml 0.9% saline) was injected through the guiding catheter into the coronary ostium, and the resultant increase in coronary blood flow velocity was recorded.

Measurements of coronary blood flow velocity

The 20-MHz 3Fr coronary Doppler catheter was used to measure the coronary artery blood flow velocity. The Doppler catheter then connected to a velocimeter (Model 100, Triton Technology, Inc) and audio signal was analyzed by the fast Fourier transform (FFT) method. The technique has been described elsewhere (19).

Data analysis

Intracoronary bolus studies.

The maximal change in coronary blood flow velocity after a bolus of intracoronary ATP or papaverine was expressed as the ratio of the maximal coronary blood flow velocity (after ATP or papaverine administration) to the resting blood flow velocity (ΔCBFV). As a measurement of the change in coronary vascular resistance, the coronary vascular resistance index (ACVRi) was calculated as the quotient of the [mean aortic pressure at peak flow (mmHg)/coronary blood flow velocity at peak flow (cm/sec)] and the [mean aortic pressure at resting flow/coronary blood flow velocity at resting flow].

The time course of the increase in coronary blood flow velocity after intracoronary vasodilator administration was characterized by three parameters. Tmax was defined as the
time from the onset of injection until coronary blood flow velocity reached the maximal increase in velocity. T_{50\%} was defined as the time from the onset of injection until the coronary blood flow velocity returned to 50\% of the maximal increase in velocity, and T_{10\%} was defined as the time from the onset of injection until flow velocity returned to within 10\% of basal flow velocity.

PQ and QTc intervals were measured. QTc interval was calculated as QT/√RR (sec^{-1/2}).

**Statistical analysis**

Data were expressed as mean ± SE. Paired differences were analyzed with a Wilcoxon signed-rank test. Linear correlation was assessed with the least-squares method.

**Results**

Baseline hemodynamic and electrocardiogram variable data are shown in Tables 1 and 2.

**Intracoronary ATP bolus**

Coronary blood flow velocity and resistance.

Intracoronary boluses of ATP produced a dose-dependent increase in coronary blood flow velocity, and in all of the patients a 16 µg bolus increased the coronary blood flow velocity to levels within 20\% of the maximal CBFV produced by intracoronary papaverine (Table 3, Figs. 1 and 2). After a 12 µg bolus of ATP into the left coronary artery, 10 of 12 patients (83\%) developed coronary hyperemia to levels within 20\% of the maximal CBFV produced by papaverine. The correlation of the maximal change in coronary blood flow velocity after ATP or papaverine was r = 0.96 (Fig. 3).

The time to reach the maximal coronary blood flow velocity (T_{max}) after ATP was much shorter than that of papaverine. The time from the onset of injection to the time coronary blood flow velocity returned to 50\% of the maximal increase in velocity and returned to within 10\% of basal levels (T_{50\%} and T_{10\%}) were increased with the dose of ATP, but both parameters were much shorter than those caused by papaverine (Table 3).

**Systemic hemodynamics and electrocardiographic changes.**

Intracoronary boluses of ATP or papaverine produced small, brief, dose-dependent reductions in mean arterial pressure. The fall in mean arterial pressure after a 12 or 16 µg bolus was significantly larger than that after 0.9\% saline, but significantly smaller than that after papaverine (Table 3).

There was no significant change in heart rate after any dose of ATP injected. But intracoronary administration of papaverine caused a significant increase in heart rate (Table 3).

**Electrocardiographic changes.**

Intracoronary bolus of ATP did not significantly change the PR or QTc intervals on the electrocardiogram in any dosage. Any grade of atrioventricular block was not induced. Intracoronary boluses of papaverine did not change the PQ interval but caused significant prolongation of the QTc interval.

**Table 1. Intracoronary ATP Boluses: Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>mBP (mmHg)</th>
<th>HR (beats/min)</th>
<th>PQ (msec)</th>
<th>QTc (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>99 ± 6</td>
<td>56 ± 3</td>
<td>149 ± 5</td>
<td>395 ± 9</td>
</tr>
</tbody>
</table>

Values are Mean ± SE; n = 12. mBP: mean blood pressure, HR: heart rate, PQ: PQ interval, QTc: correct QT interval.

**Table 2. Intravenous ATP Infusions: Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>mBP (mmHg)</th>
<th>HR (beats/min)</th>
<th>PQ (msec)</th>
<th>QTc (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>97 ± 5</td>
<td>57 ± 3</td>
<td>153 ± 4</td>
<td>396 ± 10</td>
</tr>
</tbody>
</table>

Values are Mean ± SE; n = 15. mBP: mean blood pressure, HR: heart rate, PQ: PQ interval, QTc: correct QT interval.

**Table 3. Intracoronary ATP Boluses: Dose-Response Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>ΔCBFV (X resting)</th>
<th>ΔCVRi (X resting)</th>
<th>ΔmBP (mmHg)</th>
<th>ΔHR (beats/min)</th>
<th>ΔPR (msec)</th>
<th>ΔQTc (msec)</th>
<th>Tmax (sec)</th>
<th>T50% (sec)</th>
<th>T10% (sec)</th>
<th>Percent maximal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% Saline</td>
<td>1.86 ± 0.14**</td>
<td>0.56 ± 0.03**</td>
<td>-1 ± 2**</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td>7 ± 3</td>
<td>6 ± 1</td>
<td>12 ± 1</td>
<td>15 ± 1</td>
<td>0</td>
</tr>
<tr>
<td>ATP (µg) 4</td>
<td>3.12 ± 0.25**</td>
<td>0.33 ± 0.03**</td>
<td>-3 ± 1**</td>
<td>2 ± 1</td>
<td>-2 ± 1</td>
<td>11 ± 3</td>
<td>11 ± 1</td>
<td>23 ± 1</td>
<td>29 ± 2</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>3.41 ± 0.26**</td>
<td>0.30 ± 0.02**</td>
<td>-3 ± 1*</td>
<td>1 ± 1</td>
<td>-3 ± 2</td>
<td>-9 ± 5</td>
<td>13 ± 1</td>
<td>25 ± 1</td>
<td>35 ± 2</td>
<td>58</td>
</tr>
<tr>
<td>12</td>
<td>3.65 ± 0.26</td>
<td>0.28 ± 0.02</td>
<td>-5 ± 1**</td>
<td>2 ± 1</td>
<td>2 ± 2</td>
<td>-3 ± 4</td>
<td>13 ± 1</td>
<td>28 ± 1</td>
<td>38 ± 2</td>
<td>83</td>
</tr>
<tr>
<td>16</td>
<td>3.61 ± 0.25</td>
<td>0.28 ± 0.02</td>
<td>-5 ± 1**</td>
<td>1 ± 1</td>
<td>4 ± 1</td>
<td>-2 ± 5</td>
<td>14 ± 1</td>
<td>28 ± 1</td>
<td>40 ± 2</td>
<td>83</td>
</tr>
<tr>
<td>Papaverine</td>
<td>3.76 ± 0.27</td>
<td>0.26 ± 0.02</td>
<td>-10 ± 1†</td>
<td>7 ± 2†</td>
<td>5 ± 2</td>
<td>130 ± 1†</td>
<td>27 ± 3</td>
<td>80 ± 6</td>
<td>122 ± 10</td>
<td>83</td>
</tr>
</tbody>
</table>

Values are Mean ± SE; n = 12. CBFV: coronary blood flow velocity, CVRi: coronary vascular resistance index, mBP: mean blood pressure, HR: heart rate, Tmax: Time for CBFV to reach maximum, T50\%: time for CBFV to return to 50\% of maximal flow, T10\%: time for CBFV to return to within 10\% of basal value, Percent maximal: percent of patients with ΔCVRi within 20\% of papaverine. *p<0.05, **p<0.01 vs papaverine, †p<0.05, ††p<0.01 vs 0.9\% Saline.
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Figure 1. Plots (from all patients) of the change in coronary blood flow velocity (ΔCBFV) after intracoronary bolus of ATP (12 μg) or papaverine. Both agents caused a marked increase in coronary blood flow velocity, but the response to ATP was much shorter than that to papaverine. Data are expressed as Mean ± SE.

Figure 2. Plots (from all patients) of the change in coronary blood flow velocity (ΔCBFV) after progressively greater doses of intracoronary ATP.

Figure 3. Regression plots of coronary blood flow velocity (ΔCBFV) after ATP (12 μg) and after papaverine. y = 0.99x + 0.13, r² = 0.92, p < 0.01.

Figure 4. Plots (from all patients) of the change in correct QT interval (QTc) after an intracoronary bolus of ATP (12 μg) or papaverine. Papaverine caused a marked increase in QTc.

(Tables 3, Fig. 4). One patient had non-sustained polymorphic ventricular tachycardia at about 30 seconds after injection of papaverine.

Subjective symptoms.

All 12 patients had no subjective symptoms after intracoronary boluses of ATP or papaverine.

Intravenous ATP infusions

Coronary blood flow velocity and resistance.

Intravenous infusion of ATP produced a dose-dependent increase in coronary blood flow velocity and a decrease in coronary vascular resistance up to 150 μg/kg/min (Figs. 5 and 6). The coronary vascular resistance indexes during 150, 175, and 200 μg/kg/min of ATP infusions were not significantly different from that caused by papaverine. In 11 of 15 patients (73%), the infusion rate of 150 μg/kg/min decreased the coronary vascular resistance index to within 20% of the minimal resistance index after papaverine (Table 4). But in four patients, the coronary vascular resistance index did not decrease to within 20% of that caused by papaverine.

ΔCBFV during any rate of ATP infusion was significantly smaller than that caused by papaverine. In nine of 15 patients (60%), the infusion rate of 150 μg/kg/min increased the coronary blood flow velocity to within 20% of the maximal coronary blood flow velocity produced by papaverine. In the remaining patients, even an infusion rate of 175 or 200 μg/kg/min did not increase the coronary blood flow velocity to within 20% of that
caused by papaverine.

During lower infusion rates (75–100 μg/kg/min), in nine of 15 patients (60%), the coronary blood flow velocity was markedly changed in a cyclic pattern (Fig. 7).

**Systemic hemodynamics.**

Intravenous infusions of ATP produced a dose-dependent fall in mean arterial blood pressure and a rise in heart rate (Table 4). At 150 μg/kg/min of ATP, the mean arterial pressure fell 16±4 mmHg, and the heart rate increased by 6±2 beats/min. In six of 15 patients (40%), during 150 μg/kg/min ATP infusion, the mean arterial pressure fell more than 20% from basal arterial pressure (Table 4). In one patient mean arterial pressure fell from 112 to 71 mmHg. Two patients had a mean arterial pressure fall of less than 60 mmHg during 150 μg/kg/min ATP, and another patient did so during 175 μg/kg/min. In all patients, these changes in arterial blood pressure and heart rate returned to baseline levels within 60 seconds after the termination of ATP infusions.

**Electrocardiographic changes.**

The PR and QTc intervals did not significantly change during ATP infusions (Table 4, Fig. 8). One patient had more premature atrial contractions than basal state during infusion of

![Figure 5. Bar graph of change in coronary blood flow velocity (ACBFV) during intravenous ATP infusions and after intracoronary papaverine. Data are expressed as Mean ± SE. *p<0.05, **p<0.01 compared with papaverine.](image)

![Figure 6. Bar graph of change in coronary vascular resistance index (ACVRi) during intravenous ATP infusions and after intracoronary papaverine. Data are expressed as Mean ± SE. *p<0.05, **p<0.01 compared with papaverine.](image)

<table>
<thead>
<tr>
<th>ATP (μg/kg/min)</th>
<th>ΔCBFV (X resting)</th>
<th>ΔCVRI (X resting)</th>
<th>ΔmBP (mmHg)</th>
<th>ΔHR (beats/min)</th>
<th>ΔPR (msec)</th>
<th>ΔQTc (msec)</th>
<th>Hypotension</th>
<th>AE (%)</th>
<th>Percent maximal</th>
</tr>
</thead>
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<tr>
<td>50</td>
<td>1.09 ± 0.03**</td>
<td>0.92 ± 0.03**</td>
<td>0 ± 1</td>
<td>1 ± 1</td>
<td>-1 ± 1</td>
<td>1 ± 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>75</td>
<td>1.49 ± 0.18**</td>
<td>0.78 ± 0.07**</td>
<td>-2 ± 2</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td>-2 ± 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>100</td>
<td>2.13 ± 0.22**</td>
<td>0.52 ± 0.06**</td>
<td>-8 ± 3†</td>
<td>2 ± 1</td>
<td>-5 ± 3</td>
<td>-1 ± 4</td>
<td>27</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>125</td>
<td>2.71 ± 0.28**</td>
<td>0.41 ± 0.06*</td>
<td>-11 ± 3†</td>
<td>4 ± 2</td>
<td>-3 ± 3</td>
<td>-2 ± 4</td>
<td>27</td>
<td>67</td>
<td>40</td>
</tr>
<tr>
<td>150</td>
<td>3.25 ± 0.31*</td>
<td>0.29 ± 0.03</td>
<td>-16 ± 4†</td>
<td>6 ± 2†</td>
<td>-5 ± 4</td>
<td>-2 ± 3</td>
<td>40</td>
<td>80</td>
<td>73</td>
</tr>
<tr>
<td>175</td>
<td>3.28 ± 0.35*</td>
<td>0.29 ± 0.03</td>
<td>-16 ± 4†</td>
<td>8 ± 3†</td>
<td>-4 ± 4</td>
<td>-1 ± 3</td>
<td>47</td>
<td>80</td>
<td>64</td>
</tr>
<tr>
<td>200</td>
<td>3.17 ± 0.36*</td>
<td>0.32 ± 0.05</td>
<td>-16 ± 4†</td>
<td>10 ± 3†</td>
<td>-4 ± 2</td>
<td>-2 ± 3</td>
<td>47</td>
<td>87</td>
<td>64</td>
</tr>
<tr>
<td>Papaverine</td>
<td>3.61 ± 0.26</td>
<td>0.27 ± 0.02</td>
<td>-9 ± 2†</td>
<td>6 ± 1†</td>
<td>-3 ± 1</td>
<td>-139 ± 14</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

Values are Mean ± SE; n = 15. CBFV: coronary blood flow velocity, CVRI: coronary vascular resistance index, mBP: mean blood pressure, HR: heart rate, Hypotension: percent of patients whose arterial blood pressure fell under 20% of basal conditions or 20 mmHg, AE: percent of patients with adverse symptoms, Percent maximal: percent of patients with ΔCVRI within 20% of papaverine. *p<0.05, **p<0.01 compared with papaverine, †p<0.05, ††p<0.01 compared with basal condition.
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Figure 7. Phasic coronary blood flow velocity (CBFV) in the left anterior descending coronary artery during infusion of ATP at 75 µg/kg/min. CBFV rose and fell in a cyclic pattern. A: baseline (before ATP infusion), B: 30 sec, C: 60 sec, D: 90 sec after the beginning of ATP infusion.

Figure 8. Plots of the change in correct QT interval (QTc) during ATP infusions and after intracoronary papaverine. Data are expressed as Mean ±SE. **p<0.01 compared with papaverine.

more than 100 µg/kg/min of ATP infusion. The remaining patients had no arrhythmia during ATP infusions.

Subjective symptoms.
During infusion of ATP at doses >150 µg/kg/min, 12 patients (80%) developed some unpleasant symptoms like flushing, headache, nausea, and chest oppression. But these symptoms quickly disappeared after the termination of ATP infusions.

Discussion
These data demonstrate in the normal human coronary arterial circulation that 1) intracoronary infusions of ATP can cause near-maximal vasodilation similar to that caused by papaverine, without producing clinically important changes in systemic hemodynamics or in the electrocardiogram, and 2) intravenous infusion of ATP can cause near-maximal vasodilation similar to that caused by papaverine, but in some patients it may produce a considerable decrease in arterial blood pressure. In the left coronary artery, ATP bolus of 12 µg or more was needed to cause maximal vasodilation. In most patients, intravenous infusions of 150 µg/kg/min or more caused near maximal vasodilation, and in 40% of patients the arterial blood pressure fell more than 20% below basal conditions. Both intracoronary and intravenous infusions of ATP did not cause clinically unfavorable changes or effects on the electrocardiogram.

Intracoronary bolus of ATP
Vasodilation induced by ATP has been shown to be wholly or partially endothelium dependent in several types of isolated blood vessels and in vivo microcirculation preparations (20–25). A role has been proposed for endothelium-derived relaxing factor (EDRF), thought to be nitric oxide (NO), in ATP-induced coronary dilatation (26–29). It has also been proposed that some of the vasodilation produced by ATP is due to its degradation to adenosine (25). It is unknown how much of the vasodilation caused by ATP is endothelium-dependent in human coronary resistance vessels.

Intravenous infusion of ATP
It has been known that an injection of ATP is virtually all removed by a single passage through the lung (30). It has been reported that the half-life of ATP in the perfused lung is 0.2 second or less (12). Here, when ATP was intravenously administered, ATP might have been metabolized in the pulmonary circulation, and much of the vasodilation produced by the intravenous infusion of ATP might have been due to its degradation to ADP, AMP, or adenosine.

We observed that, in 80% of patients, coronary blood flow velocity rose and fell in a cyclic pattern at lower intravenous infusion rates than that required to produce maximal hyperemia.
Wilson et al (9) reported that intravenous adenosine infusion rates just less than that required to produce a maximal fall in coronary resistance frequently cause a characteristic pattern of widely fluctuating coronary resistance. The clinical importance of this phenomenon is that low doses of intravenous ATP may not cause a sustained submaximal coronary hyperemia and may not produce significant flow inhomogeneity between ischemic and non-ischemic areas. A recent study demonstrated that significant dipyridamole-induced flow inhomogeneity causes a perfusion defect on thallium-201 imaging (31). If low dose intravenous ATP is used for producing coronary hyperemia in thallium scintigraphy, this cyclical change of hyperemia may result in a false-negative finding. However, here all patients achieved sustained coronary hyperemia during ATP infusion of more than 150 μg/kg/min. These data suggest that an infusion rate of 150 μg/kg/min should be used for producing coronary hyperemia in thallium scintigraphy.

Potential use of ATP

The advantages of ATP over papaverine or dipyridamole are its very short duration of action, the absence of QT interval prolongation on electrocardiogram, and its efficacy that can be given by intracoronary or intravenous routes.

The potential clinical use of ATP is in the measurement of coronary flow reserve in catheterization. Intracoronary papaverine is most commonly used to measure coronary flow reserve. But papaverine prolongs the QT interval and can cause polymorphous ventricular tachycardia (1, 4). In patients with impaired cardiac function like certain cardiomyopathy or old myocardial infarction, polymorphous ventricular tachycardia may be fatal arrhythmia. Intracoronary ATP may be more advantageous than papaverine because it has no important effects on electrocardiogram. In some patients, arterial pressure fell during intravenous infusion rates causing submaximal coronary vasodilation. The peak reactive hyperemia coronary flow velocity decreased linearly following the fall in arterial pressure (17, 32, 33). If the arterial pressure falls from the basal state in measuring coronary flow reserve, it would be possible to underestimate coronary flow reserve. So it is not favorable to measure coronary flow reserve by intravenous infusions of ATP.

Another potential clinical use of ATP is in providing coronary vasodilation in thallium scintigraphic study or echocardiographic study (34–37). The short half-life of ATP compared with that of dipyridamole may lessen the risk of prolonged coronary ischemia due to coronary steal and reduce the time required for redistribution of the isotope. This study demonstrated that 150 μg/kg/min of ATP infusion caused submaximal coronary hyperemia in 73% of patients. We think the optimal dose of ATP given by intravenous route is 150 μg/kg/min. Further clinical studies will be needed to define the competitive sensitivity of thallium scintigraphy obtained using ATP or dipyridamole.

References

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