

Effects of Ketamine and Its Isomers on Ischemic Preconditioning in the Isolated Rat Heart

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Background: Ischemic preconditioning protects the heart against subsequent ischemia. Opening of the adenosine triphosphate-sensitive potassium (K_{ATP}) channel is a key mechanism of preconditioning. Ketamine blocks K_{ATP} channels of isolated cardiomyocytes. The authors investigated the effects of ketamine and its stereoisomers on preconditioning.

Methods: Isolated rat hearts ($n = 80$) underwent 30 min of no-flow ischemia and 60 min of reperfusion. Two groups with eight hearts each underwent the protocol without intervention (control-1 and control-2), and, in eight hearts, preconditioning was elicited by two 5-min periods of ischemia before the 30 min ischemia. In the six treatment groups (each $n = 8$), ketamine, $R(-)$ - or $S(+)$ -ketamine were administered at concentrations of 2 or 20 $\mu\text{g/ml}$ before preconditioning. Eight hearts received 20 $\mu\text{g/ml}$ $R(-)$ -ketamine before ischemia. Left ventricular (LV) developed pressure and creatine kinase (CK) release during reperfusion were determined as variables of ventricular function and cellular injury.

Results: Baseline LV developed pressure was similar in all groups: 104 ± 28 mmHg (mean \pm SD). Controls showed a poor recovery of LV developed pressure ($17 \pm 8\%$ of baseline) and a high CK release (70 ± 17 IU/g). Ischemic preconditioning improved recovery of LV developed pressure ($46 \pm 14\%$) and reduced CK release (47 ± 17 IU/g, both $P < 0.05$ vs. control-1). Ketamine (2 $\mu\text{g/ml}$) and 2 or 20 $\mu\text{g/ml}$ $S(+)$ -ketamine had no influence on recovery of LV developed pressure compared with preconditioning (47 ± 18 , 43 ± 8 , $49 \pm 36\%$) and CK release (39 ± 8 , 30 ± 14 , 41 ± 25 IU/g). After administration of 20 $\mu\text{g/ml}$ ketamine and 2 or 20 $\mu\text{g/ml}$ $R(-)$ -ketamine, the protective effects of preconditioning were abolished (LV developed pressure-recovery, 16 ± 14 , 22 ± 21 , $18 \pm 11\%$; CK release, 67 ± 11 , 80 ± 21 , 82 ± 41 IU/g; each $P < 0.05$ vs. preconditioning). Preischemic treatment with $R(-)$ -ketamine had no effect on CK

release (74 ± 8 vs. 69 ± 9 IU/g in control-2, $P = 0.6$) and functional recovery (LV developed pressure 12 ± 4 vs. 9 ± 2 mmHg in control-2, $P = 0.5$).

Conclusion: Ketamine can block the cardioprotective effects of ischemic preconditioning. This effect is caused by the $R(-)$ -isomer.

REPEATED short periods of ischemia render the heart more resistant against a subsequent sustained ischemic period, a phenomenon known as ischemic preconditioning. The pronounced antiischemic effects provided by ischemic preconditioning have been shown by an improved postischemic functional recovery, by a reduction of myocardial infarct size, and of the incidence and severity of arrhythmias.¹ One key mechanism involved is the activation of the adenosine triphosphate-regulated potassium (K_{ATP}) channel²; pharmacologic opening of this channel can mimic ischemic preconditioning and reduce infarct size or improve functional recovery of ischemic-reperfused viable ("stunned") myocardium. In contrast, pharmacologic blockade of the K_{ATP} channel can antagonize the cardioprotective effects of ischemic preconditioning.³ Ketamine was recently reported to block the K_{ATP} channel in isolated cardiomyocytes at concentrations that may be clinically relevant.⁴ Therefore, it was suggested that ketamine may block the cardioprotective effects of ischemic preconditioning, presenting a potential hazard to a patient with coronary artery disease.⁴ The current investigation tested in isolated rat hearts the hypothesis that ketamine treatment before a preconditioning ischemia blocks the cardioprotective effects of ischemic preconditioning. It was also tested whether such an effect is stereospecific for the $R(-)$ - or $S(+)$ -isomer of ketamine.

Materials and Methods

The study was performed in accordance with the Guiding Principles in the Care and Use of Animals as approved by the Council of the American Physiologic Society and with the regulations of the German Law on the Protection of Animals.

Experimental Preparation

Hearts from male Wistar rats (body weight, 250–300 g), anesthetized with halothane, were quickly excised and mounted on a Langendorff perfusion system. Retrograde perfusion was initiated with an oxygenated modified Krebs-Henseleit buffer containing 116 mm NaCl,

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4.7 mM KCl, 1.1 mM MgSO₄, 1.17 mM KH₂PO₄, 24.9 mM NaHCO₃, 2.52 mM CaCl₂, 8.3 mM glucose, and 2.2 mM pyruvate; gassed with 95% O₂-5% CO₂. Flow in the system was controlled by a calibrated roller pump (Model 7518; Cole-Parmer Instruments, IL). After ligating both caval veins, the right ventricle was vented *via* the pulmonary artery with a catheter (1.2 mm OD). Heart rate was maintained at 350 beats/min by atrial pacing. The stimulation voltage was maintained at 20% above threshold (control, 2–4 V) and was continuously adjusted throughout the experiment (up to 12 V in reperfused hearts, if necessary). After completion of the experimental preparation, the heart at 37°C was placed in a water-jacketed chamber filled with humidified, warmed air. The hearts were perfused at a constant perfusion pressure of 80 mmHg throughout the perfusion period. During ischemia, the heart chamber was filled with normal saline to keep the heart temperature at 37°C and gassed with N₂ to prevent oxygen supply to the ischemic myocardium by diffusion. Ketamine, *R*(–) or *S*(+)-ketamine dissolved in Krebs-Henseleit buffer was infused into the perfusion system near the aortic cannula at 1/100 of total coronary flow in order to achieve final concentrations of 2 or 20 μg/ml, respectively, using a calibrated syringe pump (Model 5003; Precidior Infors, Basel, Switzerland).

Hemodynamic Measurements

For measurements of left ventricular (LV) pressure, a latex balloon (size No. 4, Hugo Sachs Elektronik, March, Germany) was introduced into the left ventricle *via* the cut mitral valve. The balloon was fixed at the tip of a stainless steel cannula (length, 5.9 cm), which was directly connected to a pressure transducer (Gould P23, Cleveland, OH). LV pressure, and-by electronic differentiation-the velocity of the change of LV pressure (dP/dt) were continuously monitored on an ink recorder (Mark 260; Gould). At the beginning of each experiment, the latex balloon was filled, air bubble-free, with the perfusion buffer to achieve an LV end-diastolic pressure (LVEDP) of 5 mmHg. This volume was then kept constant for the rest of the experiment. The LV pressure and coronary perfusion pressure signals were digitized at a sampling rate of 500 Hz using an analog-to-digital converter (Data Translation 2801, Marlboro, MA) and then further processed on a personal computer system. LV end-diastole was determined as the point when dP/dt started its rapid upstroke after crossing the zero line.⁵ LVEDP, LV developed pressure, and maximum and minimum dP/dt (dP/dt_{max} and dP/dt_{min}) were obtained from the digitized signals. Only hearts with a LV developed pressure higher than 80 mmHg during the initial control period were used for the study. Coronary flow was measured continuously with an ultrasonic flow-probe (T 208; Transonic Systems Inc., Ithaca, NY) and by weighting the coronary effluent at times indicated.

Metabolic Measurements

Aliquots from the perfusion medium and the coronary venous effluent perfusate were sampled anaerobically at times indicated. Samples were immediately processed for partial pressure of oxygen (P_{O₂}) measurements (ABL 30; Radiometer, Copenhagen, Denmark). Oxygen consumption (\dot{V}_{O_2}) was calculated according to the Fick principle with the use of the Bunsen absorption coefficient ($\alpha' = 0.036 \mu\text{l} \cdot \text{mmHg}^{-1} \cdot \text{ml}^{-1}$) at 37°C as follows:

$$\dot{V}_{O_2}(\mu\text{l}/\text{min}) = (P_{O_2a} - P_{O_2v})\alpha'CF$$

where P_{O₂a} is arterial P_{O₂}, P_{O₂v} is venous P_{O₂} (both in mmHg) and CF is coronary flow (in ml/min).

For determination of creatine kinase (CK) release, 1-min samples of the effluent were collected at the times indicated in table 2 (this table can be found in the Web Enhancements at www.anesthesiology.org) and after each preconditioning ischemia. For determination of the total CK release, the coronary venous effluent was collected during the reperfusion period. CK activity was measured using an "optimized standard method" according to the recommendations of the Deutsche Gesellschaft für Klinische Chemie (CK test, Boehringer, Mannheim, Germany).⁶ The values are expressed as IU/g wet weight.

Experimental Protocol

After mounting the heart on the Langendorff apparatus, a preparation and stabilization period of 20 min was allowed. The experimental protocol consisted of four phases: equilibration, intervention period, no-flow ischemia, and reperfusion (fig. 1). During the 20 min baseline period, two control measurements of all experimental variables were performed. The hearts were then randomized into eight groups. In the preconditioning group, ischemic preconditioning was induced during the intervention period by two 5-min periods of ischemia interspersed with 10 min of reperfusion. In the six treatment groups, ketamine or *R*(–)- or *S*(+)-ketamine in concentrations of 2 or 20 μg/ml were added for 5 min to the perfusate before ischemic preconditioning. The control group (control-1) underwent no treatment during this period. The hearts of all groups then underwent 30 min of no-flow ischemia followed by 60 min of reperfusion.

To test whether *R*(–)-ketamine may have itself any effect on myocardial ischemia in this experimental setting, *R*(–)-ketamine was administered to unpreconditioned hearts (n = 8) using a similar protocol; 20 μg/ml *R*(–)-ketamine was added to the perfusate directly before the long ischemia for two 5-min intervals, each followed by a 5-min washout period. A second control group (control-2, n = 8) underwent this protocol without treatment. This slightly different protocol was nec-

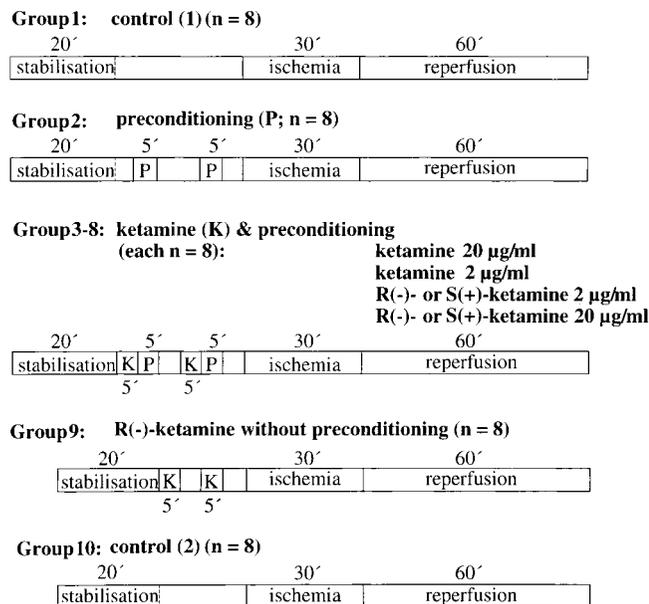


Fig. 1. Experimental protocol. All hearts were subjected to 30 min of ischemia followed by reperfusion. In the preconditioning group, ischemic preconditioning (PC) was induced by two 5-min periods of ischemia (P). In the six preconditioning and ketamine groups, preconditioning was preceded by 5-min infusions (K) of ketamine, R(-)-ketamine, or S(+)-ketamine, each at two different concentrations. In an additional group, R(-)-ketamine was administered to unpreconditioned hearts before the 30 min ischemia in two 5-min intervals, each followed by a 5-min washout period. This group was accompanied by a second control group (group 10) with the same preischemic time period.

essary to have similar washout times before ischemia, as in the preconditioning experiments. In these two groups, \dot{V}_{O_2} was not measured.

To test the effects of both concentrations of the substances on normal myocardium, ketamine or R(-)- or S(+)-ketamine was administered to 15 nonischemic hearts; after 30 min of baseline perfusion, three groups of five hearts each received one of the three substances for 5 min at either 2 or 20 µg/ml. After a 20-min washout period, the second concentration of the same substance was administered to each heart. The sequence of the two concentrations was randomized.

Data Analysis

Data are presented as mean and standard deviation (SD). To assess treatment (experimental groups) or time effects, a two-way analysis of variance was performed. Only if an overall significance for time effects was found, comparison was performed for each group using repeated measurements one-way analysis of variance followed by the Dunnett posttest. If an overall significance for group effects was found, we used one-way analysis of variance followed by the Dunnett test, with preconditioning as the reference group for further analysis. The effects of R(-)-ketamine on unpreconditioned hearts was compared with the respective control group using a

t test, and the effect of all substances on normal myocardium was assessed using a paired *t* test. All *t* tests were two-tailed and α was set at 0.05 in all statistical tests.

Results

A total of 111 hearts were used; 80 hearts for the ischemia-reperfusion experiments, 15 hearts for the test of the experimental substances on normal myocardium in this experimental model. Sixteen hearts were excluded because they did not fulfill the predefined quality criteria (LV developed pressure > 80 mmHg).

Effects of Ketamine, R(-)-Ketamine or S(+)-Ketamine on Normal Myocardium

The effect of the substances on normal myocardium are shown in table 1. Only the R(-)-isomer had a small negative inotropic effect at the high concentration (20 µg/ml) and reduced LV developed pressure to 90% ($P < 0.05$) and dP/dt to 92% ($P = 0.052$), whereas coronary flow remained unchanged. In all other cases, hemodynamics were not significantly changed during administration of ketamine, S(+)-ketamine and the low concentration of R(-)-ketamine ($P = 0.7-0.9$).

Hemodynamic Function during the Preischemic Period

Hemodynamic baseline conditions were not significantly different between the 10 groups (table 2, this table can be found in the Web Enhancements). The administration of ketamine or its isomers had no effect on ventricular function or oxygen consumption of the isolated hearts. After the preconditioning ischemia, ventricular function rapidly recovered within 5 min to baseline values.

End-diastolic Pressure during Ischemia-Reperfusion

In the isovolumic isolated heart preparation, LVEDP is an index of ventricular stiffness and myocardial contracture. During ischemia, LVEDP progressively increased in all groups (at the end of ischemia: control-1: 39 ± 4 mmHg; preconditioning: 39 ± 2 mmHg; preconditioning and ketamine 2 µg/ml: 36 ± 3 mmHg; preconditioning and ketamine 20 µg/ml: 43 ± 2 mmHg; preconditioning and S(+)-ketamine 2 µg/ml: 39 ± 3 mmHg; preconditioning and S(+)-ketamine 20 µg/ml: 42 ± 3 mmHg; preconditioning and R(-)-ketamine 2 µg/ml: 41 ± 2 mmHg; preconditioning and R(-)-ketamine 20 µg/ml: 42 ± 3 mmHg; R(-)-ketamine 20 µg/ml without preconditioning: 38 ± 4 mmHg; and control-2: 34 ± 8 mmHg), indicating the development of ischemic contracture.

With the onset of reperfusion, all groups showed a further increase of LVEDP to values between 70-102 mmHg (reperfusion contracture; table 2, this

Table 1. Effects of Ketamine and Its Isomers on Normal Myocardium

	Control	Ketamine (2 μ g/ml)	Control	Ketamine (20 μ g/ml)
LVDP (mmHg)	129 \pm 8	125 \pm 9	114 \pm 8	110 \pm 9
dP/dt _{max} (mmHg/s)	4,036 \pm 209	4,004 \pm 279	3,770 \pm 214	3,621 \pm 222
Coronary flow (ml/min)	13 \pm 0.7	13 \pm 0.8	12 \pm 0.4	12 \pm 0.5
	Control	S(+)-ketamine (2 μ g/ml)	Control	S(+)-ketamine (20 μ g/ml)
LVDP (mmHg)	99 \pm 6	96 \pm 5	113 \pm 9	110 \pm 9
dP/dt _{max} (mmHg/s)	3,101 \pm 152	3,172 \pm 123	3,777 \pm 291	3,640 \pm 324
Coronary flow (ml/min)	20 \pm 3.1	19 \pm 3.1	18 \pm 2	17 \pm 2.0
	Control	R(-)-ketamine (2 μ g/ml)	Control	R(-)-ketamine (20 μ g/ml)
LVDP (mmHg)	94 \pm 1	91 \pm 1	108 \pm 7	98 \pm 5*
dP/dt _{max} (mmHg/s)	3,259 \pm 190	3,040 \pm 174	3,609 \pm 215	3,391 \pm 255†
Coronary flow (ml/min)	16 \pm 0.6	15 \pm 0.8	13 \pm 0.9	13 \pm 0.8

Values are mean \pm SEM, n = 5 for each measurement.

* $P < 0.05$ versus control. † $P = 0.052$ versus control.

LVDP = left ventricular developed pressure; dP/dt_{max} = maximum velocity of the change in ventricular pressure.

table can be found in the Web Enhancements). Until the end of the reperfusion period, LVEDP recovered in all groups to values between 40–65 mmHg. There were no differences in the behavior of LVEDP between the groups.

Recovery of Contractile Function during Reperfusion

Figure 2 shows the recovery of LV developed pressure as a variable of contractile function. During baseline conditions, LV developed pressure was similar in all groups (between 95 \pm 10 and 120 \pm 18 mmHg). During reperfusion, recovery of LV developed pressure was very poor in the control-1 group, reaching only 17 \pm 8% of baseline values at 60 min of reperfusion. After ischemic preconditioning, recovery of LV developed pressure was markedly improved to 46 \pm 14% of baseline ($P < 0.05$ compared with control-1). In the groups pretreated with 2 μ g/ml ketamine or S(+)-ketamine in both concentrations, recovery of LV developed pressure was similar to the preconditioned hearts. In the hearts pretreated before preconditioning with 20 μ g/ml ketamine or R(-)-ketamine in both concentrations, functional recovery was comparable to the unpreconditioned control-1 and significantly lower than in the preconditioned hearts (each $P < 0.05$). In unpreconditioned hearts, preischemic treatment with R(-)-ketamine had no effect on the recovery of LV developed pressure (at 60 min of reperfusion: control-2, 9 \pm 2 mmHg vs. R(-)-ketamine 12 \pm 4 mmHg; $P = 0.53$). In all groups, the recovery of dP/dt_{max} as a variable of myocardial contractility was in parallel to the recovery of LV developed pressure (table 2, this table can be found in the Web enhancements).

Coronary Vascular Resistance during Reperfusion

Coronary flow (table 2, this table can be found in the Web Enhancements) is a direct measure of coronary

vascular resistance in this experimental model because perfusion pressure was kept constant. In all groups, coronary flow at 5 min of reperfusion was reduced to values between 57–69% of the initial baseline flow, indicating an increased vascular resistance. During the rest of the reperfusion period, coronary flow remained unchanged in all groups.

Creatine Kinase

Creatine kinase activity in the coronary venous effluent was determined as a variable of cellular injury (fig. 3). In the control group, CK release increased rapidly during the early reperfusion period with a peak value of 1.2 \pm 0.45 IU/min at 5 min of reperfusion. This initial peak CK release was attenuated in the preconditioned hearts (0.7 \pm 0.2) and after pretreatment with 2 μ g/ml ketamine (0.6 \pm 0.2) or S(+)-ketamine in both concentrations (0.4 \pm 0.2 and 0.6 \pm 0.3). With eight groups and five repeated measurements, these changes did not reach overall statistical significance. Total CK release (fig. 3) during reperfusion was reduced after ischemic preconditioning by 32% compared with controls. A similar reduction of total CK release was seen in the groups pretreated before preconditioning with 2 μ g/ml ketamine or S(+)-ketamine in both concentrations ($P < 0.05$ each). In the groups pretreated before preconditioning with 20 μ g/ml ketamine or R(-)-ketamine in both concentrations, total CK release was not different from unpreconditioned control-1 ($P = 0.99$ and 1.0, respectively). In unpreconditioned hearts, pretreatment with R(-)-ketamine had no effect on total CK release during reperfusion (control-2, 69 \pm 4 IU/g vs. R(-)-ketamine, 74 \pm 8 IU/g; $P = 0.59$).

Oxygen Consumption

During baseline conditions, $\dot{V}O_2$ was not different between groups (table 2, this table can be found in the

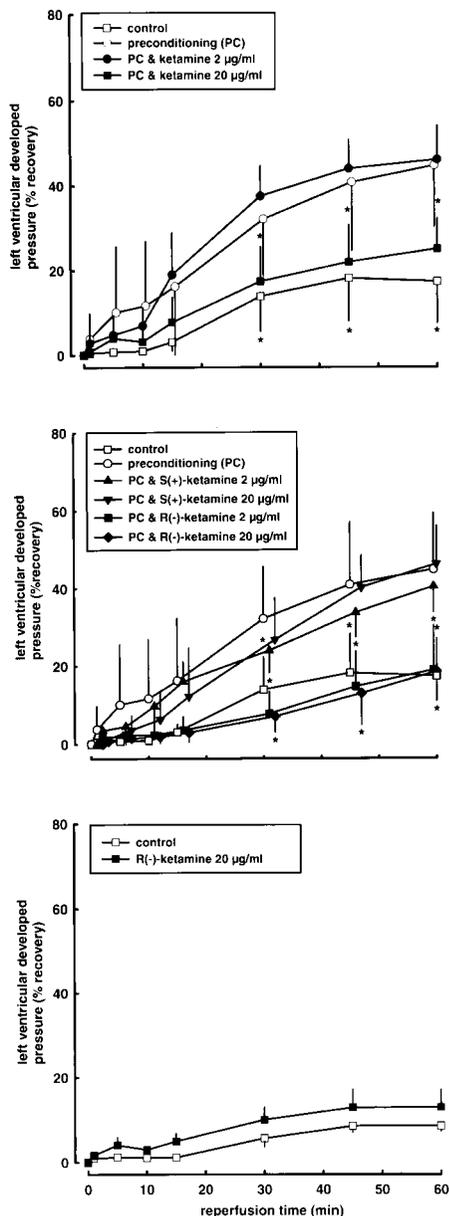


Fig. 2. Recovery of left ventricular developed pressure during reperfusion. Data are mean values and standard deviation, n = 8, *P < 0.05 versus preconditioning group.

Web Enhancements). With the onset of reperfusion, $\dot{V}O_2$ of the reperfused myocardium immediately recovered in all groups, despite the markedly reduced contractile state, and then slowly decreased during the reperfusion period. Although $\dot{V}O_2$ tended to be higher in the groups with a better functional recovery, these values only reached statistical significance in the group treated with 2 µg/ml S(+)-ketamine.

Discussion

The main finding of the current study was that ketamine can abolish the cardioprotective effects of isch-

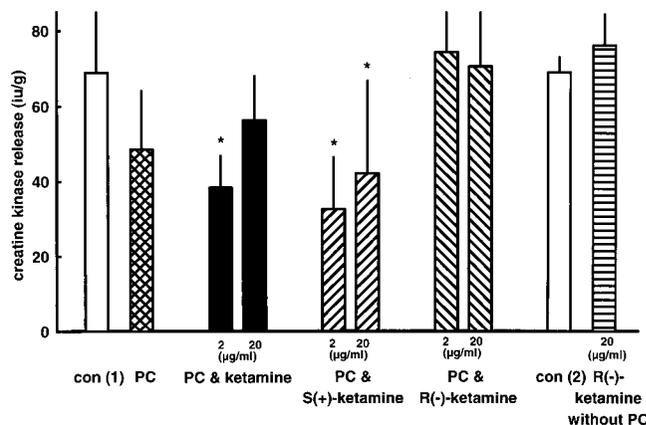


Fig. 3. Cumulative creatine kinase release during reperfusion as a variable of cellular damage. Data are mean values and standard deviation, n = 8; *P < 0.05 versus control group; PC = ischemic preconditioning.

emic preconditioning in isolated rat hearts *in vitro*. The effect is stereospecific for the R(-)-isomer.

The current study used an isolated buffer-perfused heart model. This experimental model has the advantage of excluding systemic and most humoral side effects of ketamine and was chosen to assess the direct myocardial effects of ketamine on ischemic preconditioning. Consequently, the effect of ketamine and its isomers *in vivo* may be different from what was observed in the current study.

In this study, preconditioning was induced by two 5-min cycles of ischemia before the prolonged ischemic period. The better functional recovery (LV developed pressure) of the preconditioned hearts in comparison with the control hearts shows the effectiveness of our preconditioning protocol in this experimental preparation.

The anesthetic potency of ketamine and its isomers is different, with S(+)-ketamine being twice as potent and R(-)-ketamine less potent as ketamine. In this study, we did not use “equianesthetic” doses, but the same concentrations of the three substances. However, we hypothesized that the blockade of ischemic preconditioning by ketamine is a receptor-mediated mechanism. Therefore, the absolute number of molecules available at the receptors should be relevant for the comparison of the three substances with regard to preconditioning and not the use of “equianesthetic” concentrations. The concentrations were in the same range, as they can be seen in patients, 1–3 min after intravenous bolus injection of 2 mg/kg body weight.⁷ Because ketamine is not significantly bound to plasma proteins,⁸ we did not correct for protein binding. *In vivo*, the situation may be different because differences in anesthetic depth may also have an influence on the severity of myocardial ischemia.

Ischemic preconditioning is a very powerful endoge-

nous protective mechanism against subsequent myocardial ischemia, which was seen in all species tested, including humans.⁹ Although the cellular mechanisms of preconditioning are complex and still not fully understood,^{10, 11} there is general agreement that the final step is most likely the activation of K_{ATP} channels.²

In the current study, ketamine abolished the cardioprotective effect of ischemic preconditioning in isolated rat hearts: hearts pretreated before the induction of preconditioning with 20 $\mu\text{g/ml}$ of ketamine had similar poor functional recovery and high release of creatine kinase as unpreconditioned controls. Pretreatment of unpreconditioned hearts with 20 $\mu\text{g/ml}$ of the $R(-)$ -isomer—the concentration that produced the greatest antagonistic effect on preconditioning—had no direct effect on ischemia-reperfusion injury. These findings confirm the study hypothesis that ketamine blocks ischemic preconditioning. This hypothesis was generated on the basis of a previous investigation.⁴ In that study, Ko *et al.*⁴ used inside-out and cell-attached configurations of patch clamp techniques with supraphysiologic adenosine triphosphate concentrations on isolated rat cardiomyocytes and measurements of action potential duration in isolated cat papillary muscles to assess the effects of ketamine (62.9 μM = 17.2 $\mu\text{g/ml}$) on the K_{ATP} channel. They found a concentration-dependent inhibition of K_{ATP} channel activity and an increase in action potential duration by ketamine. However, both techniques used in that study can only assess the function of the sarcolemmal K_{ATP} . More recent work suggested that not—as previously thought—the sarcolemmal but the mitochondrial K_{ATP} channel may be primarily responsible for the cardioprotection of ischemic preconditioning.¹² From the finding that ketamine blocks ischemic preconditioning, one might therefore speculate that the mitochondrial K_{ATP} channel may be also inhibited by ketamine.

In addition to a direct action on K_{ATP} channels, other effects of ketamine may interfere with ischemic preconditioning; ketamine can inhibit the catecholamine reuptake of myocardial tissue, resulting in an enhancement of intensity and duration of an adrenergic response.¹³ α -Adrenoceptor activation is a strong stimulus for the induction of myocardial preconditioning.¹⁴ However, this action of ketamine may not be relevant because it should enhance and not block the effect of ischemic preconditioning. In a recent study, Graf *et al.*¹⁵ found some evidence in isolated guinea pig hearts that the $S(+)$ -isomer leads to an increased availability of catecholamines. This finding explained the smaller negative inotropic effect of the $S(+)$ -isomer in isolated hearts found in their and also in our study. Similar effects have been reported in isolated human myocardium.¹⁶ We cannot rule out that an increased availability of catecholamines at the receptors may have contributed to the cardioprotection seen after ischemic preconditioning in the presence of $S(+)$ -ketamine. A negative inotro-

pic effect of the substances may *per se* limit the effectiveness of ischemic preconditioning by a reduction of the severity of the preconditioning ischemia. Negative inotropic effects of ketamine can be seen in most studies that used isolated preparations.^{15, 17} However, in the rat, ketamine may even have a positive inotropic effect that is independent of its effects on β adrenoceptors.¹⁸ In the current study, we used relatively lower concentrations of ketamine, and an effect on myocardial inotropy was only seen with the higher concentration of the $R(-)$ -isomer. Therefore, a contribution of an influence on myocardial inotropy to the effects of ketamine on ischemic preconditioning seems very unlikely.

Our results clearly show that the blockade of ischemic preconditioning by ketamine is a stereospecific phenomenon and is caused by the $R(-)$ -isomer. Although it is well-established that ketamine binds stereoselectively to receptors in the central nervous system, there is only little information regarding stereoselective effects in myocardial tissue. Graf *et al.*¹⁵ investigated the effect of ketamine and its stereoisomers in isolated guinea pig hearts. They found a lesser cardiac depression with the $S(+)$ -isomer compared with the $R(-)$ -isomer, racemic ketamine having an intermediate effect. However, previous depletion of myocardial catecholamine stores completely inhibited these differences. Thus, different effects of the stereoisomers on myocardial contractility are caused by an inhibition of catecholamine uptake by $S(+)$ -ketamine and not by a direct effect on the myocardium itself. These findings have been recently confirmed in isolated human myocardium.¹⁶ In isolated cardiac sodium channels, ketamine and the $R(-)$ -isomer reduced the peak sodium current, whereas $S(+)$ -ketamine had no influence on sodium channel behavior.¹⁹ Our findings provide further evidence that ketamine has a direct stereoselective effect at the myocardial level. Stereoselectivity is consistent with receptor-mediated pharmacologic mechanisms. Therefore, it is likely that the stereoselective effects of ketamine on myocardial preconditioning are also receptor mediated. The K_{ATP} channel that mediates ischemic preconditioning is linked to a sulfonylurea receptor subunit, which is the site of action of other blockers of ischemic preconditioning, such as glibenclamide.¹² The mechanism by which $R(-)$ -ketamine blocks the K_{ATP} channel is not known.

In conclusion, we found that ketamine stereoselectively blocked ischemic preconditioning in isolated rat hearts at concentrations as they occur during clinical ketamine anesthesia. However, *in vivo* the pathophysiology of preconditioning and ischemia-reperfusion injury becomes more complex, and the conclusions from this study should be restricted to the mechanism of the blockade of ischemic preconditioning by ketamine found *in vitro*.

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