Transpl Int (1995) 8: 207–213
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ORIGINAL ARTICLE

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Protection of canine renal grafts by renin-angiotensin inhibition through nucleoside transport blockade

Received: 21 April 1994
Accepted: 26 September 1994

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Abstract The aims of this study were (1) to investigate the effect of R 75231, a nucleoside transport inhibitor, on renin-angiotensin release after renal ischemia-reperfusion and (2) to establish a possible protective effect of this drug on renal function. We used a canine model for autotransplantation of kidneys that had been subjected to 30 min of warm ischemia and subsequently to 24 h of cold storage in HTK preservation solution, with immediate contralateral nephrectomy. R 75231 was injected intravenously into six dogs in two equal portions of 0.05 mg/kg both 30 min and 10 min before reanastomosis was established. Another six dogs were used as a control group. At 2 weeks post-transplantation, five out of six dogs in the R 75231 group and one out of six in the control group were still alive. Starting on day 4, serum creatinine was lower in the R 75231 group than in the control group ($p < 0.05$). In contrast to the control group, an inversion of the median preischemia adenosine/inosine ratio was observed in the R 75231 group after reperfusion (0.4 preischemia vs 4.0 after 60 min of reperfusion). Reperfusion of the graft resulted in an immediate increase in renin, angiotensin I, and angiotensin II venous blood levels in the control group. In the R 75231 group, renin, angiotensin I, and angiotensin II levels were significantly lower. We conclude that administration of R 75231 before reperfusion has a protective effect on post-transplant function of kidneys that have been subjected to prolonged warm ischemia. This effect may, at least in part, be ascribed to inhibition of the breakdown and disposal of endogenous adenosine which, in turn, inhibits the excessive stimulation of the renin-angiotensin system in the early phase of reperfusion.

Key words Ischemia, kidney, dog · Nucleoside blockade, kidney transplantation · Renin-angiotensin, kidney transplantation

Introduction

Since the availability of nonischemic donor organs is limited, the use of ischemically damaged kidneys for transplantation is increasing [28]. Unfortunately, post-transplant outcome of these so-called non-heart-beating donor kidneys is characterized by a high percentage of delayed recovery of normal function due to the ischemic damage to the organ [8]. The theory that a significant portion of the organ injury after ischemia develops during the reperfusion phase offers possibilities for therapeutic intervention.

R 75231 is a nucleoside transport inhibitor. The effect of such an agent is to delay the breakdown and disposal of endogenous adenosine, large amounts of which are produced during ischemia [4–7, 23]. Cessation of the oxygen supply to a tissue causes breakdown of nucleotides (ATP, ADP, AMP) in the cells. As a result, adeno-

sine is released in the interstitium. The accumulation of adenosine in the interstitial space is transient. Functional nucleoside transporters at the interstitial side of the endothelial cell carry the adenosine across the endothelial membrane into the endothelial cell, where it is metabolized to inosine and hypoxanthine. Moreover, adenosine is rapidly released from the interstitium into the vessel lumen upon reperfusion. This process is also mediated by nucleoside transporters. By inhibiting the nucleoside transporters, it is possible to prolong the physiological actions of adenosine. One of the physiological actions of adenosine is a direct inhibition of the renin-secreting cells [1, 17]. Excessive stimulation of the renin-angiotensin system is known to have an adverse effect on renal viability [2].

The aims of this study were (1) to investigate the effect of R 75231 on renin-angiotensin release after renal ischemia-reperfusion and (2) to establish a possible protective effect on this drug on renal function in a dog autotransplant model of kidneys subjected to prolonged warm ischemia.

Materials and methods

R 75231

R 75231 [(±)-2-(aminocarbonyl)-N-(4-amino-2,6-dichlorophenyl)-4-[5,5-bis(4-fluorophenyl)pentyl]-1-piperazineacetamide], which was kindly provided by H. van Belle, Janssen Pharmaceutics, Beerse, Belgium, is a racemic mixture of which the 1-enantiomer is the active substance. R 75231 is a specific inhibitor of nucleoside transports with no other known relevant pharmacological action. Based on previous experiments with R 75231, a dosage of 0.1 mg/kg was chosen to treat the dogs [3].

Animals and anesthesia

Experiments were performed on 12 female beagle dogs, aged 2–4 years and weighing 10–12 kg. The animals were fasted for 12 h prior to surgery with free access to water. Anesthesia was induced with thiopentotal (20 mg/kg body weight) and maintained with a nitrous oxide-oxygen gas mixture delivered continuously by a positive pressure respirator via an endotracheal tube. An antibiotic prophylaxis of 500 mg ampicillin was given before each operation. During surgery the dogs were hydrated by intravenous infusion of 500 ml Ringers' lactate solution, and body temperature was kept constant (37 °C) using a thermostatic water mattress.

Surgical protocol

The kidneys were exposed via a midline abdominal incision. The left kidney was carefully dissected from the surrounding tissue. Heparin (1000 IU) was given 10 min prior to induction of warm ischemia in order to prevent thrombosis. Ischemia was induced by crossclamping the left renal vessel pedicle. During the ischemic interval, the abdomen was kept closed to maintain the kidney at body temperature. After 30 min the kidney was removed and flushed with 200 ml 4 °C histidine tryptophan ketoglutarate (HTK) solution [18]. Flushing was performed by gravity from a bottle at a height of 100 cm. Subsequently, the kidney was wrapped in a sterile plastic bag containing 500 ml HTK solution and stored for 24 h on melting ice. The following day, the operation started with the introduction of a catheter into the left carotid artery to monitor the arterial blood pressure and of a catheter into the left jugular vein for blood sampling. Morphine (0.5 mg/kg) was administered intravenously in order to prevent intestinal invagination. After removal of the right kidney, the preserved left kidney was then reimplanted autologously onto the iliac vessels in the right lower abdomen. In six dogs, R 75231 was injected intravenously in two equal portions of 0.05 mg/kg in 10 ml saline 30 min and 10 min before unclamping was established. The other six dogs did not receive R 75231 and were used as a control group. During vascular anastomosis, rewarming was prevented by maintaining the kidney at 4 °C with sterile saline. Sorbitol 20 %, 150 ml, was administered intravenously after completion of the anastomoses in order to induce osmotic diuresis. The ureter was implanted in the bladder using a technique described by Politano and Leadbetter [24]. A 10-Charière catheter was placed in the bladder and connected to a urine bag for urine production measurement. After recovery from surgery, the dogs were allowed free access to food and water.

Cortical biopsies for measurement of energy metabolites

Wedge-shaped cortical biopsies were taken from the left kidney at two time points: before induction of warm ischemia and 60 min after reperfusion of the graft. All tissue samples were immediately frozen in liquid nitrogen and stored at –80 °C. The concentration of energy metabolites in the cortical biopsies was determined using an HPLC method described by Maessen et al. [21]. In short, before analysis, the tissue samples were lyophilized at –30 °C. Adherent blood was removed. The samples were weighed and extracted in 25–50 µl/mg tissue $HCLO_4$ (2 mol/l) containing 5 mmol/l dithiothreitol. The tissue $HCLO_4$ mixture was centrifuged at 1200 g for 5 min at 4 °C and the supernatant was frozen in liquid nitrogen. Following the addition of 40–80 µl/mg tissue $KHCO_3$ (2 mol/l) to the supernatant, this mixture was allowed to thaw during centrifugation at 1200 *g* at 4 °C for 1 h, during which neutralization took place. A Varian Vista 5000 (Varian, Wallnut Creek, Calif, USA) equipped with a narrow bore, stainless steel column filled with spherical liChrosorb RP-18 particles of 5 µm (Merck, Darmstadt, Germany) was used for a gradient HPLC analysis. Injection volume of standard or sample extract was 10 µl. After each single run, which took 30 min, the column was re-equilibrated for 15 min. All chemicals were obtained from Merck. Peaks were quantitated at 254 nm with a Varian 604 data system, using a conversion factor of peak area per concentration of a known external standard. Standards were of the highest purity available. ADP, AMP, and IMP were purchased from Boehringer (Mannheim, Germany) hypoxanthine (HX) and adenosine (ADO) from Merck, and ATP, inosine (INO) and xanthine (X) from Sigma (St. Louis, Mo., USA).

Renin, angiotensin I, and angiotensin II measurements

Venous blood samples were taken before implantation and subsequently 1, 2, 4, 6, 8 and 24 h after reperfusion of the graft. The concentration of angiotensin I and angiotensin II was determined by radioimmunoassay. During two incubation periods, radiolabeled angiotensin I or angiotensin II competed with unlabelled angiotensin I or angiotensin II in test samples, standards, and controls (0.1 or 0.3 ml, respectively) for a limited number of specific antibody-

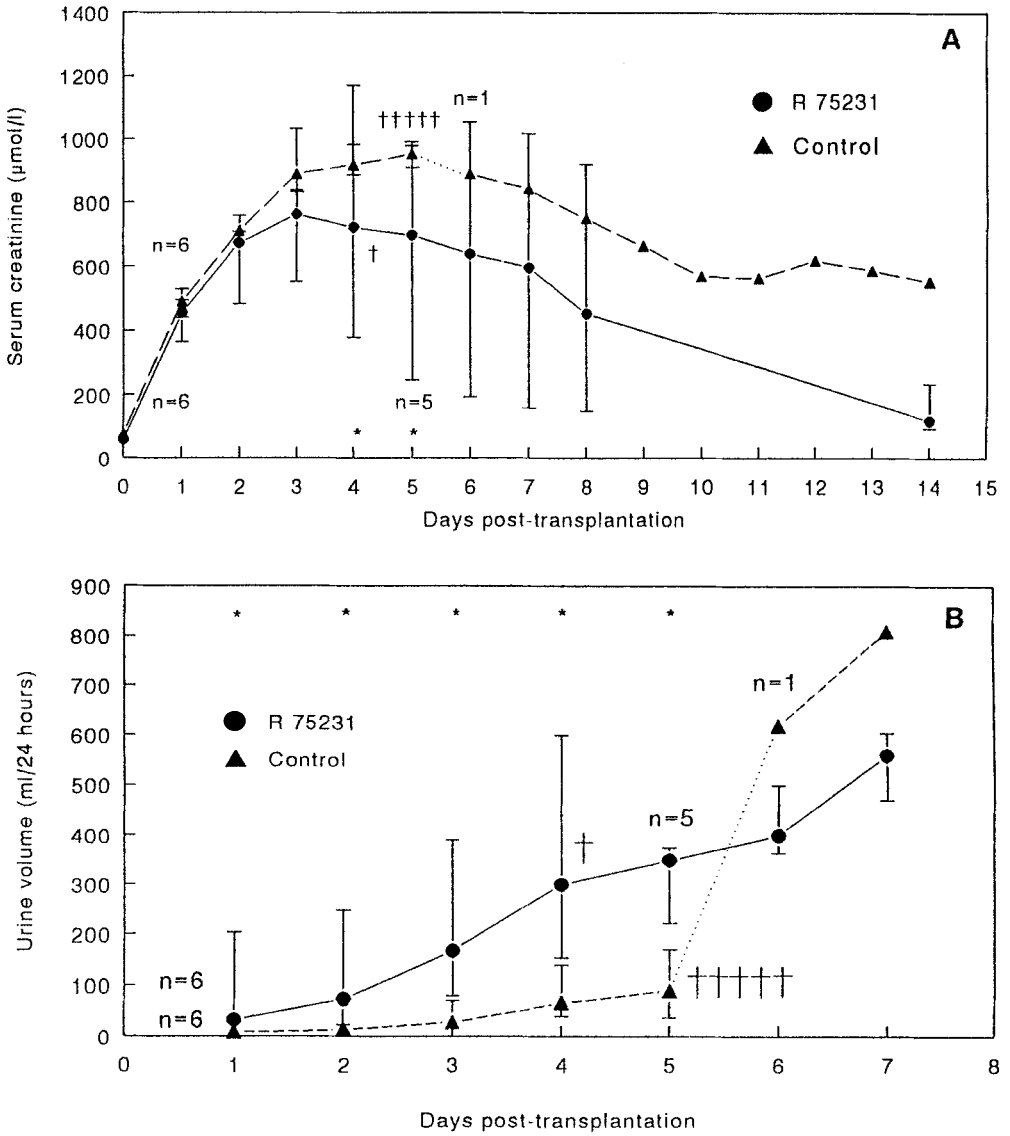


Fig. 1 A Daily serum creatinine values (µmol/l) during the first 14 days post-transplantation and **B** daily 24-h urine production (ml) during the first 7 days post-transplantation in both groups. Data are given as medians with interquartile ranges (25th and 75th percentiles). In the R 75231 group (•), a rapid return of renal function was observed. Serum creatinine values decreased from day 4 onward and returned to almost normal values at day 14 post-transplantation. Starting on day 1, the daily 24-h urine production was significantly higher in the R 75231 group than in the control group (▲). + refers to death of an animal. $*P < 0.05$ between the two groups

binding sites (angiotensin I or angiotensin II). At the end of the incubation periods, antibody-bound angiotensin I or angiotensin II were separated from unbound angiotensin I or angiotensin II using anti-sheep (donkey)-coated cellulose in suspension as the solid phase. Following a brief incubation and centrifugation, the unbound angiotensin I or angiotensin II was measured in a gamma counter. Using a standard curve, sample concentrations were expressed in pg/ml. The lower limit of detection was 1.1 fmol/tube for angiotensin I and 0.7 fmol/tube for angiotensin II. The intra-assay coefficient of variation was 7.3 % and interassay variation was 14.1 %. Plasma renin activity (ng/l per min) was measured by incubation of plasma at 37 °C and 0 °C for 2 h in the presence of renin substrate and was expressed as the formation of angiotensin I, measured by radioimmunoassay.

Post-transplant function and survival

Renal function was determined by measuring the daily serum creatinine concentration (in µmol/l) using a Dimension creatinine kit (DuPont de Nemours, Wilmington, MI, USA) and the daily 24-h urine production (in ml). Animals with life-sustaining function up to 14 days were considered to be survivors.

Data analysis

All values reported are medians with interquartile ranges (25th and 75th percentiles). Energy metabolite measurements are given in µmol/g dry weight of tissue. Total adenine nucleotide (TAN) levels were defined as the sum of ATP, ADP, and AMP. The total levels of degradation products (TDP) were determined by summing IMP, ADO, INO, HX, and X. For statistical analysis of differences between the two experimental groups, the non-parametric Kruskal-Wallistest was used. The level of significance was set at 5 %.

Table 1 Energy metabolites (μmol/g tissue dry weight) in renal cortical tissue before warm ischemia (0 min WI) and 1 h after reperfusion (60 min REP) in the control group and the R 75231 group. Median values with interquartile ranges (25th and 75th percentiles) are given (*TAN* total adenine nucleotides, *TDP* total level of degradation products, *ADO* adenosine, *INO* inosine, *HX* hypoxanthine, *X* xanthine)

	0 min WI		60 min REP	
	Control	R 75231	Control	R 75231
TAN	9.53 (7.63–11.96)	8.97 (8.11–9,69)	4.06 (3.40–4.65)	4.67 (4.16–5.52)
ATP	3.34 (2.40–5.58)	3.94 (2.84–3.92)	1.45 (1.13–1.78)	1.59 (1.35–1.93)
ADP	3.97 (2.88–4.43)	3.52 (3.26–3.90)	1.63 (1.37–1.73)	2.02 (1.69–2.26)
AMP	2.18 (2.00–2.45)	1.67 (1.49–2.37)	0.98 (0.79–1.23)	1.02 (0.86–1.20)
TDP	3.33 (2.76–4.37)	2.30 (1.76–3.02)	0.54 (0.36–1.22)	0.86 (0.43–1.45)
IMP	1.26 (1.15–1.53)	0.91 (0.65–1.23)	0.00 (0.00–0.27)	0.30 (0.09–0.43)
ADO	0.26 (0.00–0.82)	0.16 (0.00–0.64)	0.06 (0.00–0.23)	0.20 (0.05–0.50)
INO	0.53 (0.42–0.79)	0.43 (0.21–0.95)	0.09 (0.00–0.29)	0.05 (0.00–0.12)
HX	0.74 (0.00–0.83)	0.29 (0.00–0.76)	0.00 (0.00–0.26)	0.00 (0.00–0.36)
X	0.70 (0.00–0.79)	0.00 (0.00–0.75)	0.00 (0.00–0.63)	0.00 (0.00–0.52)

* $p < 0.05$ compared to control group

Results

Post-transplant renal function and survival

A clear difference in the survival rate between the two experimental groups was observed. One animal in the control group survived although the serum creatinine remained high (> 500 μmol/l) throughout the 14-day study period. The other five control dogs all died of renal insufficiency on postoperative day 5. In the R 75231 group, five dogs survived. One dog died on postoperative day 4 after renal artery thrombosis. Daily serum creatinine values up to 14 days post-transplantation and daily 24-h urine production up to 7 days post-transplantation in both groups are shown in Fig. 1.

Energy metabolites

Data are shown in Table 1. Except for a statistically significant higher level of IMP in the control group, tissue samples taken before induction of warm ischemia showed no differences in energy metabolite content between the two groups. After 60 min of reperfusion, TAN levels were 43% (control group) and 52% (R 75231 group) of preischemic values. This difference between the two groups was, however, not statistically significant. In the R 75231 group, the level of ADP was higher than that in the control group ($p < 0.05$). Both groups showed a marked decrease in TDP compared to the preischemia levels. Although the levels of ADO and INO were not statistically different between the two groups, an inversion of the preischemia adenosine/inosine ratio was observed in the R 75231 group after 60 min of reperfusion (0.4 before induction of warm ischemia versus 4.0 60 min after reperfusion). This phenomenon was not seen in the control group (0.5 preischemia versus 0.7 60 min after reperfusion).

Systemic side effects

Administration of R 75231 resulted in a slight decrease in mean arterial blood pressure and a concomitant increase in heart rate. Changes in both parameters were, however, not significantly different from corresponding measurements in the control group (Fig. 2).

Renin-angiotensin system

Data are shown in Fig. 3. In the control group, reperfusion of the graft resulted in a marked increase in renin, angiotensin I, and angiotensin II levels. Maximum values were measured in the first 2 h after reperfusion. In the R 75231 group, renin, angiotensin I, and angiotensin II levels were statistically significantly lower than the levels measured in the control group. In both experimental groups, all three parameters returned to normal values within 24 h after reperfusion.

Discussion

The renin-angiotensin system is considered to be an important mediator in the development of postischemic renal failure [2]. Following renal ischemia, renin release is stimulated as a compensatory response in order to preserve the glomerular filtration rate, urea excretion, and the ability to concentrate urine. Excessive stimulation of the system might, however, have an adverse effect on renal viability. Gravas et al. showed that intravenous administration of high doses of angioten-

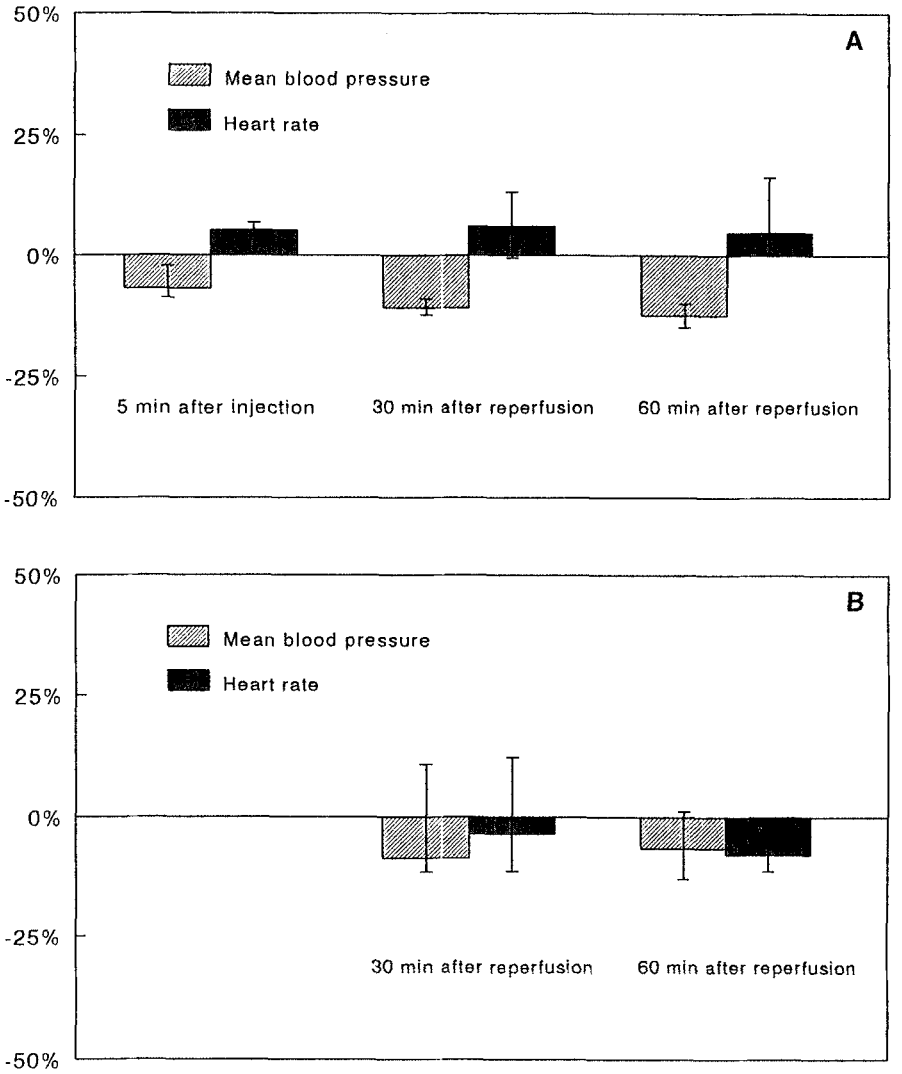
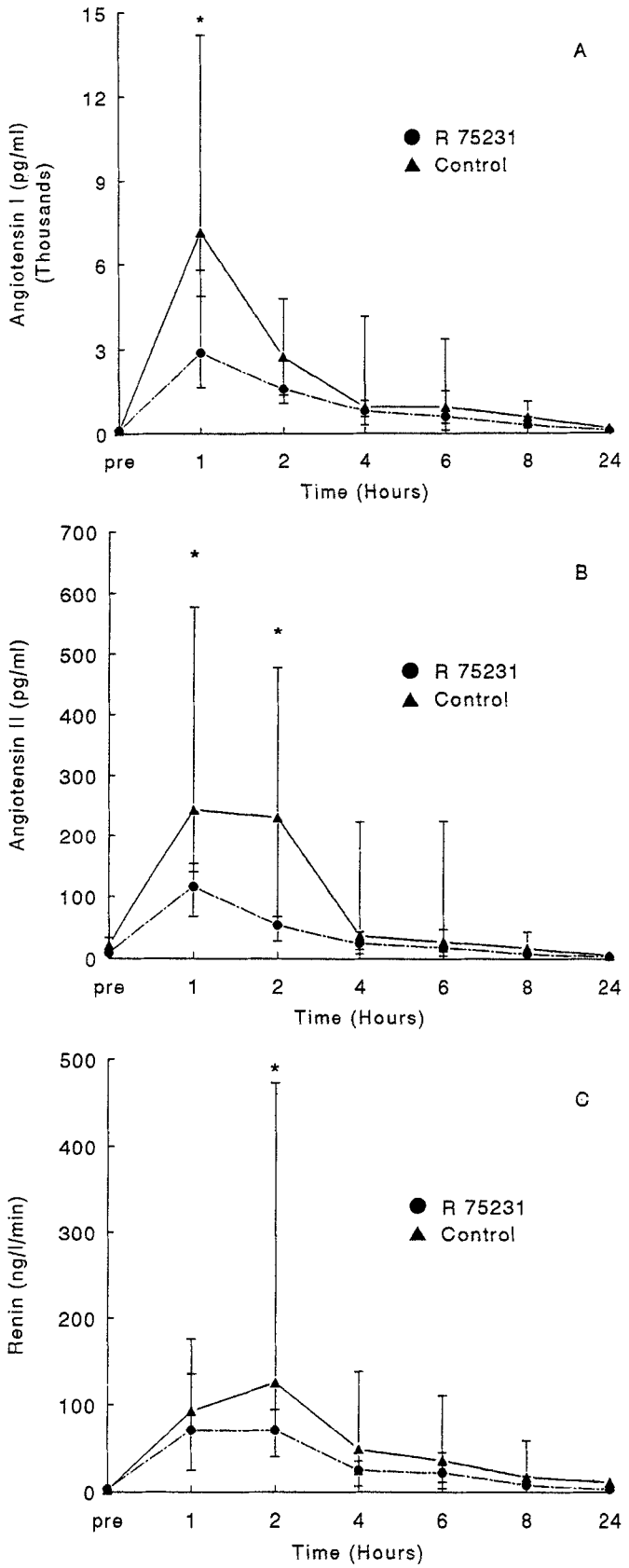


Fig. 2 A, B Percentile changes in mean arterial pressure (▨) and heart rate (■) measured 5 min after administration of R 75231 and subsequently 30 min and 60 min after reperfusion of the graft. Data are given as medians with interquartile ranges (25th and 75th percentiles). No significant changes in either parameter were observed **A** in the R 75231 group compared to the corresponding measurements **B** in the control group

sin II induced acute renal failure with the histological manifestations of ischemic tubular necrosis in rabbits [12]. Moreover, elevated plasma concentrations of renin and angiotensin were observed by several investigators in patients with acute renal failure [9, 20, 27]. The present study shows an excessive stimulation of the renin-angiotensin system immediately following transplantation of kidneys that have been subjected to prolonged warm ischemia. Maximum venous blood levels of renin, angiotensin I, and angiotensin II were observed in the first 2 h after reperfusion of the graft. Although the high levels of renin and angiotensin returned to normal values after 24 h of reperfusion, all except one dog in the untreated control group developed severe renal failure, resulting in death of the animals within 5 days post-transplantation.

Pretreatment with R 75231, administered 30 min and 10 min before reperfusion, successfully inhibited the excessive activation of the renin-angiotensin system in our model. Moreover, superior post-transplant renal function and survival was seen in the R 75231 group. The direct pharmacological effect of R 75231 is the inhibition of the active transport (transporter-mediated) of endogenous adenosine across the endothelial membranes [23]. Following tissue ischemia, nucleoside transport inhibition results in the accumulation of adenosine in the interstitial space. This adenosine can only be released slowly into the circulation, bypassing the endothelial cell layer, by paracellular passage. The net result is a continuous, prolonged action of adenosine in the early phase of reperfusion. Although the inversion of the preischemia adenosine/inosine ratio; measured in cortical tissue samples taken after reperfusion of the graft in the R 75231 group, indicates inhibition of the adenosine transport in our model, we did not observe an accumulation of adenosine in these samples. This discrepan-



cy probably results from the fact that the renal biopsies were taken 60 min after the start of reperfusion. By that time the major part of the adenosine pool might already have leaked out of the tissue and into the renal circulation. Pretransplant administration of R 75231 had no effect on the recovery of TAN during reperfusion, which makes it unlikely that adenosine was used to rebuild adenine nucleotides through the so-called salvage pathway [14]. Therefore, all protective effects of nucleoside transport inhibition in our model must be attributed to the physiological actions of adenosine itself, inhibition of renin release being one of them.

The use of exogenous adenosine as a therapeutic tool to prevent single organ ischemia-reperfusion damage is restricted, due to the extremely short half-life of adenosine and the risk of severe hemodynamic and cardiac side effects. No statistically significant systemic side effects of R 75231 administration were observed in our study. This suggests that the action of the endogenous adenosine was restricted to the local ischemic area.

Angiotensin II antagonists and angiotensin I converting enzyme inhibitors have been shown to lessen the severity of acute renal failure in both experimental and clinical models, including kidney transplantation [15, 16, 22]. It is, therefore, tempting to ascribe the superior post-transplant renal function and survival in the R 75231 group exclusively to the inhibition of the excessive renin release in our model. Other physiological actions of adenosine might, however, have played an important additional role. Theoretically, adenosine is well suited to counteract many of the deleterious factors that cause ischemia-reperfusion damage: it acts as a platelet aggregation inhibitor [19], modulates presynaptic release and postsynaptic actions of catecholamines [11, 25], and has a direct effect on renal vessel wall tension [26]. Moreover, adenosine is known to be a potent antagonist of leukocyte activation [10, 13]. Studies concerning the impact of these actions of adenosine on the development of ischemia-reperfusion injury as seen in grafted kidneys are currently being carried out in our department.

In conclusion, the administration of R 75231 before reperfusion has a protective effect on the post-transplant function of kidneys that have been subjected to prolonged warm ischemia. This effect may, at least in part, be ascribed to the inhibition of the breakdown

Fig. 3 A–C Venous blood levels of: **A** angiotensin I (pg/ml), **B** angiotensin II (pg/ml), and renin (ng/l per min) measured before induction of warm ischemia and subsequently 1, 2, 4, 6, 8 and 24 h after reperfusion of the graft. Data are given as medians with interquartile ranges (25th and 75th percentiles). In the R 75231 group (•), renin, angiotensin I, and angiotensin II levels were significantly lower than the corresponding levels measured in the control group (▲). * $p < 0.05$ between the two groups

and disposal of endogenous adenosine which, in turn, inhibits excessive stimulation of the renin-angiotensin system in the early phase of reperfusion.

Acknowledgements The authors would like to thank Dr. P.M.H. Schiffers, Laboratory of Clinical Pharmacology, University Hospital Maastricht, Maastricht, The Netherlands, for performing the renin, angiotensin I, and angiotensin II measurements and Prof. Dr. G.J. van der Vusse, Department of Physiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands, for performing the energy metabolite measurements.

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