British Journal of Pharmacology (1998) 123, 1666–1672
http://www.stockton-press.co.uk/bjp

Effects of CGS 21680, a selective A_{2A} adenosine receptor agonist, on cardiac output and vascular resistance in acute heart failure in the anaesthetized rat

Ali A. Nekooeian & [1,2]Reza Tabrizchi

Department of Pharmacology & Therapeutics, Faculty of Medicine, The University of British Columbia, 2176 Health Sciences Centre, Vancouver, BC, Canada, V6T 1Z3 and [1]Basic Medical Sciences, Faculty of Medicine, Memorial University of Newfoundland, The Health Sciences Centre, St. John's, NF, Canada, A1B 3V6

1 The effects of CGS 21680, a selective A_{2A} adenosine receptor agonist, on cardiac output, blood pressure, mean circulatory filling pressure (P_{mcf}), arterial and venous resistances, heart rate and left ventricular end-diastolic pressure were assessed in rats with acute heart failure by means of coronary artery occlusion.

2 Animals ($n=6$ in each group) were divided into five groups: group I, sham-operated vehicle-treated (0.9% saline; 0.018 mL min^{-1}); groups II-V, subject to coronary artery occlusion and treated with vehicle (0.9% saline; 0.018 ml min^{-1}) and CGS 21680 (0.1, 0.3 and 1.0 $\mu g\ kg^{-1}\ min^{-1}$), respectively. Haemodynamic measurements were taken one hour after completion of surgery, ninety minutes after coronary artery occlusion (except in group I), and fifteen minutes after infusion of saline or CGS 21680.

3 Baseline haemodynamic measurements before occlusion were found not to differ significantly between the different groups of animals. However, after occlusion, cardiac output, rate of rise in left ventricular pressure ($+dP/dt$) and blood pressure were significantly reduced when compared to corresponding values in sham-operated animals. In addition, occlusion of the coronary artery resulted in a significant elevation in venous resistance, P_{mcf} and left ventricular end-diastolic pressure as compared to corresponding values in sham-operated animals.

4 Infusion with CGS 21680 at the highest dose significantly reduced blood pressure, arterial resistance and left ventricular end-diastolic pressure when compared to occluded vehicle-treated animals (group II). Administration of CGS 21680 at the highest dose also significantly increased cardiac output (28%) and heart rate (10%) in comparison to occluded vehicle-treated animals. In addition, the highest dose of CGS 21680 significantly reduced P_{mcf} (9%) and venous resistance (62%) in comparison to occluded vehicle-treated animals. Administration of CGS 21680 did not significantly affect $+dP/dt$ when compared to occluded vehicle-treated animals.

5 The results from the present investigation indicate that occlusion of the coronary artery in rats results in a state of heart failure characterized by reduced arterial pressure and cardiac output, and increased venous resistance, P_{mcf} and left ventricular end-diastolic pressure. Administration of CGS 21680 to animals with acute heart failure resulted in increased cardiac output which was due to reduced venous resistance, as well as increased heart rate.

Keywords: A_{2A} adenosine receptors; acute heart failure; venous resistance; cardiac output; anaesthetized

Introduction

It is recognized that adenosine produces its physiological effects by interacting with membrane bound receptors located on the plasma membrane (for review see Collis & Hourani, 1993; Fredholm *et al*., 1997). Evidence in the current literature supports the view that the physiological effects of adenosine are mediated through the activation of at least four subtypes of adenosine receptors (A_1, A_{2A}, A_{2B} and A_3) (for review see Fredholm *et al*., 1997). The cardiovascular actions of adenosine appear to be mediated via the activation of A_1, A_{2A}, A_{2B} and A_3 adenosine receptors (for review see Collis & Hourani, 1993). The stimulation of A_1 adenosine receptors results in bradycardia, whereas activation of A_2 receptors produces arterial relaxation.

Certainly, the presence of A_2 adenosine receptors has been demonstrated *in vitro* in many preparations, as well as, in a number of different species. For example, A_2 receptors have been shown to be present in the aorta of rat (Lewis *et al*., 1994), femoral artery and vein of rat (Abiru *et al*., 1995), pulmonary vasculature of cat (Neely & Matot, 1996), mesenteric arterial bed of rat (Rubino *et al*., 1995), internal mammary artery and saphenous vein of man (Makujina *et al*., 1992) and saphenous vein of dog (Hargreaves *et al*., 1991). In addition, this subtype of adenosine receptor has been shown to be present in the coronary artery of dog (Kusachi *et al*., 1983), cattle (Cushing *et al*., 1991), man (Makujina *et al*., 1992), guinea-pig (Vials & Burnstock, 1993) and pig (Abebe *et al*., 1994).

It is known that the stimulation of A_2 adenosine receptors decreases blood pressure as a result of a reduction in arterial resistance (Nekooeian & Tabrizchi, 1996). We have also found that administration of CGS 21680 (2-*p*-(2-carboxyethyl)phenethylamino-5′-N-ethylcarboxamidoadenosine hydrochloride), a selective A_{2A} adenosine receptor agonist (Jarvis *et al*., 1989), can produce an increase in cardiac output in anaesthetized rats (Nekooeian & Tabrizchi, 1996). In addition, administration of CGS 21680 can increase mean circulatory filling pressure (P_{mcf}), an index of the body's total venous tone, due to hypotension-induced activation of sympathetic tone (Tabrizchi, 1997). The increase in cardiac output and P_{mcf} due

[2] Author for correspondence.

to administration of CGS 21680 can be abolished in ganglion-blocked animals (Tabrizchi, 1997).

In acute heart failure, an increase in arterial resistance can accentuate reductions in cardiac output. The influence that venous resistance has on cardiac output in acute heart failure is less clear. However, under normal circumstances, it is believed that an increase in both arterial and venous resistance can result in a reduction in cardiac output (Wang *et al*., 1995a). We recently demonstrated that an increase in vascular impedance resulting in reduced cardiac output following continuous infusion with phenylephrine could be alleviated after stimulation of A_2 adenosine receptors with CGS 21680 in pentobarbitone-anaesthetized rats (Nekooeian & Tabrizchi, 1996). Our objectives in the present investigation were to examine further the influence of CGS 21680 on cardiac output, blood pressure and P_{mcf}, as well as, arterial and venous resistances following induction of acute heart failure after coronary artery ligation in anaesthetized rats.

Methods

Surgical preparation of animals

Male Sprague-Dawley rats (350–450 g) were anaesthetized with sodium pentobarbitone (65 mg kg^{-1}), i.p. Catheters (polyethylene tubing; i.d. 0.58 mm, o.d. 0.965 mm) were inserted into the left and right iliac arteries and veins. The left venous catheter was advanced into the inferior vena cava and used for the measurement of central venous pressure. The left arterial and right venous catheters were used for the measurement of blood pressure, and drug/vehicle administration, respectively, while the right arterial catheter was used for blood withdrawal of radiolabelled microspheres. An additional catheter was inserted into the left ventricle via the right carotid artery for measurement of the left ventricular end-diastolic pressure and injection of radiolabelled microspheres. A saline-filled balloon-tipped catheter was placed in the right atrium via the right external jugular vein for the purpose of transient circulatory stop as necessary for the measurement of mean circulatory filling pressure (P_{mcf}) (Tabrizchi *et al*., 1993). The animals were tracheotomized, intubated and ventilated with a small animal ventilator (C.F. Palmer Ltd., U.K.). To expose the heart a left thoracotomy was performed at the level of the 4th intercostal space. A prolene 6-0 suture ('occluder') was placed around the left main coronary artery and exteriorized (Johnston *et al*., 1983). The incision was closed, the animals were disconnected from the ventilator and allowed to stabilize for a period of 1 h while arterial pressure, ventricular pressure, central venous pressure and heart rate were monitored continuously.

All catheters were filled with heparin-treated saline (25 iu ml^{-1}). Body temperature was maintained at 37°C via a rectal thermometer and a heating pad connected to a Thermistemp Instrument Controller (Yellow Spring Instrument Co., OH, U.S.A.; Model 71). Arterial blood pressure, as well as left ventricular end-diastolic and central venous pressure were recorded with a pressure transducer (Gould Statham, CA, U.S.A.; Model PD23B) connected to a polygraph (Grass Instruments Co., MA, U.S.A.; Model 79D). Heart rate was derived from the upstroke of the arterial pulse pressure by a tachograph (Grass Instruments Co., MA, U.S.A.; Model 7P4G), and the rate of rise in left ventricular pressure ($+dP/dt$) was measured with an electronic differentiator (Grass Instruments Co., MA, U.S.A.; Model 7P20C). Cardiac output was measured by the reference sample microsphere method, and P_{mcf} was measured after circulation was transiently stopped by inflating the balloon in the right atrium. Final arterial pressure and venous plateau pressure were recorded at 5–7 s after the circulatory stop (Pang & Tabrizchi, 1986).

Reference sample microsphere method

This technique has been described in detail elsewhere (Pang, 1983). Briefly, suspensions of microspheres (Du Pont Canada Inc.; 15 μm diameter) labelled with ^{57}CO (25,000–30,000 in 150 μl) were injected into the left ventricle over a period of 10 s. Blood was withdrawn from the right femoral artery at the rate of 0.35 ml min^{-1} starting 15 s before microsphere injection, by use of an infusion/withdrawal pump (Harvard Apparatus Inc., MA, U.S.A.; Model 940). The blood sample and syringes used for injection of microspheres or withdrawal of blood were counted for radioactivity at 80–160 Kev with a Searl 185 dual channel automatic γ counter (Nuclear-Chicago, IL, U.S.A.). The withdrawn blood sample was slowly injected back into the animals immediately after counting of radioactivity.

Experimental protocol

Animals were randomly assigned to 5 groups ($n=6$). Group I, sham-operated vehicle-treated animals in which the coronary artery was not occluded and Group II, coronary artery occluded vehicle-treated animals, received normal saline (0.018 ml min^{-1}) as vehicle. Groups III, IV and V were coronary artery-occluded and received CGS 21680 at 0.1, 0.3 or 1.0 μg kg^{-1} min^{-1}, respectively (each dose of CGS 21680 was given in a separate group of animals). Coronary artery occlusion was achieved by tightening the occluder around the artery (Johnston *et al*., 1983).

After the completion of surgery, blood pressure, heart rate and left-ventricular pressure were continuously monitored for 60 min. Following the 60 min stabilization period, the first measurements of cardiac output and P_{mcf} were taken. Coronary artery occlusion was performed in the four groups of animals, and the second measurements of cardiac output and P_{mcf} were taken 90 min later. Following the second measurements of cardiac output and P_{mcf}, each animal was infused with either vehicle or CGS 21680 for 15 min. Subsequently, the third cardiac output and P_{mcf} measurements were taken. In sham-operated animals, the coronary artery was not occluded and experiments were carried out in parallel to the coronary artery occluded groups. At the end of each experiment, the heart was excised and the non-perfused zone was determined by means of the method described by Johnston *et al*. (1983). Briefly, hearts were perfused via the aortic root with normal saline to remove blood followed by perfusion with cardio-green dye (10 mg ml^{-1}). The non-perfused region remained pale red in colour, while the perfused tissue appeared green. The weights of the occluded zone and the ventricles were recorded.

Chemicals

CGS 21680 was dissolved in normal saline (0.9% NaCl). It was purchased from Research Biochemical International (Natick, MA, U.S.A.).

Calculations and statistical analysis

Blood pressure (mmHg) is presented as diastolic pressure plus one third of the difference between systolic and diastolic

pressures. Cardiac output (ml min^{-1}) was calculated as the rate of withdrawal of blood multiplied by total injected c.p.m. divided by c.p.m. in withdrawn blood. Arterial resistance (mmHg min ml^{-1}) was obtained by dividing blood pressure by cardiac output, and venous resistance (mmHg min ml^{-1}) was calculated as the difference of P_{mcf} and central venous pressure divided by cardiac output (Wang *et al*., 1995a). The percentage of myocardium not perfused was estimated as a ratio of the non-perfused weight to total ventricular weight multiplied by 100 (Johnston *et al*., 1983).

The data were analysed by one-way analysis of variance with repeated measure for comparison. Newman-Keuls multiple range test was used for comparison between means. A difference of $P<0.05$ was considered to be significant.

Results

Baseline haemodynamic measurements were found not to differ significantly between the different groups of animals (Table 1). However, after a stabilization period of 90 min, the left ventricular end-diastolic pressure of animals with coronary artery occlusion was found to be significantly ($P<0.05$; $n=6$) elevated compared to sham-operated animals (Table 2). Moreover, the rate of rise in left ventricular pressure ($+dP/dt$) was significantly ($P<0.05$; $n=6$) reduced with coronary artery occlusion as compared to sham-operated animals (Table 2). In addition, cardiac output and blood pressure were significantly ($P<0.05$; $n=6$) reduced in animals that had undergone coronary artery occlusion compared to sham-operated animals (Table 2). Cardiac output and blood pressure reduced by 26% and 25%, respectively, in animals that received vehicle with coronary artery occlusion in comparison to sham-operated animals treated with vehicle. The reductions in cardiac output and blood pressure in groups of animals that were to be treated with CGS 21680 were of similar magnitude to coronary artery occluded vehicle-treated animals. We also found that occlusion of the coronary artery resulted in a significant ($P<0.05$; $n=6$) elevation in venous resistance and P_{mcf} (Table 2). The magnitude of the increase for venous resistance was found to range from 48% to 90%, while that for P_{mcf} ranged from 15% to 19% in the various groups of animals with occlusion in comparison to sham-operated animals. In contrast to these alterations in haemodynamics, we found neither arterial resistance nor heart rate to be significantly altered in occluded animals when compared to sham-operated animals after the stabilization period (Table 2).

Haemodynamic changes that occurred following the occlusion of the coronary artery are indicative of cardiac output failure. The estimated non-perfused area of myocardium for the various groups of animals were as follows: vehicle-treated animals, 34.8±2.1%; and CGS 21680-treated animals at doses 0.1, 0.3 and 1.0 $\mu g\ kg^{-1}\ min^{-1}$, 35.6±1.9%, 35.5±2.6% and 37.2±2.6%, respectively. These were found not to differ significantly between the various groups.

Administration of CGS 21680 lowered the blood pressure (Figure 1a), and this reduction in blood pressure was found to be

Table 1 Baseline blood pressure (BP; mmHg), cardiac output (CO; ml min^{-1}), heart rate (HR; beats min^{-1}), left ventricular end-diastolic pressure (LVEDP; mmHg), mean circulatory filling pressure (P_{mcf}; mmHg), rate of rise of left ventricular pressure ($+dP/dt$; mmHg s^{-1}), arterial resistance (A_R; mmHg min ml^{-1}) and venous resistance (V_R; mmHg min ml^{-1}) of the different groups of rats

Groups	*I* *SV*	*II* *L-V*	*III* *L-CGS 21680* (0.1)	*IV* *L-CGS 21680* (0.3)	*V* *L-CGS 21680* (1.0)
BP	86±3.4	83±2.8	86±3.3	93±5.4	82±1.4
CO	74.5±3.6	74.0±1.3	76.0±3.4	76.3±2.5	79.0±2.8
HR	385±3.6	357±11	360±4	363±11	350±7
[1]LVEDP	−3.1±0.8	−1.7±0.8	−1.2±0.8	−3.3±0.9	−2.1±1.0
P_{mcf}	4.90±0.30	4.85±0.08	4.92±0.07	4.80±0.17	4.75±0.20
$+dP/dt$	4000±193	3775±127	3777±100	4000±316	3860±135
A_R	1.17±0.07	1.11±0.04	1.15±0.06	1.23±0.01	1.05±0.05
V_R	0.040±0.004	0.043±0.003	0.035±0.002	0.036±0.002	0.034±0.002

Each value represents means±s.e.mean of six experiments. The groups of rats were: sham operated vehicle-tested (SV; 0.9% NaCl; 0.018 ml min^{-1}), coronary artery-ligated vehicle-treated (L-V; 0.9% NaCl; 0.018 ml min^{-1}) and CGS 21860-treated ($\mu g\ kg^{-1}\ min^{-1}$). [1]Relative to baseline at atmospheric pressure.

Table 2 Blood pressure (BP; mmHg), cardiac output (CO; ml min^{-1}), heart rate (HR; beats min^{-1}), left ventricular end-diastolic pressure (LVEDP; mmHg). mean circulatory filling pressure (P_{mcf}; mmHg), rate of rise of left ventricular pressure ($+dP/dt$; mmHg s^{-1}), arterial resistance (A_R; mmHg min ml^{-1}) and venous resistance (V_R; mmHg min ml^{-1}) of the different groups of rats 90 min post-coronary artery occlusion (except SV) before the administration of vehicle or drug

Groups	*I* *SV*	*II* *L-V*	*III* *L-CGS 21680* (0.1)	*IV* *L-CGS 21680* (0.3)	*V* *L-CGS 21680* (1.0)
MAP	86±4	64±28*	70±2*	72±3*	66±3*
CO	72.7±2.5	53.2±4.1*	51.5±5.3*	55.3±2.0*	54.1±3.0*
HR	391±9	355±14	375±7	373±9	361±14
[1]LVEDP	−2.9±0.7	3.1±1.0*	4.0±0.8*	3.8±1.1*	3.1±0.8*
Pmcf	4.86±0.24	5.74±0.21*	5.70±0.54*	5.63±0.16*	5.83±0.15*
$+dP/dt$	3900±232	2875±185*	3120±125*	2900±222*	2840±214*
A_R	1.19±0.05	1.24±0.10	1.40±0.09	1.32±0.10	1.24±0.09
V_R	0.041±0.004	0.078±0.001*	0.070±0.005*	0.061±0.003*	0.065±0.005*

Each value represents means±s.e.mean from six experiments. The different groups of rats were: sham-operated vehicle (SV; 0.9% NaCl; 0.018 ml min^{-1}), coronary artery-ligated vehicle (L-V; 0.9% NaCl; 0.018 ml min^{-1}) and CGS 21680 ($\mu g\ kg^{-1}\ min^{-1}$). *Significantly different from sham-operated vehicle-treated group, $P<0.05$. [1]Relative to baseline at atmospheric pressure.

significant ($P<0.05$; $n=6$) at the highest dose of CGS 21680 administered, when compared to vehicle treatment in coronary artery occluded animals. In addition, administration of the two higher doses of CGS 21680 significantly ($P<0.05$; $n=6$) reduced arterial resistance when compared to corresponding values in coronary artery occluded vehicle-treated animals (Figure 1b).

Infusion with CGS 21680 at the highest dose significantly ($P<0.05$; $n=6$) increased cardiac output (28%) and heart rate (10%) in comparison to corresponding values in vehicle-treated rats that were subjected to coronary artery occlusion (Figure 2a and b). In addition, the highest dose of CGS 21680 significantly ($P<0.05$; $n=6$) reduced P_{mcf} (9%) and venous resistance (62%) in comparison to coronary artery occluded vehicle-treated rats (Figure 3a and b). Moreover, the highest dose of CGS 21680 administered also significantly ($P<0.05$; $n=6$) reduced left ventricular end-diastolic pressure when compared to coronary artery occluded vehicle-treated rats (Figure 4a). Neither an infusion of vehicle nor CGS 21680 was able to influence significantly the rate of rise in left ventricular pressure (Figure 4b).

Discussion

The results of the present study show that occlusion of the left main coronary artery results in a state of acute heart failure characterized by decreased blood pressure and cardiac output, and increased left ventricular end-diastolic pressure, venous resistance and P_{mcf}. In these animals with acute heart failure, administration of a selective A_{2A} adenosine receptor agonist, CGS 21680 (Jarvis *et al*., 1989), decreased blood pressure, arterial and venous resistances and P_{mcf}. In addition, heart rate and cardiac output increased following administration of CGS 21680.

In acute heart failure, reductions in cardiac output are accompanied by a rise in P_{mcf}. This is an attempt by the cardiovascular system to maintain venous return. However, due to the impairment of cardiac contractility, the rise in P_{mcf} will mainly accentuate the increase in left ventricular end-diastolic pressure. In general, an impairment in myocardial contractility results in an increase in left ventricular end-diastolic pressure. An increase in left ventricular end-diastolic pressure was found to be prominent in a number of studies where acute heart failure has been produced. This has been observed with acute heart failure induced by embolization of the coronary artery with mercury (Leddy *et al*., 1983) or plastic microspheres (Gorodetskaya *et al*, 1990). The mercury-induced acute heart failure was associated with a significant decrease in blood pressure, cardiac output and left ventricular dP/dt, and a significant increase in left ventricular end-diastolic pressure (Leddy *et al*., 1983). The microsphere-induced acute heart failure also caused a significant decrease in cardiac contractility, blood pressure and cardiac output, and an increase in left ventricular end-diastolic pressure and right

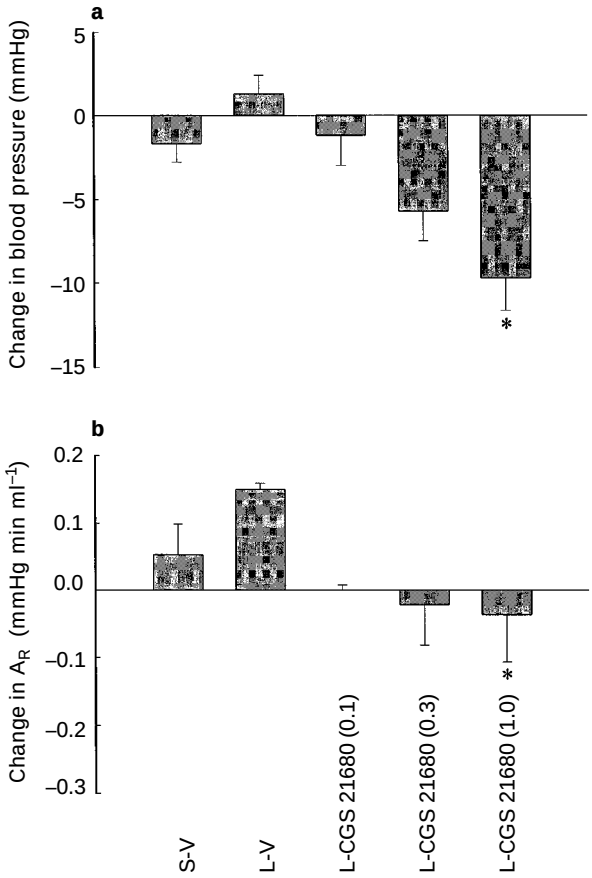

Figure 1 Changes from pretreatment values of arterial pressure (a) and arterial resistance (b) of the sham-operated vehicle-treated (SV; 0.9% NaCl; 0.018 ml min^{-1}), coronary artery-ligated vehicle-treated (L-V; 0.9% NaCl; 0.018 ml min^{-1}) and CGS 21680-treated (L-CGS 21680; 0.1, 0.3 and 1.0 μg kg^{-1} min^{-1}) rats. *Significant difference from L-V group, $P<0.05$.

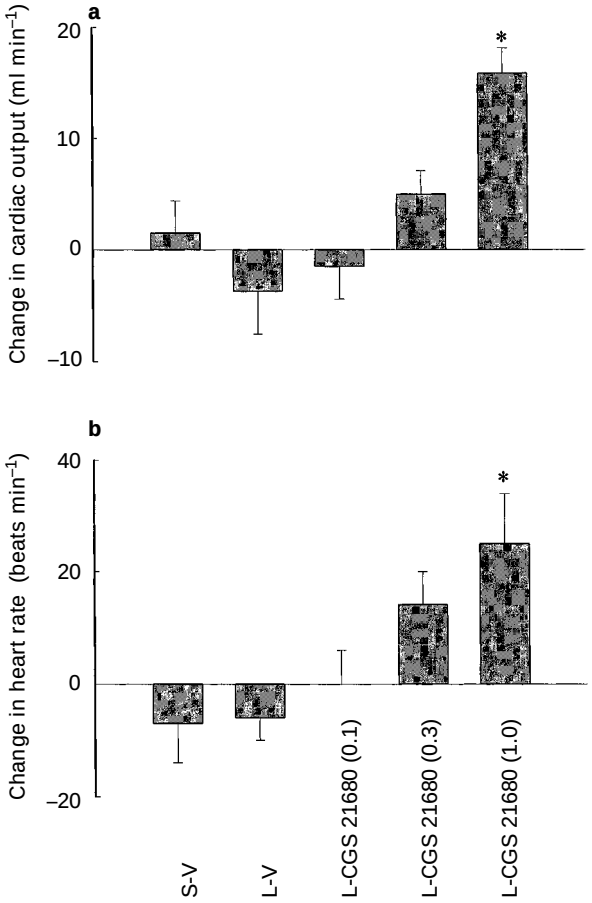

Figure 2 Changes from pretreatment values of cardiac output (a) and heart rate (b) of the sham-operated vehicle-treated (SV; 0.9% NaCl; 0.018 ml min^{-1}), coronary artery-ligated vehicle-treated (L-V; 0.9% NaCl; 0.018 ml min^{-1}) and CGS 21680-treated (L-CGS 21680; 0.1, 0.3 and 1.0 μg kg^{-1} min^{-1}) rats. *Significant difference from L-V group, $P<0.05$.

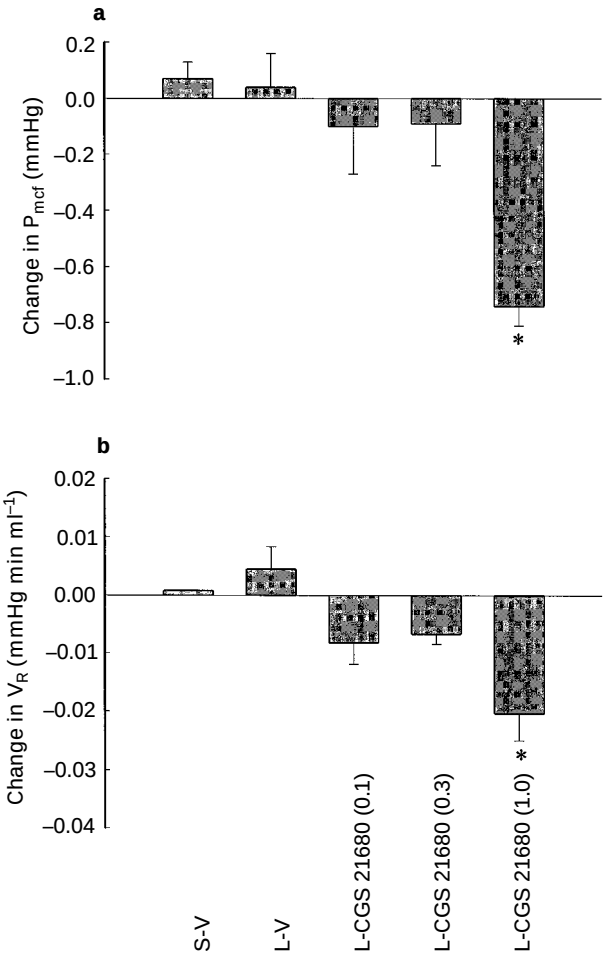

Figure 3 Changes from pretreatment values of mean circulatory filling pressure (P_{mcf}) (a) and venous resistance (b) of the sham-operated vehicle-treated (SV; 0.9% NaCl; 0.018 ml min^{-1}), coronary artery-ligated vehicle-treated (L-V; 0.9% NaCl; 0.018 ml min^{-1}) and CGS 21680-treated (L-CGS 21680; 0.1, 0.3 and 1.0 μg kg^{-1} min^{-1}) rats. *Significant difference from L-V group, $P<0.05$.

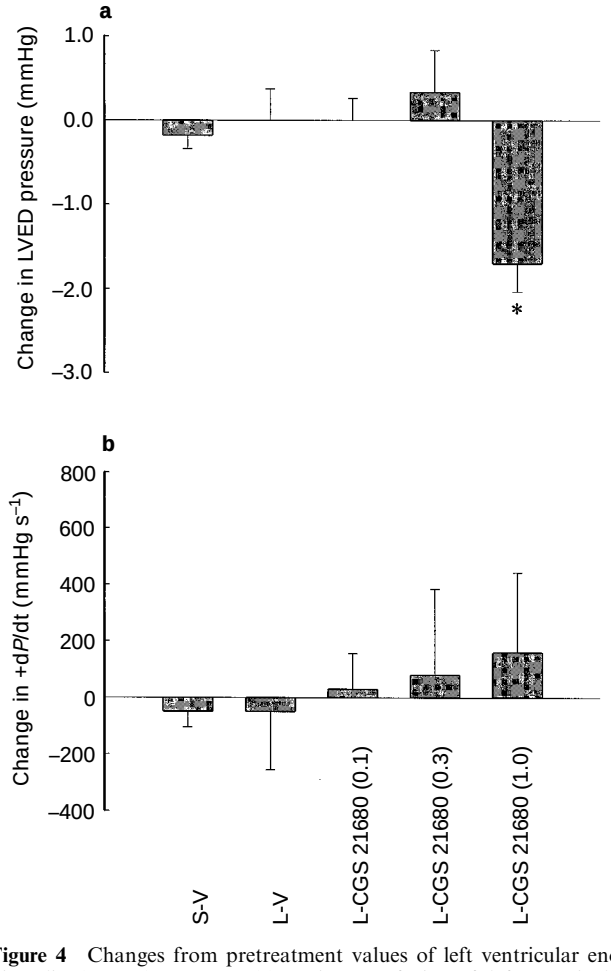

Figure 4 Changes from pretreatment values of left ventricular end-diastolic (LVED) pressure (a) and rate of rise of left ventricular pressure (+dP/dt) (b), of the sham-operated vehicle-treated (SV; 0.9% NaCl; 0.018 ml min^{-1}), coronary artery-ligated vehicle-treated (L-V; 0.9% NaCl; 0.018 ml min^{-1}), and coronary artery-ligated CGS 21680-treated (L-CGS 21680; 0.1, 0.3 and 1.0 μg kg^{-1} min^{-1}) rats. *Significant difference from L-V group, $P<0.05$.

atrial pressure (Schölkens *et al*., 1986; Gorodetskaya *et al*., 1990).

An increase in left ventricular end-diastolic pressure has been observed in other models of acute heart failure, as well. For example, Wong and colleagues (1993) demonstrated that propranolol-induced acute heart failure in dogs was associated with a significant decrease in cardiac output and a significant increase in left ventricular end-diastolic pressure with no change in arterial resistance. Redfield and colleagues (1989) employed rapid right ventricular pacing (250 beats min^{-1}) to induce acute heart failure in dogs. In both cases, heart failure was associated with a significant decrease in arterial pressure and cardiac output, and a significant increase in pulmonary capillary wedge and right atrial pressures. Nekooeian and colleagues (1995) combined rapid right ventricular pacing with volume loading to induce heart failure. In this model, significant reductions of arterial blood pressure, and increases in P_{mcf} and venous resistance, as well as, pulmonary artery, pulmonary capillary wedge and right atrial pressures occurred.

The haemodynamic status that has been created as a result of left coronary artery occlusion in the present study shares similar haemodynamic changes with a number of the above mentioned models. In acute heart failure, an increase in neurohormonal activity can result in venoconstriction and consequently decreased venous capacitance (Maekawa *et al*., 1983; Kelly *et al*., 1996). This is in agreement with the findings of Robinson and Colleagues (1990) in that acute heart failure induced by embolization of coronary arteries with microspheres was associated with a significant decrease in unstressed vascular volume and, therefore, venous capacitance. In the present investigation, the increase in cardiac output produced by infusion with CGS 21680 was, in part, due to a reduction in venous resistance.

It is recognized that the effects of CGS 21680 on blood pressure and arterial resistance are mediated via the activation of A_{2A} adenosine receptors (Hutchison *et al*., 1989; Fozard & Carruthers, 1993). Furthermore, stimulation of adenosine receptors in veins produces relaxation. For example, adenosine was shown to relax noradrenaline-precontracted rings of saphenous vein of dog (Verhaeghe, 1977), portal vein of rat (Sjöberg & Wahlström, 1975), hind limb vein of dog (Cotterrell & Karim, 1982) and dorsal hand vein of man (Ford *et al*., 1992). Infusion of adenosine in dogs has also been shown to result in an increase in adipose tissue volume, suggesting the occurrence of dilatation of capacitance blood vessels in the adipose tissue (Sollevi & Fredholm, 1981). In addition, administration of adenosine to rats causes a reduction in P_{mcf} (Glick *et al*., 1992; Tabrizchi, 1997). The findings of the present study indicate that CGS 21680 has venodilating properties because it decreased P_{mcf} and venous resistance. Recently, Abiru and colleagues (1995) demonstrated that CGS 21680

could also cause relaxation of the rat isolated femoral vein. Evidence from our laboratory revealed that infusion of CGS 21680 can reduce venous resistance and P_{mcf} in ganglion-blocked rats. On the other hand, in animals not treated with a ganglion-blocker, the infusion of CGS 21680 increased P_{mcf} without any effect on venous resistance (Tabrizchi, 1997). This increase in P_{mcf} following administration of CGS 21680 was the result of hypotension-induced activation of the sympathetic nervous system. In the present investigation, CGS 21680 lowered P_{mcf} as venous tone became elevated due to cardiac dysfunction.

Stimulation of A_2 adenosine receptors, presumably A_{2A} receptors, in the venous system was responsible for the reduction in venous resistance. However, this interpretation is only tentative. Nevertheless, the reduction in preload was most likely responsible for the decrease in left ventricular end-diastolic pressure. In support of this interpretation, a study of Wang and colleagues (1995b) previously demonstrated that nitroglycerin and enalapril decreased left ventricular end-diastolic pressure in acute heart failure by reducing venous tone. In contrast to this finding, hydralazine, which is known to lack a venodilator effect, was unable to affect left ventricular end-diastolic pressure at an equi-hypotensive dose to those of nitroglycerin and enalapril (Wang *et al*., 1995b). Furthermore, a decrease in left ventricular end-diastolic pressure can lead to a decrease in wall tension developed during systole and to a subsequent decline in oxygen consumption (Sonnenblick & Lejemtel, 1989). This coupled with the ability of CGS 21680 to increase coronary artery conductance and coronary blood flow (Nekooeian & Tabrizchi, 1996), can result in an improvement in cardiac function. The increase in cardiac output, in part, could also have been achieved through an increase in heart rate. The increase in heart rate during infusion with CGS 21680 was most likely due to reflex-mediated activation of the sympathetic nervous system (Hutchison *et al*., 1989; Fozard & Carruthers, 1993; Nekooeian & Tabrizchi, 1996). However, the modest increase in heart rate observed in the present study cannot entirely account for the increase in cardiac output, and, more importantly, for the reduction of end-diastolic ventricular pressure. Based on our present findings, an agonist, such as CGS 21680, capable of stimulating A_{2A} adenosine receptors will be useful in the treatment of acute heart failure in clinical situations.

In summary, the results of the present study suggest that occlusion of the coronary artery in the rat resulted in a state of heart failure characterized by reduced arterial pressure and cardiac output, and increased venous resistance and P_{mcf}. Administration of the A_{2A} adenosine receptor agonist, CGS 21680, to rats with acute heart failure resulted in increased cardiac output which was due to reduced venous resistance, as well as increased heart rate.

This work was supported by grant-in-aid from Heart and Stroke Foundation of British Columbia & Yukon. A.A.N. is a recipient of Heart and Stroke of Foundation of British Columbia & Yukon research traineeship. R.T. is a Scholar of Heart and Stroke Foundation of Canada.

References

ABEBE, W., MAKUJINA, S.R. & MUSTAFA, S.J. (1994). Adenosine receptor-mediated relaxation of porcine coronary artery in the presence and absence of endothelium. *Am. J. Physiol.,* **266,** H2018 – H2025.

ABIRU, T., ENDO, K. & MACHIDA, H. (1995). Differential vasodilatory action of 2-octynyladenosine (YT-146), an adenosine A_2 receptor agonist, in the isolated rat femoral artery and vein. *Eur. J. Pharmacol.,* **281,** 9 – 15.

COLLIS, G.C. & HOURANI, S.M.O. (1993). Adenosine receptor subtypes. *Trends Pharmacol. Sci.,* **14,** 360 – 366.

COTTERRELL, D. & KARIM, F. (1982). Effects of adenosine and its analogues on the perfused hind limb artery and vein of anaesthetised dogs. *J. Physiol.,* **323,** 473 – 482.

CUSHING, D.J., BROWN, G.L., SABOUNI, M.H. & MUSTAFA, S.J. (1991). Adenosine receptor-mediated coronary artery relaxation and cyclic nucleotide production. *Am. J. Physiol.,* **261,** H343 – H348.

FORD, G.A., HOFFMAN, B.B., VESTAL, R.E. & BLASCHKE, T.F. (1992). Age-related changes in adenosine and β-adrenoceptor responsiveness of vascular smooth muscle in man. *Br. J. Clin. Pharmacol.,* **33,** 83 – 87.

FOZARD, J.R. & CARRUTHERS, A.M. (1993). The cardiovascular effects of selective adenosine A_1 and A_2 receptor agonists in the pithed rat: no role for glibenclamide-sensitive potassium channels. *Naunyn-Schmiedeberg's Arch. Pharmacol.,* **347,** 192 – 196.

FREDHOLM, B.B., ABBRACCHIO, M.P., BURNSTOCK, G., DUBYAK, G.R., HARDEN, T.K., JOCOBSON, K.A., SCHWABE, U. & WILLIAMS, M. (1997). Towards a revised nomenclature for P1 and P2 receptors. *Trends Pharmacol. Sci.,* **18,** 79 – 82.

GLICK, M.R., GEHMAM, J.D. & GASCHO, J.A. (1992). Adenosine increases total venous capacitance in awake instrumented rats. *J. Cardiovasc. Pharmacol.,* **19,** 709 – 713.

GORODETSKAYA, E.A., DUGIN, S.F., MEDVEDEV, O.S. & ALLABERGENOVA, A.E. (1990). Simple method to produce acute heart failure by coronary vessel embolization in closed chest rats with microspheres. *J. Pharmacol. Meth.,* **24,** 43 – 51.

HARGREAVES, M.B., STOGGALL, S.M. & COLLIS, M.G. (1991). Evidence that the adenosine receptor mediating relaxation in dog lateral saphenous vein and guinea-pig aorta is of the A_{2b} subtype. *Br. J. Pharmacol.,* **102,** 198P.

HUTCHISON, A.J., WEBB, R.L., OEI, H.H., GHAI, G.R., ZIMMERMAN, M.B. & WILLIAMS, M. (1989). CGS 21680C, and A_2 selective adenosine receptor agonist with preferential hypotensive activity. *J. Pharmacol. Exp. Ther.,* **251,** 47 – 55.

JARVIS, M.F., SCHULZ, R., HUTCHISON, A.J., DO, U.H., SILLS, M.A. & WILLIAMS, M. (1989). [^{3}H]CGS 21680, a selective A_2 adenosine receptor agonist directly labels A_2 receptors in rat brain. *J. Pharmacol. Exp. Ther.,* **251,** 888 – 893.

JOHNSTON, K.M., MACLEOD, B.A. & WALKER, M.J.A. (1983). Effects of aspirin and prostacyclin on arrhythmias resulting from coronary artery ligation and on infarct size. *Br. J. Pharmacol.,* **78,** 29 – 37.

KELLY, R.F., HURSEY, T.L., SCHAER, G.L., PIOTROWSKI, M.J., DEE, S.V., PARRILLO, J.E. & HOLLENBERG, S.M. (1996). Cardiac endothelin release and infarct size, myocardial blood flow, and ventricular function in canine infarction and reperfusion. *J. Invest. Med.,* **44,** 575 – 582.

KUSACHI, S., THOMPSON, R.D. & OLSSEN, R.A. (1983). Ligand selectivity of dog coronary adenosine receptor resembles that of adenylate cyclase stimulatory (Ra) receptors. *J. Pharmacol. Exp. Ther.,* **227,** 316 – 321.

LEDDY, C.L., WILEN, M. & FRANCIOSA, J.A. (1983). Effects of a new angiotensin converting enzyme inhibitor, enalapril, in acute and chronic left ventricular failure of dogs. *J. Clin. Pharmacol.,* **23,** 189 – 198.

LEWIS, C.D., HOURANI, S.M., LONG, C.J. & COLLIS, M.G. (1994). Characterization of adenosine receptors in the rat isolated aorta. *Gen. Pharmacol.,* **25,** 1381 – 1387.

LINDEN, J. (1994). Cloned adenosine A_3 receptors: pharmacological properties, species differences and receptor functions. *Trends Pharmacol. Sci.,* **15,** 298 – 306

MAEKAWA, K., LIANG, C.S. & HOOD, Jr, B.W. (1983). Comparison of dobutamine and dopamine in acute myocardial infarction: Effects of systemic haemodynamics, plasma catecholamines, blood flows and infarct size. *Circulation,* **67,** 750 – 759.

MAKUJINA, S.R., SABOUNI, M.H., BHATA, S., DOUGLAS, F.L. & MUSTAFA, S.J. (1992). Vasodilatory effects of adenosine A_2 receptor agonists CGS 21680 and CGS 22492 in human vasculature. *Eur. J. Pharmacol.,* **221,** 243 – 247.

NEELY, C.F. & MATOT, I. (1996). Pharmacological probes for A_1 and A_2 adenosine receptors *in vivo* in feline pulmonary vascular bed. *Am. J. Physiol.,* **270,** H610 – 619.

NEKOOEIAN, A.A., OGILVIE, R.I. & ZBOROWSKA-SLUIS, D. (1995). Acute hemodynamic effects of drugs acting on the renin-angiotensin system in acute heart failure. *Can. J. Cardiol.,* **11,** 59 – 64.

NEKOOEIAN, A.A. & TABRIZCHI, R. (1996). Effects of adenosine A_{2A} receptor agonist, CGS 21680, on blood pressure, cardiac index and arterial conductance in anaesthetised rats. *Eur. J. Pharmacol.,* **307,** 163 – 169.

PANG, C.C.Y. (1983). Effect of vasopressin antagonists and saralasin on regional blood flow following hemorrhage. *Am. J. Physiol.,* **245,** H749 – H755.

PANG, C.C.Y. & TABRIZCHI, R. (1986). The effects of noradrenaline, B-HT 920, methoxamine, angiotensin II and vasopressin on mean circulatory filling pressure in conscious rats. *Br. J. Pharmacol.,* **89,** 389 – 394.

REDFIELD, M.M., EDWARDS, B.S., MAGOON, M.D., HEUBLEIN, D.M., AARHUS, L.L. & BURNETT, Jr, J.C. (1989). Failure of atrial natriuretic factor to increase with volume expansion in acute and chronic congestive heart failure in the dog. *Circulation,* **80,** 651 – 657.

ROBINSON, V.J., SMISETH, O.A., SCOTT-DOUGLAS, N.W., SMITH, E.R., TYBERG, J.V. & MANYARI, D.E. (1990). Assessment of the splanchnic vascular capacity and capacitance using quantitative equilibrium blood-pool scintigraphy. *J. Nucl. Med.,* **31,** 154 – 159.

RUBINO, A., RALEVIC, V. & BURNSTOCK, G. (1995). Contribution of P_1-(A_{2b} subtype) and P_2-purinoceptors to the control of vascular tone in the rat isolated mesenteric arterial bed. *Br. J. Pharmacol.,* **115,** 648 – 652.

SCHÖLKENS, B.A., MARTORANA, P.A., GÖBEL, H. & GEHRING, D. (1986). Cardiovascular effects of the converting enzyme inhibitor ramipril (HOE 498) in anaesthetised dogs with acute ischemic left ventricular failure. *Clin. Exp. Hypertens. [A],* **8,** 1033 – 1048.

SJÖBERG, B. & WAHLSTRÖM, B.A. (1975). The effect of ATP and related compounds on spontaneous mechanical activity in the rat portal vein. *Acta Physiol. Scand.,* **94,** 46 – 53.

SONNENBLICK, E.H. & LEJEMTEL, T.H. (1989). Pathophysiology of congestive heart failure: role of angiotensin-converting enzyme inhibitors. *Am. J. Med.,* **87,** 88S – 91S.

SOLLEVI, A. & FREDHOLM, B.B. (1981). Role of adenosine in adipose tissue circulation. *Acta Physiol. Scand.,* **112,** 293 – 298.

TABRIZCHI, R. (1997). Effects of adenosine and adenosine analogues on mean circulatory filling pressure and cardiac output in anaesthetised rats. *Naunyn-Schmiedeberg's Arch. Pharmacol.,* **356,** 356 – 369.

TABRIZCHI, R., LIM, S.L. & PANG, C.C.Y. (1993). Possible equilibration of portal venous and central venous pressures during circulatory arrest. *Am. J. Physiol.,* **264,** H259 – H261.

VERHAEGHE, R.H. (1977). Action of adenosine and adenine nucleotides on dogs' isolated veins. *Am. J. Physiol.,* **233,** H114 – H121.

VIALS, A. & BURNSTOCK, G. (1993). A_2-purinoceptor-mediated relaxation in the guinea-pig coronary vasculature: a role for nitric oxide. *Br. J. Pharmacol.,* **109,** 424 – 429.

WANG, Y.-X., LIM, S.L. & PANG, C.C.Y. (1995a). Increase by N^G-nitro-L-arginine methyl ester (L-NAME) of resistance to venous return in rats. *Br. J. Pharmacol.,* **114,** 1454 – 1458.

WANG, S.Y., MANYARI, D.E., SCOTT-DOUGLAS, N., SMISETH, O.A., SMITH, E.R. & TYBERG, J.V. (1995b). Splanchnic venous pressure-volume relation during experimental acute ischemic heart failure: Differential effects of hydralazine, enalapril and nitroglycerin. *Circulation,* **91,** 1205 – 1212.

WONG, P.C., ALDRICH, P.E., CHIU, A.T., EARL, R.A., HART, S.D., JOHNSON, A.L., MA, P., MCCALL, D.E., PRICE, W.A., SMITH, R.D., WEXLER, R.R. & TIMMERMANS, P.B.M.W.M. (1993). Pharmacology of 2-amino-1,4,-dihydro-4-(2-{4-[4-(2-methoxy-phenyl)-1-piperazinyl]butylsulfinyl}phenyl)-6-methyl-5-nitro-3-pyridine carboxylic-acid methyl-ester (Xb513), a novel calcium agonist with alpha-1 adrenergic receptor antagonistic property. *J. Pharmacol. Exp. Ther.,* **265,** 1088 – 1095.

(Received August 18, 1997
Revised January 5, 1998
Accepted January 7, 1998)