Effects of Intravenous and Intracoronary Adenosine 5′-Triphosphate as Compared With Adenosine on Coronary Flow and Pressure Dynamics

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Background—Measurements of Doppler derived coronary flow reserve (CFR) and pressure derived fractional flow reserve (FFR) for coronary stenosis assessment depend on the induction of maximal hyperemia. Adenosine is the most widely used pharmacological agent but is expensive and poorly tolerated by some patients.

Methods and Results—The objective of this study was to test the equivalency of adenosine 5′-triphosphate (ATP) to adenosine in their ability to cause maximal hyperemia as compared with the hyperemic response of complete coronary occlusion in 6 canines. Intracoronary administration of either ATP or adenosine resulted in a significant increase in CFR (2.79 ± 0.64 and 2.22 ± 0.7 for 10 μg versus 4.65 ± 1.22 and 4.25 ± 0.78 for 100 μg for ATP and adenosine, respectively, P for trend < 0.001) but not reaching the level of coronary occlusion (6.35 ± 2.26). Additionally, FFR and CFR were measured in 35 different stenoses using ATP, adenosine, and coronary occlusion. There was an excellent linear correlation between ATP and adenosine for both CFR (R = 0.934, P < 0.001) and FFR (R = 0.985, P < 0.001). However, hyperemia with either ATP or adenosine was less than postocclusion hyperemia, resulting in significantly different reserve measurements (CFR: 1.93 ± 0.66 and 2.08 ± 0.81 versus 2.35 ± 0.97, P < 0.001; FFR: 0.62 ± 0.24 and 0.63 ± 0.23 versus 0.58 ± 0.2, P < 0.001).

Conclusions—1) Step up in dosage of ATP and adenosine beyond currently recommended clinical doses resulted in a significant increase in coronary hyperemia; 2) ATP was equivalent to adenosine for both CFR and FFR; and 3) complete coronary occlusion yielded a better hyperemic response than either drug, indicating that maximal hyperemia was not achieved by either pharmacological stimulus. (Circulation. 2000;101:318-323.)

Key Words: adenosine ▪ coronary disease ▪ pressure ▪ stenosis

Assessment of the morphology of coronary lesions by angiography or intravascular ultrasound does not necessarily reflect the impairment of flow by the stenosis. Therefore, coronary flow and pressure measurements as physiological parameters have been introduced as an adjunct to lumen measurements in the assessment of coronary stenoses. The introduction of the fractional flow reserve (FFR), which is a modification of the translesional pressure gradient, is a promising technique that reliably detects a clinically relevant lumen narrowing. However, for an accurate calculation of FFR, it is of crucial importance to achieve a maximum, steady state hyperemia. In a submaximal hyperemic condition, FFR will be artificially high and the stenosis severity underestimated.

The current clinical standard for the induction of coronary hyperemia is the administration of adenosine, either by intracoronary or intravenous routes. Both methods have potential limitations. Because adenosine has an extremely short half-life, an intracoronary bolus may not last long enough to reach a steady state required for the measurement of FFR. Intravenous administration of adenosine requires much higher dosages and is therefore associated with more side effects. Recently, the side effects of adenosine were reported from a multicenter trial registry including >9000 patients. Eighty-one percent of patients reported some adverse effects, of which the most severe was an AV block occurring in 7.6%.

Adenosine 5′-triphosphate (ATP) is a precursor of adenosine and therefore would be expected to last longer while inducing the same degree of coronary hyperemia as adenosine. Its safety via both intracoronary and intravenous routes has been established in man, and it appears that the occurrence of AV block is rare. ATP has been shown to induce maximal hyperemia for coronary flow reserve (CFR) measurements and Thallium-201 myocardial tomography. However, it has never been validated for FFR measurements and has not been compared directly to adenosine. The aim of this study was to compare the effects of both drugs on...
coronary flow and pressure measurements in a canine model and to establish a dose-response relationship for intracorony and intravenous administration.

**Methods**

**Animal Preparation**

Six healthy mongrel dogs weighing between 20 and 30 kg were preanesthetized with morphine sulfate (2 mg/kg) and anesthetized with pentobarbital sodium (30 mg/kg), intubated, and placed on a Harvard apparatus room air ventilator. A 5F sheath was inserted in the left jugular vein and central position was verified by contrast injection. Right femoral arterial access was obtained using an 8F sheath. Continuous ECG and systemic blood pressure monitoring from the side arm of the femoral sheath was performed on a physiological recorder (Quinton custom-made EP and Physiology recorder). An 8F hockey stick guide catheter was then passed via the femoral sheath and positioned in the left coronary ostium. A 0.014-inch diameter Doppler FloWire (EndoSonic) was introduced via the guide into the left circumflex coronary artery (LCx) and the wire advanced distally. Measurements of average peak velocity (APV) were made at baseline and after injection of bolus doses of intracoronary ATP and adenosine in different concentrations and CFR was calculated. After the completion of the intracoronary series, ATP and adenosine were administered intravenously in increasing doses and the flow response was monitored. In all cases, a stable Doppler signal was obtained before starting a series of measurements, and the signal was not changed throughout the series for optimal comparability.

In the second part of the study, a left thoracotomy was performed in 6 dogs at the fourth intercostal space, the pericardium was opened and the left atrial appendage retracted from the underlying LCx. At 2 separate sites, ~1 and 2 cm from the left main bifurcation with no side branch in between, the LCx was dissected free from surrounding tissue and a No. 2 nylon suture placed around the artery. A length of polyethylene tubing (PE240) was introduced over the free ends of the suture so as to make a snare that was continuously adjustable from a minimal constriction to a maximum total occlusion. The distal suture was used for complete coronary occlusion without changing the degree of stenosis at the proximal suture site. After all measurements, the proximal suture was used to create a stenosis, and the stenosis was left in place until all measurements were completed. The distal suture was used for the complete occlusion without changing the degree of stenosis at the proximal suture site. After all measurements for each individual stenosis were completed, the stenosis was released and hemodynamic stabilization was allowed for a period of 5 to 10 minutes. In each dog, a total of 5 to 7 different stenoses were produced and documented by angiography.

**Dose/Response Protocol**

In the first part of the experiment, CFR was measured after the induction of coronary hyperemia by a bolus dose of intracoronary ATP and adenosine in a random order. Doses ranged from 10 to 100 μg for both drugs (doses of 10, 20, 30, 40, 50, 60, and 100 μg were tested). All measurements were performed on at least 2 separate occasions to achieve a reproducible result with a mean value calculated. After each measurement, care was taken that APV returned to baseline before the administration of the next dose. Hyperemia was also induced using ATP and adenosine in increasing dosages intravenously. An intravenous infusion of each drug was started at a dose of 100 μg · kg⁻¹ · min⁻¹ and increased every 3 to 5 minutes by additional 50 μg · kg⁻¹ · min⁻¹ up to a total dose of 400 μg · kg⁻¹ · min⁻¹. For all measurements using both drugs and both routes of administration, changes in heart rate, blood pressure, and ECG were recorded.

In the second part, both CFR and FFR were measured simultaneously for a wide range of stenoses (10% to 99%) with the wires positioned distally of the stenosis sites in the LCx. Hyperemia was induced by 40 μg of intracoronary ATP and adenosine, and the flow reserve values were compared with the hyperemic response of a complete, proximal coronary occlusion for 30 s. The dose of 40 μg was found to be more potent than lower doses with an acceptable side effect profile in the first part of the study. During a series of measurements, the proximal suture was used to create a stenosis, and the stenosis was left in place until all measurements were completed. The distal suture was used for the complete occlusion without changing the degree of stenosis at the proximal suture site. After all measurements for each individual stenosis were completed, the stenosis was released and hemodynamic stabilization was allowed for a period of 5 to 10 minutes. In each dog, a total of 5 to 7 different stenoses were produced and documented by angioscopy.

**Calculations of Fractional and Coronary Flow Reserve**

The myocardial FFR is defined as the ratio of the hyperemic flow in a stenotic artery to the hyperemic flow in the same artery if there was no stenosis present.¶ FFR therefore expresses maximum hyperemic blood flow in a stenotic vessel as a fraction of its normal value. FFR can be calculated from intracoronary pressure measurements obtained during maximal hyperemia by the following equation:

\[ \text{FFR} = \frac{P_v}{P_a} \]

where \( P_v \) is the mean proximal coronary pressure (mean aortic pressure), \( P_a \) is the mean distal coronary pressure, and \( P_a \) is the mean central venous pressure.

The coronary flow (velocity) reserve is the ratio of maximum hyperemic coronary flow velocity and is used as a surrogate for CFR. Using the FloMap (EndoSonics), APV throughout the cardiac phase is measured and CFR calculated from \( \text{APV}_{\text{hyperemia}} / \text{APV}_{\text{baseline}} \). Statistical analysis of the hyperemic response and of hemodynamic data without the presence of stenosis was performed with paired t-test. Results were considered statistically significant at \( P < 0.05 \).

**Results**

Intracoronary ATP and Adenosine

A total of 6 animals were studied in which 7 different doses of intracoronary ATP and adenosine were tested and compared with the hyperemic response after 30 s of complete coronary occlusion. Figure 1 shows the mean CFR for all doses for both drugs and coronary occlusion. There was a significant stepwise increase in CFR with increasing doses of both drugs (\( P \) for trend <0.001). Coronary occlusion yielded a higher CFR (6.35±2.26, \( P=0.02 \) compared with 60 μg).
than the largest dose of either drug, indicating that maximal hyperemia was not achieved by the pharmaceutical agents. ATP yielded a stronger hyperemic response with higher CFRs than adenosine, but the difference reached statistical significance only for the 30- and 40-μg doses, respectively (P<0.05). Time of maximal hyperemia (defined as time during which blood flow velocity remained 90% or more of the maximal peak velocity) was significantly prolonged with ATP as compared with adenosine (13.3±3.0 versus 10.9±3.2 s, P<0.001). Intracoronary boluses of both drugs produced a dose-dependent increase in heart rate and a decrease in mean arterial pressure (Figure 2) with no significant difference between the drugs. No significant changes in PR, QRS, or QT intervals on the ECG were noted, even in the highest dose administered; no AV-nodal blocks occurred.

**Intravenous ATP and Adenosine**

ATP and adenosine were administered intravenously in increasing doses in a range of 100 to 400 μg · kg⁻¹ · min⁻¹. There was a significant stepwise increase in CFR after each increase in dose (P<0.05 for each step) until a plateau was reached at 300 μg · kg⁻¹ · min⁻¹ (Figure 3). No statistically significant difference was noted between ATP and adenosine in the hyperemic response. Side effects were more pronounced with intravenous administration as compared with intracoronary boluses and resulted in a substantial increase in heart rate and drop in mean arterial pressure (Figure 2). Adenosine led to a significantly higher increase in heart rate at dosages ranging from 200 to 300 μg · kg⁻¹ · min⁻¹ than ATP. No AV-nodal block or other changes in the ECG were noted.

**ATP and Adenosine in Coronary Stenosis Assessment**

Intracoronary ATP was compared with adenosine in a dose of 40 μg for stenosis assessment measuring CFR and FFR in a total of 35 stenoses in 6 canines. There was an excellent linear correlation between the drugs for both CFR (R=0.934, P<0.001) and FFR (R=0.985, P<0.001) (Figure 4). The agreement between the 2 sets of measurements was also high with a mean difference in CFR of 0.15±0.31 and in FFR of 0.007±0.041 (Figure 4).

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**Figure 1.** CFR measurements with different doses of intracoronary ATP and adenosine and after 30 s of complete coronary occlusion in nonstenotic LCx coronary arteries. *P<0.05; **P<0.01.

**Figure 2.** Changes in heart rate (Δ HR in beats per minute) and mean arterial blood pressure (Δ BP in mm Hg) at different doses of ATP and adenosine. Results are shown for both intracoronary bolus injection and continuous intravenous infusion. *P<0.05; **P<0.01.

**Figure 3.** CFR measurements with increasing doses of intravenous ATP and adenosine infusions in nonstenotic LCx coronary arteries. Plateau is reached at 300 μg · kg⁻¹ · min⁻¹, with no significant increase in CFR at higher doses. *P<0.05.
ATP and Adenosine Versus Complete Coronary Occlusion in Stenosis Assessment

Both pharmaceutical agents were tested in their ability to induce maximal coronary hyperemia against the stimulus of complete coronary occlusion. Although there was a good correlation in CFR ($R=0.838, P<0.001$) and FFR ($R=0.936, P<0.001$) between adenosine and coronary occlusion (Figure 5), hyperemia with either ATP or adenosine was less than postocclusion hyperemia, resulting in a significant difference in CFR (1.93 ± 0.66 and 2.08 ± 0.81 versus 2.35 ± 0.97, $P<0.001$) and FFR (0.62 ± 0.24 and 0.63 ± 0.23 versus 0.58 ± 0.2, $P<0.001$). The mean difference between adenosine and coronary occlusion in CFR was 0.88 ± 1.03 and in FFR, $-0.066 ± 0.079$ (Figure 5). Similarly, the mean difference between ATP and coronary occlusion in CFR was 1.03 ± 1.15 and in FFR, $-0.06 ± 0.076$.

Discussion

This is the first study to evaluate the effects of ATP in direct comparison to adenosine for the induction of coronary hyperemia in CFR and FFR measurements. Those effects were compared with the maximal hyperemic stimulus of complete coronary occlusion. At the same dosages, ATP seems to be slightly more potent than adenosine for the measurements of both CFR and FFR in stenotic and nonstenotic coronary arteries. Dose-response curves for both drugs demonstrated that coronary blood flow could be further augmented with an increase in dosage independent of the route of administration (intravenous and intracoronary). However, complete coronary occlusion for 30 s yielded a better hyperemic response than either drug in the maximal tested dose, resulting in a significantly higher CFR and correspondingly lower FFR. On the basis of these results, coronary hyperemia induced by these pharmaceutical agents for coronary physiology measurements in clinical practice might be submaximal; there is, therefore, the potential for underestimating the lesion severity.

Finding a reliable way of inducing maximal coronary hyperemia is of practical clinical importance in order for a broader acceptance of physiology-based decision making in the cardiac catheterization laboratory. Adenosine has been validated for CFR and FFR measurements in many studies, mostly those comparing it to papaverine. However, in a more detailed dose-response study, the maximal tested dose of adenosine was 16 mg for the left and 12 mg for the right coronary system and 140 mg kg$^{-1}$ min$^{-1}$ as IV infusion. With this regimen, 16% of patients did not reach a maximal hyperemic response as compared with papaverine. In fact, from discussions with other investigators involved in FFR trials, it appears that a step up in dosage has recently become common in clinical practice. This may be due to the fact that in general clinical practice many patients are seen with chronic ischemic heart disease, microvascular disorders, and other conditions possibly accompanied by a decreased sensitivity of the vascular system to the hyperemic effects of adenosine. The results of the current study indicate that much higher doses may be needed to induce near complete coronary hyperemia. In fact, the maximal hyperemic response (as observed with complete coronary occlusion) was not achieved by the pharmaceutical stimuli. Although it is pos-

Figure 4. Linear regression analysis of CFR and FFR measurements performed with intracoronary ATP and adenosine at a dose of 40 μg (top). Agreement between the 2 sets of measurements is shown in bottom panels according to the statistical approach proposed by Bland and Altman. Difference between measurements with ATP and adenosine has been plotted against their mean.
sible that these results are due to intrinsic differences in coronary anatomy or drug metabolism between canines and humans, this seems unlikely because the basic parameters of coronary physiology have been shown to be consistent between canines and humans.2,14,17 Another explanation for this difference could be the difference in relative heart size between dogs and humans. The heart weight in canines compared with the total body mass is approximately 1.5 to 2 times as high as in humans. Thus the dosage for adenosine or ATP should possibly be determined on the basis of the estimated heart weight instead of the body weight. This may provide a potential explanation for the difference in the hyperemic response to a certain dose between humans and canines. However, it is readily explainable that a complete coronary occlusion causes a higher degree of vasodilatation than adenosine administration, because many metabolic products and endogenous factors are released by the endothelium in addition to adenosine during ischemia.18 Preliminary results of a study in 20 patients comparing intracoronary adenosine to postischemic hyperemia indicate that the hyperemic response is significantly less with the pharmacological stimulus.19

The use of ATP over adenosine has potentially significant advantages. ATP as a precursor is metabolized into adenosine diphosphate, adenosine monophosphate, and eventually into adenosine before degradation to inosine, hypoxanthine, xanthine, uric acid, and allantoin.20 Because all components from ATP to adenosine are metabolically active, the half-life of ATP is slightly longer than that of adenosine, and the hyperemic response might be prolonged. This is confirmed by the present study, as ATP lasted slightly longer than adenosine (13.3±3.0 versus 10.9±3.2 s, P<0.001), producing a prolonged peak hyperemia. It also appears that the safety profile of ATP is relatively favorable. Whereas AV block occurred in 7.6% of the 9256 patients from the Adenosine Multicenter Trial Registry,10 it occurred in only 2% of patients in a single center trial using an ATP infusion rate of 160 μg · kg⁻¹ · min⁻¹.11,12 For the termination of paroxysmal supraventricular tachycardia, ATP has been used safely even in much higher doses.21,22 Two recent studies comparing ATP to papaverine as an intracoronary bolus injection indicate that ATP yielded a similar hyperemic response without the observed side effects common for papaverine (QTc prolongation, polymorphic ventricular tachycardia, ventricular fibrillation).11,13 ATP was used as an IV infusion for Thallium-201 myocardial scintigraphy in >250 patients with an acceptable specificity and sensitivity similar to that with adenosine for detecting coronary artery disease.12

The results of the present study indicate that ATP is equivalent to adenosine in the respective dose in the extent of hyperemia for CFR and FFR measurements, with the advantage of potentially lower cost, longer duration, and lower rate of side effects. ATP may be preferable to adenosine as the routine clinical agent. It is important to note however, that ATP is not approved by the Food and Drug Administration for clinical usage in the United States.

Finally, this study confirms a previous report from De Bruyne et al, showing the high reproducibility of FFR

Figure 5. Linear regression analysis of CFR and FFR measurements performed with intracoronary adenosine at a dose of 40 μg and postocclusion (top). Agreement between the 2 sets of measurements is shown in the bottom panels according to the statistical approach proposed by Bland and Altman.16 Difference between measurements with adenosine and postocclusion has been plotted against their mean.
measurements as compared with CFR. In our study, the correlation between adenosine and ATP for FFR measurements was considerably better ($R=0.985$) than for CFR measurements ($R=0.934$). This is most likely due to independence of the FFR on hemodynamic variations, whereas CFR is highly dependent on changes of heart rate and blood pressure.

Several limitations in the study design must be considered. All dose-response curves for ATP and adenosine were performed using the left coronary artery in this study. The hyperemic response to either drug in the right coronary artery remains to be studied. Coronary flow reserve was determined as increase in flow velocity, not as absolute increase in coronary blood flow. If the cross-sectional vessel area changes between the baseline and the hyperemic measurement, flow velocity will not be a good indicator of absolute volumetric flow. To alleviate this potential problem, all CFR measurements were performed after the intracoronary injection of nitroglycerin to achieve maximal epicardial coronary dilatation.

In conclusion, ATP seems to be equivalent to adenosine in achieving coronary hyperemia for CFR and FFR measurements. However, to yield a near maximal hyperemic response with either drug, much higher doses may be needed than currently used in clinical practice. Because the ideal vasodilating agent has not yet been found, this might represent a potential source of error in the reserve measurements, resulting in an underestimation of the physiological significance of a coronary artery stenosis. Further studies of a safe and maximally effective method to induce complete coronary hyperemia will be mandatory.

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