EFFECTS OF A 2-SUBSTITUTED ADENOSINE DERIVATIVE, 
2-(P-METHOXYPHENYL)-ADENOSINE (CV-1674) ON 
CORONARY AND CARDIOHEMODYNAMICS, AND 
MYOCARDIAL ENERGETICS

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Abstract—In dogs, intracoronary doses of CV-1674, adenosine (ADS) and 2-Cl-ADS for doubling coronary flow were estimated as 5.0, 2.0 and 0.4 μg/dog, and i.v. doses 31, 71 and 2.5 μg/kg, respectively. ADS and 2-Cl-ADS decreased, while CV-1674 increased LV dp/dt. Intravenous infusion (30 min) of CV-1674 (10 μg/kg per min) and ADS (700 μg/kg per min) decreased coronary resistance to approximately the same extent. Decreases in blood pressure, total peripheral resistance and myocardial O2 consumption with ADS were more prominent than those with CV-1674. ADS produced a marked bradycardia that was not evident with CV-1674. Neither agent had a significant influence on myocardial efficiency. In guinea pig atria, ADS and 2-Cl-ADS exerted negative effects while those with CV-1674 were positive inotropic and chronotropic. In cats, intraduodenal ADS (10 mg/kg) produced no effects on cardiohemodynamic parameters. CV-1674 (250 and 500 μg/kg) increased myocardial tissue blood flow (MBF) with a slight hypotension in a dose-dependent manner, whereas 2-Cl-ADS (100, 250 and 500 μg/kg) increased MBF only with the highest dose concomitantly with marked hypotension and bradycardia. These results suggest that CV-1674 induces selective coronary vasodilation with less depression on cardiohemodynamics, and is relatively well absorbed from the intestinal tract. The pharmacological profile of the compound, therefore, differs from that of ADS and 2-Cl-ADS.

Adenosine (ADS) is well known as a potent coronary vasodilator (1), but causes myocardial depression, bradycardia and hypotension (2). These effects, however, are short-lived, mainly because of rapid biochemical inactivation, the mechanisms of which include uptake by red blood cells and tissues such as in the lung, and its breakdown to inosine by adenosine deaminase (3, 4).

Attempts have been made to find derivatives more resistant to the inactivating mechanisms and more selective for the coronary system. Among these derivatives, 2-chloroadenosine (2-Cl-ADS) has been found to be more potent and longer-acting as a coronary vasodilator, but has a stronger cardiac depressant action than ADS (5, 6). Recently, Marumoto, et al. (7) synthetized several C2-substituted derivatives

**FIG. 1.** Chemical structure of CV-1674
which were more selective than ADS for the coronary vasculature. Among these derivatives, CV-1674, the chemical structure of which is shown in Fig. 1, appeared to be the most interesting. The present paper describes effects of the agent on coronary hemodynamics and myocardial energetics in anesthetized animals and the cardiac actions in isolated preparations as compared with those of ADS and 2-Cl-ADS.

MATERIALS AND METHODS

Hemodynamic and myocardial energetic studies in dogs

Mongrel dogs of either sex weighing 7.0 to 12.0 kg for coronary hemodynamics and 15.0 to 35.0 kg for myocardial energetic studies were anesthetized with sodium pentobarbital (30 mg/kg, i.v.).

In experiments of coronary hemodynamics, the animals were artificially respired with room air, the chest was opened by an incision at the 5th intercostal space and the heart hammocked in the pericardial cradle. After heparinization (500 units/kg, i.v.), the circumflex branch of the left coronary artery was ligated near the bifurcation, and cannulated antegradely with polyethylene tubing. The blood supplying the circumflex area was led from the left carotid artery via an extracorporeal circuit in which a cannulating-type flow probe of an electromagnetic flowmeter (EMF) (Nihon Kohden, MF-2) was interposed to measure coronary blood flow (CBF). The left femoral artery was cannulated for measurement of systemic blood pressure (BP) with an electromanometer (Nihon Kohden, MP-4T), and the ipsilateral femoral vein for i.v. injection of agents. Polyethylene tubing was inserted into the left ventricular cavity through the left auricle to measure the left ventricular pressure (LVP) and its dp/dt (LV dp/dt).

An intracoronary injection of agents was made through a T-glass tube interposed in the extracorporeal circuit.

In experiments of hemodynamics and myocardial energetics, the animal was artificially respired and the right chest opened by an incision at the 4th intercostal space. A polyethylene Morawitz-type cannula was inserted into the coronary sinus through the right auricle. Coronary sinus outflow was led into the right external jugular vein via an extracorporeal circuit, in which a cannulating-type EMF probe was interposed to measure CBF. A non-cannulating-type flow probe of an EMF (Nihon Kohden, MF-46) was set around the ascending aorta to measure aortic blood flow (AF). After these instruments were secured in place, the chest was closed under a negative intrapleural pressure of about 50 cm H₂O, experiments were conducted under spontaneous respiration. The right common carotid artery was cannulated for measurement of BP. Heart rate (HR) was registered with a pulse rate tachometer (Nihon Konden, RT-2) triggered by BP pulses. These hemodynamic parameters were recorded on an ink-writing polygraph recorder (Nihon Kohden, RM-150). Mean CBF was registered through an electronically integrated circuit, and mean AF was calculated planimetrically from 3 cardiac cycles recorded at a chart speed of 5 cm/sec.

The blood sampling from the femoral artery and the coronary sinus for biochemical analysis was started under a stable hemodynamic condition between 40 to 60 min after the
operative procedure. The samplings were repeated six times at 20-min intervals thereafter, except for a 25-min interval between the 3rd and 4th samplings. Infusion of test agents was started 15 min after the 2nd sampling.

PH and pO₂ in arterial and venous blood samples were measured with an IL meter (Instrumentation Laboratory Inc., Model 113), and hematocrit value (Ht) in arterial blood with a microhematocrit centrifuge. Hemoglobin (Hb) content was colorimetrically measured by a cyanomethemoglobin method (8) in duplicated aliquots of arterial blood. Optical density was determined using a spectrophotometer (Hitachi, Model 102).

From hemodynamic and blood gas determinations, the following calculations were made. Stroke volume (SV, ml/beat): AF × HR, external cardiac work load (CW, g.m/min): AF × BP × 13.6, stroke work load (SW, g.m/beat): CW × HR, total peripheral resistance (TPR, mmHg/ml/min): BP ÷ AF, coronary resistance (CR, mmHg/ml/min): BP ÷ CBF. In TPR, the term of CR was not included. Blood oxygen content (VO₂, ml O₂/100 ml blood): pO₂ × 0.003 × SO₂ × 1.39, where SO₂ stands for oxygen saturation percent of Hb, myocardial oxygen consumption (MVO₂, ml/O₂/100 g tissue): JVO₂ × CBF, where JVO₂ stands for an arterio-venous difference of oxygen, myocardial efficiency (Eff., g.m/ml O₂/min/100 g tissue): CW = MVO₂. In the calculation of MVO₂, CBF/100 g left ventricle was used by approximately estimating coronary sinus outflow as 70% of total coronary blood flow (9).

The results were statistically treated according to a multiple comparison procedure.

Hemodynamic and myocardial tissue blood flow studies in cats

Cats of either sex weighing 2.0 to 4.5 kg were anesthetized with a combination of α-chloralose (40 mg/kg, i.v.) and urethane (250 mg/kg, i.v. and 250 mg/kg, i.p.). In a series of experiments, BP and HR were monitored as described above. In another series, the animals were artificially respired with room air, the chest opened by a midsternal incision and the heart hammedocked in a pericardial cradle. Changes in myocardial tissue blood flow (MBF) were relatively estimated according to a heat clearance method (10) with a wire-type cross-thermocouple element (Shin-ei Denki, W-73) implanted into the interior of the left ventricular wall.

Agents were administered intraduodenally (i.d.) via polyethylene tubing inserted into the duodenum.

Experiments on isolated guinea pig atria

Male Hartley guinea pigs weighing 250 to 400 g were sacrificed by a blow on the head, and the heart was immediately removed. Atria dissected from ventricles were separated into left and right atrium, and both preparations were suspended in a same bath containing 20 ml of oxygenated Krebs-Henseleit's solution maintained at 30°C. A resting tension of 0.5 g was applied. Left atrium was driven by electrical stimuli (5 V, 1 msec) at a constant rate of 60 beats/min. The developed tension was isometrically recorded via a strain gauge transducer (Nihon Kohden, SB-1T), and the beating rate of spontaneously beating right atrium was registered with a pulse rate tachometer (Nihon Kohden, RT-2) triggered by the
developed tension. After an equilibration period (40 to 60 min), test agents were added to the bath, and the effects were observed for 10 min thereafter.

Agents used were ADS, CV-1674, 2-Cl-ADS and aminophylline (APL) (Fujisawa, Co.). ADS and its derivatives were synthetized by Marumoto et al. (7). ADS and 2-Cl-ADS were dissolved in 0.9% saline solution. CV-1674 was dissolved in less than 10% polyethylene-glycol-400 (PEG) solution.

RESULTS

Coronary vasodilator activities of CV-1674 administered via different routes

a) Intracoronary injection in dogs

Intracoronary (i.e.) bolus injections of 1.0 to 100 μg/dog of CV-1674 produced a dose-dependent increase in CBF (Fig. 2A), which reached a peak within 30 sec and decayed.
thereafter. The duration of the action was also dose-dependent, being longer than 5 min with more than 30 μg/dog.

Bolus injections of 0.3 to 10.0 μg/dog of ADS also caused a dose-dependent increase in CBF (Fig. 2A), which was more rapid in onset and much shorter in duration than that of CV-1674, i.e., the increase in CBF reached a peak in about 10 sec and almost completely subsided within 30 to 60 sec after injection. 2-Cl-ADS was the most potent in increasing CBF among three analogues (Fig. 2A). The highest dose tested of 2-Cl-ADS, elicited systemic hypotension and bradycardia, whereas CV-1674 and ADS produced little changes in BP and HR even at the highest dose tested.

The doses of CV-1674, ADS and 2-Cl-ADS required to double CBF were estimated as 5.0, 2.0 and 0.4 μg/dog, respectively.

b) Intravenous injection in dogs

Intravenous bolus administrations of CV-1674 produced an increase in CBF with doses of 3.0 to 300 μg/kg in a dose-dependent manner (Figs. 2B & 3A). Three to 10 μg/kg of CV-1674 transiently increased CBF, but did not affect BP and HR. Doses higher than 30 μg/kg of CV-1674 produced a much greater and longer-lasting increase in CBF concomitantly with hypotension, which was characterized by increased pulse pressure resulted from greater decrease in diastolic than systolic pressure (Fig. 3A). The increase in CBF nearly reached

![Graphs showing coronary and cardiohemodynamic effects of CV-1674 and 2-chloroadenosine in dogs (i.v.).](image)

**A:** CV-1674; **B:** 2-chloroadenosine. SP, DP and MP: systolic, diastolic and mean blood pressure, respectively. LVP and max. LVdp/dt: left ventricular pressure and its dp/dt. HR: heart rate, CBF: coronary blood flow. n: number of experiments.
a plateau with 100 µg/kg, but the longer was the duration with the higher dose of the agent. CV-1674 slightly decreased LVP with a moderate increase in max. LVdp/dt in higher doses (Fig. 3A). The agent elicited a transient, slight increase followed by a slight decrease in HR (Fig. 3A).

Although ADS elicited no hemodynamic alteration with a dose of 10 µg/kg, i.v., doses ranging from 30 to 250 µg/kg produced an immediate and dose-dependent increase in CBF (Fig. 2B) and decreases in BP, LVP and its dp/dt. These effects of ADS were short-lived and disappeared within a few min after injection. 2-Cl-ADS also produced a dose-dependent increase in coronary blood flow with doses over 0.3 µg/kg, and the maximum effect was reached with 3 µg/kg (Fig. 2B). The agent, however, significantly depressed all hemodynamic parameters, except for a slight increase in max. LVdp/dt early after administration of lower doses, and a less increase in CBF due to systemic hypotension was observed with 10 µg/kg (Figs. 2B & 3B).

The i.v. doses of CV-1674, ADS and 2-Cl-ADS required to double CBF were estimated as 31, 71 and 2.5 µg/kg, respectively.

c) Intraduodenal administration to cats

To assess the intestinal absorption of test agents, chloralose-urethanized cats were used.

![Graphs showing effects of intraduodenal administration](image-url)

**Fig. 4.** Effects of intraduodenal administration of CV-1674 and 2-chloroadenosine on myocardial blood flow and systemic hemodynamics in cats. A: CV-1674, B: 2-chloroadenosine. BP: blood pressure, MBF: myocardial blood flow as expressed by changes in voltages.
instead of pentobarbitalized dogs, since maintenance of a stable cardiohernodynamic condition required for evaluation of a slow-developing, long-lasting effect of test agents administered intraduodenally was found to be easier in the former preparations than in the latter.

Intraduodenal administration of 250 and 500 µg/kg of CV-1674 increased MBF in a dose-dependent manner, with concomitant decreases in BP and HR with the higher dose. The increase in MBF reached a maximum 20 to 30 min after the administration and lasted for more than 120 min (Fig. 4A). On the other hand, i.d. administration of 2-Cl-ADS increased the MBF only in the highest dose (500 µg/kg, i.d.) tested. However, the depressant effects of 2-Cl-ADS on BP and HR were more marked than those of CV-1674 (Fig. 4B). ADS produced no effect on MBF, BP and HR with an i.d. dose of 10 mg/kg.

With this route of administration, CV-1674 was found to be the most potent among the three analogues.

Inotropic and chronotropic actions in isolated guinea pig atria

Effects of CV-1674 on isolated guinea pig atria differed from those of ADS and 2-Cl-ADS. In isolated, electrically driven left atria CV-1674 produced a slight positive inotropic action with rather high doses of $10^{-5}$–$10^{-4}$ g/ml, as shown in Fig. 5. The inotropic action appeared gradually after application of the agent, and attained the maximum at the end of a 10-min incubation period. Beating rate in spontaneously beating right atria slightly increased on application of the agent, although the effect did not appear to be dose-dependent (Fig. 5). In these preparations $3 \times 10^{-6}$ g/ml did not affect contractile force nor beating rate. In contrast, ADS ($10^{-7}$–$10^{-6}$ g/ml) and 2-Cl-ADS ($10^{-8}$–$10^{-7}$ g/ml) decreased contractile force of electrically driven left atria and beating rate of spontaneously beating right atria in a dose-dependent manner (Fig. 5). The effects of both compounds appeared immediately after application, and attained the maximum within a few min. The effects of ADS decayed with time, while those of 2-Cl-ADS were maintained thereafter.

![Fig. 5. Inotropic and chronotropic effects of adenosine and its derivatives in isolated guinea pig atria.](image)

CF: contractile force of left atria (○—○), BR: beating rate of right atria (∗——∗).
Interaction with aminophylline in cats

The effect of pretreatment with APL on the hypotensive action of CV-1674 and ADS was studied in cats, since the cardiovascular actions of ADS are known to be inhibited by APL (11, 12).

The pretreatment with 5 mg/kg i.v. of APL 10 min prior to challenging with CV-1674 (100 μg/kg) or ADS (500 μg/kg) markedly inhibited the hypotensive action of both agents, and the negative chronotropic action of ADS (Fig. 6).

Cardiohemodynamic and myocardial energetics

In this series of experiments, test agents were infused intravenously to determine the effects in a steady state. Ten and 700 μg/kg per min for 30 min of CV-1674 and ADS, respectively, were used as test doses, since it was found in preliminary experiments that these doses decreased CR to a comparable extent.

Of all the cardiohemodynamic parameters changed with CV-1674 administration, the increase in CBF was the most prominent, the flow having increased from 49.7 ± 8.1 ml/min (mean ± SEM) before to 83.5 ± 16.3 ml/min (p < 0.01, against the pre-infusion value) at 5 min, and 98.0 ± 23.3 ml/min (p < 0.01) at 30 min after the commencement of infusion. The effect lasted even after the cessation of administration, and the decrease in CR was statistically significant even 40 min after the cessation. The increase in CBF was not statistically significant 20 min after stopping i.v. infusion (Table 1A). On the other hand, changes in CBF after ADS differed in degree and direction from one animal to another probably due to prominent cardiohemodynamic depressions, although CR decreased in all preparations during infusion of ADS (Table 1B). The flow rate increased in 3 out of 5 experiments, and decreased slightly in 2.

Either agent significantly lowered BP, although ADS exerted a more prominent hypotensive effect than CV-1674 (Table 1). Mean AF was not significantly affected by either agent, while SV increased after ADS. TPR significantly decreased after either agent (Table 1). ADS produced prominent bradycardia, from 158 ± 10 beats/min immediately before to 127 ± 6 (p < 0.01) and 130 ± 6 (p < 0.05) beats/min 5 and 30 min after administration, respectively. CV-1674 slightly increased HR in the early stages and decreased it at the end of infusion (Table 1).

SW and CW slightly decreased after either agent, and the decrease in CW were statistically significant at the end of infusion (Table 1). MVO₂ decreased slightly but signifi-
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CANTY AT THE END OF INFUSION OF CV-1674, BUT THE DECREASE RECOVERED AFTER THE CESSION OF INFUSION (Table 1A). EFF. WAS NOT AFFECTED BY THE AGENT (Table 1A). ADS SIGNIFICANTLY DECREASED MVO_2 DURING THE PERIOD OF INFUSION (Table 1B). THE DECREASE WAS MORE PROMINENT THAN THAT IN CW, AND EFF. SLIGHTLY INCREASED, ALTHOUGH SUCH WAS NOT STATISTICALLY SIGNIFICANT (Table 1B).

IN ALL SERIES OF EXPERIMENTS, THE SOLVENT (PEG) IN CONCENTRATIONS LESS THAN 10%, USED TO DISSOLVE CV-1674, DID NOT SIGNIFICANTLY AFFECT THE PARAMETERS IN QUESTION.

DISCUSSION

A NEWLY SYNTHETIZED ADENOSINE DERIVATIVE, CV-1674, SHOWS INTERESTING PHARMACOLOGICAL FEATURES AS COMPARED WITH ADS AND 2-CI-ADS IN THE FOLLOWING RESPECTS: 1) A DIFFERENCE IN RELATIVE POTENCIES TO INCREASE CORONARY BLOOD FLOW DEPENDING ON DIFFERENT ROUTES OF ADMINISTRATION, AND 2) A LESS DEGREE OF DEPRESSION IN CARDIOHEMODYNOmICS.

IN DOGS, THE CORONARY VASODILATOR POTENCY OF CV-1674 WAS LESS THAN HALF THAT OF ADS WITH I.C. INJECTION (Fig. 2A). WITH I.V. ADMINISTRATION, ESPECIALLY CONTINUOUS INFUSION, HOWEVER, CV-1674 HAD A HIGHER POTENCY THAN ADS, ALTHOUGH CV-1674 WAS MUCH LESS POTENT THAN 2-CI-ADS EVEN WITH THIS ROUTE OF ADMINISTRATION (Fig. 2B & Table 1A). THE RATIO OF THE I.V. DOSE TO THAT OF I.C. (E.G., REQUIRED TO DOUBLE CBF), GIVES AN INDICATION OF THE DEGREE OF THE RESISTANCE OF EACH COMPOUND TO INACTIVATING MECHANISMS THAT INCLUDE UPTAKE BY RED BLOOD CELLS AND TISSUES SUCH AS IN THE LUNG AND ITS DEGRADATION TO INACTIVE METABOLITES (3, 4). THIS RATIO FOR ADS WAS ABOUT 35 (71 μg/kg, I.V. TO 2.0 μg/dog, I.C.), WHEREAS THOSE OF CV-1674 AND 2-CI-ADS WERE ABOUT 6 (31 and 2.5 μg/kg, I.V. TO 5.0 AND 0.4 μg/dog, I.C., RESPECTIVELY), INDICATING THAT CV-1674 AND 2-CI-ADS ARE MORE RESISTANT TO INACTIVATING MECHANISMS THAN ADS. FURTHERMORE, CV-1674 WAS FOUND TO BE MORE POTENT THAN 2-CI-ADS WITH I.D. ADMINISTRATION IN CATS (Fig. 4), SUGGESTING THAT CV-1674 IS RELATIVELY WELL ABSORBED FROM THE INTESTINAL TRACT. ADS WAS PRACTICALLY INACTIVE IN THIS RESPECT.

ADS AND 2-CI-ADS ARE KNOWN TO EXERT CARDIOHEMOmODYNOMIC DEPRESSIONS IN ADDITION TO CORONARY VASODILATION (2). IN THE PRESENT STUDY, PROMINENT CARDIOHEMOmODYNOMIC EFFECTS OF ADS WERE BRADYCARDIA IN DOGS (Table 1B) AND NEGATIVE INOTROPIC AND CHRONOTROPIC ACTIONS IN ISOLATED GUINEA PIG ATRIA (Fig. 5). 2-CI-ADS RESEMBLED ADS IN THIS RESPECT. CV-1674, HOWEVER, DID NOT PRODUCE PROMINENT BRADYCARDIA IN CATS AND DOGS (Figs. 3A & 6, & Table 1A), INCREASED LVdp/dt IN DOGS (Fig. 3A), AND CAUSED SLIGHTLY POSITIVE INOTROPIC AND CHRONOTROPIC ACTIONS IN ISOLATED GUINEA PIG ATRIA (Fig. 5). THE RESULTS CLEARLY INDICATES THAT CV-1674 HAS A SPECIFICITY FOR THE CORONARY BED. IN CATS, A DEPRESSOR EFFECT OF CV-1674 AND ADS WAS INHIBITED BY PRETREATMENT WITH APL (Fig. 6). CONSIDERING THE SIMILARITY OF THE STRUCTURE OF CV-1674 AND ADS, IT IS SUGGESTED THAT CV-1674 ACTS ON THE SAME VASCULAR RECEPTORS AS ADS. ADS APPARENTLY AFFECTS MVO_2 IN A VARIOUS MANNER DEPENDING ON PREPARATIONS USED. HIRCHE (13) AND WEISSEL ET AL. (14) REPORTED AN INCREASE, AND BACHE ET AL. (15) NO CHANGE, WHILE RABERGER ET AL. (16), LAMMERTAN ET AL. (17) AND RECENTLY GROSS ET AL. (18) REPORTED A DECREASE IN MVO_2 IN CAT AND DOG HEARTS. IN OUR PREPARATIONS, ADS AND CV-1674 DECREASED MVO_2 (Table 1). RABERGER ET AL. (16) AND SCHAUMAN ET AL. (19) PROPOSED THAT ADS PRODUCED


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<td>Coronary Blood Flow (ml/min)</td>
<td>49.7 ± 8.1</td>
<td>83.5 ± 16.3**</td>
<td>98.0 ± 23.3**</td>
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<td>Coronary Resistance (mmHg·ml/min)</td>
<td>2.72 ± 0.36</td>
<td>1.45 ± 0.28**</td>
<td>1.22 ± 0.30**</td>
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<td>Stroke Volume (ml/beat)</td>
<td>15.0 ± 3.5</td>
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<td>Aortic Flow (ml/min)</td>
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<tr>
<td>Total Peripheral Resistance (mmHg·ml/min)</td>
<td>0.056 ± 0.010</td>
<td>0.045 ± 0.000**</td>
<td>0.043 ± 0.000**</td>
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<td>Stroke Work Load (g·m/beat)</td>
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<td>Cardiac Work Load (g·m/min)</td>
<td>4520 ± 1094</td>
<td>4137 ± 1034</td>
<td>3638 ± 1086*</td>
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<td>Cardiac Efficiency (g·m/min/ml O₂/100 g)</td>
<td>480.4 ± 113.0</td>
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<td>500.8 ± 143.1</td>
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<td>Arterial Oxygen Level (ml O₂/dl blood)</td>
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<td>Myocardial Oxygen Consumption (ml O₂/min/100 g)</td>
<td>9.33 ± 0.80</td>
<td>8.25 ± 1.05</td>
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* Indicates significant difference from baseline, ** indicates very significant difference.
### ADENOSINE ANALOG AND CARDIOHEMODYNAMICS

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<td>Coronary Resistance (mmHg/ml min)</td>
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<td>Aortic Flow (ml/min)</td>
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<td>Total Peripheral Resistance (mmHg/ml min)</td>
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<td>Stroke Work Load (g.m/beat)</td>
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<td>Cardiac Efficiency (g/min/ml O2/100 g)</td>
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<td>Myocardial Oxygen Consumption (ml O2/min 100 g)</td>
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<td>4.85 ± 0.90*</td>
<td>4.40 ± 0.62*</td>
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A: CV-1674 (10 μg/kg per min for 30 min, n=6),  B: adenosine (700 μg/kg per min for 30 min, n=5)  
Figures shown are means ± SEM. Each column from left to right shows values of each parameter before (Before), 5 (5 min) and 30 min (30 min) after the commencement of i.v. infusion of the agents, and 20 min after stopping the infusion.  
*: p < 0.05,  **: p < 0.01 as compared with the values before infusion.
a decrease in MVO$_2$ via an action on myocardial substrate metabolism. Lammerant et al. (17) suggested that the decrease in MVO$_2$ might be due to a redistribution of blood flow from a high O$_2$ extracting region (subendocardium) to a low O$_2$ extracting one (subepicardium) of the myocardium. It has also been argued that MVO$_2$ is closely related to the product of the systolic blood pressure and heart rate (20). Thus, it seems likely that the decrease in MVO$_2$ after ADS and CV-1674 as noted in the present study may reflect changes in cardiohemodynamics, since ADS, which elicited prominent hypotension and bradycardia, decreased MVO$_2$ more prominently than CV-1674, which elicited only a lesser degree of hypotension (Table 1). Both CV-1674 and ADS decreased CW as the result of a decrease in afterload of aortic blood pressure, however, myocardial efficiency remained unaffected because of a concomitant decrease in MVO$_2$ (Table 1).

In conclusion, CV-1674 induces selective coronary vasodilation with less depression on cardiohemodynamics, and is relatively well absorbed from the intestinal tract. Furthermore, unlike ADS and 2-Cl-ADS, CV-1674 produced slightly positive inotropic and chronotropic actions on isolated guinea pig atria. The pharmacological profile of the compound, thus, differs from that of ADS and 2-Cl-ADS.

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