

Late Preconditioning is Blocked by Racemic Ketamine, But Not by S(+)-Ketamine

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Racemic ketamine blocks K_{ATP} channels in isolated cells and abolishes short-term cardioprotection against prolonged ischemia. We investigated the effects of racemic ketamine and S(+)-ketamine on ischemic late preconditioning (LPC) in the rabbit heart *in vivo*. A coronary occluder was chronically implanted in 36 rabbits. After recovery, the rabbits divided into four groups (each $n = 9$). LPC was induced in conscious rabbits by a 5-min coronary occlusion. Twenty-four hours later, the animals were instrumented for measurement of left ventricular systolic pressure (LVSP, tip manometer), cardiac output (CO, ultrasonic flowprobe) and myocardial infarct size (triphenyltetrazolium staining). All rabbits were then subjected to 30-min coronary occlusion and 2 h reperfusion. Controls underwent the ischemia-reperfusion program without LPC. To test whether

racemic ketamine or S(+)-ketamine blocks the cardioprotection induced by LPC, the drugs (10 mg/kg) were given 10 min before the 30-min ischemia. Hemodynamic values were not significantly different between groups during the experiments (baseline: LVSP, 94 ± 3 mm Hg [mean $\pm$ SEM] and CO, 243 ± 9 mL/min; coronary occlusion: LVSP, $93\% \pm 4\%$ of baseline and CO, $84\% \pm 4\%$; after 2 h of reperfusion: LVSP, $85\% \pm 4\%$ and CO, $83\% \pm 4\%$). LPC reduced infarct size from $44\% \pm 3\%$ of the area at risk in controls to $22\% \pm 3\%$ ($P = 0.002$). Administration of racemic ketamine abolished the cardioprotective effects of LPC ($44 \pm 4\%$, $P = 0.002$). S(+)-ketamine did not affect the infarct size reduction induced by LPC ($26 \pm 6\%$, $P = 0.88$).

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Brief sublethal periods of myocardial ischemia enhance the tolerance of the myocardium to a period of sustained ischemia. This phenomenon was first described by Murry et al. (1) and is known as “ischemic preconditioning” (PC). PC has been reported in several mammalian species, including humans (2). The initial protective effect of classic or early preconditioning (EPC) is transient, disappearing 1–2 h after the preconditioning ischemia. It has been demonstrated that cardioprotection from PC reappears 24 h after the initial stimulus and lasts for approximately 48 h. Thus, there is a second endogenous cardioprotective mechanism that has been termed “late preconditioning” (LPC) or “second window of protection” (3). LPC may be important for patients with coronary artery disease and is thought to play a role in

the warm-up phenomenon (i.e., less angina with reexercise after a brief rest) and in mediating the beneficial effects of preinfarction angina (4).

Racemic ketamine was recently shown to block EPC in isolated rat hearts (5) and in rabbits *in vivo* (6). This effect was stereoselective for the R(-)-isomer, and most likely caused by a blockade of mitochondrial and/or sarcolemmal adenosine triphosphate (ATP)-regulated potassium (K_{ATP}) channels. However, the signal transduction pathway of LPC differs considerably from that of EPC and the effects of racemic ketamine on LPC have not been investigated. Ketamine may not only block the K_{ATP} channel, which is assumed to also be involved in the cardioprotection induced by LPC (7), but it may also interfere with earlier steps of the signal transduction cascade of LPC, e.g., by blocking nitric oxide (NO) synthase (8) and by inhibiting NF- κ B activity (9).

In patients at risk for myocardial infarction during the perioperative period, drugs known to block LPC should be used with caution, whereas those known to elicit EPC or LPC (e.g., opioids, isoflurane, sevoflurane) might even offer new therapeutic potential. The present study investigated the effect of a single bolus

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dose of racemic ketamine or S(+)-ketamine on LPC in chronically instrumented rabbits.

Methods

The present study conforms to the Guiding Principles in the Care and Use of Animals as approved by the Council of the American Physiologic Society and was approved by the local institutional Animal Care Committee.

After local anesthesia with lidocaine/prilocaine cream, a marginal ear vein was cannulated in 43 male New Zealand White rabbits weighing 2550–3150 g (mean, 2870 ± 29 g). The animals were anesthetized with IV xylazine 6 mg/kg, ketamine 6 mg/kg, and propofol 10 mg/kg. The trachea was intubated (tube 3.0 mm internal diameter), and the lungs were ventilated (Sulla 808; Dräger AG, Lübeck, Germany) with a frequency of 30–35/min and a tidal volume of 15–20 mL to maintain end-expiratory CO_2 at approximately 35 mm Hg (Datex Capnomac Ultima; Division of Instrumentarium, Helsinki, Finland). Anesthesia was maintained by inhaled isoflurane (2–4 vol%) and nitrous oxide (50 vol%). All surgical procedures were performed under sterile conditions, and IV antibiotic prophylaxis (cephazolin 35 mg/kg) was given. The chest was opened by a left thoracotomy in the fourth intercostal space, and a small incision was made in the pericardium. The left anterior descending coronary artery was encircled with two 5–0 prolene sutures with atraumatic needles (Ethicon 5/0, 1-metric, TF; Ethicon, Somerville, NJ). Care was taken to keep the distance between both sutures <1 mm. In general, the site of vessel encirclement was on the long axis of the left ventricle toward the apex, approximately one quarter of the distance from the atrioventricular groove to the left ventricular apex. A reinforced tube (2.5 mm internal diameter, Mallinckrodt Medical, Athlone, Ireland) was tunneled subcutaneously and externalized between the scapulae. The internal end was placed close to the sutures around the coronary artery and fixed at the pericardium. The two sutures were then externalized through this tube. Finally the tube was filled with Vaseline to prevent the development of a pneumothorax and fixed at the skin. The chest wound was then closed in layers and air aspirated from the thorax. Postoperative analgesia and antibiotic prophylaxis were provided by subcutaneous injection of piritramide 2 mg/kg and amoxicillin 15 mg/kg, respectively. The wound was covered by a vest (Rabbit jacket size M, Byron, Grand Island, NY) to protect the tube and the externalized sutures until the end of the experiments.

Rabbits were allowed to recover for 7–10 days. Then one pair of sutures was tightened for 5 min, thereby occluding the coronary artery. This was verified by the

immediate occurrence of ST segment increases in the electrocardiogram (ECG) (Siemens AG SC 9000, Siemens, Düsseldorf, Germany). At the end of the 5-min period of coronary artery occlusion, the suture was released and removed to ensure proper reperfusion, which was verified by the disappearance of the ECG changes within 5 min in every animal.

Twenty-four hours after the LPC protocol, animals were again anesthetized with IV propofol (10 mg/kg) followed by a continuous infusion of α -chloralose ($40 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). The trachea was intubated and the lungs were ventilated as described above. The experimental preparation has been described in detail previously (10). The rabbits were instrumented for measurement of aortic pressure (Statham transducer PD23; Gould, Cleveland, OH), left ventricular (LV) pressure (Millar tip catheter 5F, SPC-340; Millar, Houston, TX) and cardiac output (CO) minus coronary flow volume (4S ultrasonic flowprobe, T 208; Transonic Systems, Ithaca, NY). The remaining second suture around the coronary artery was dissected free and a plastic tube was placed around this suture for later coronary artery occlusion. Temperature was measured inside the pericardial cradle (GTH 1160 digital thermometer; Geisinger Electronic, Germany) and maintained between 38.3°C and 38.7°C by adjusting a heating pad and an infrared lamp.

The rabbits of all groups were then subjected to 30 min of coronary artery occlusion by tightening the snare. The effectiveness of this maneuver was verified by the appearance of epicardial cyanosis and changes in the surface ECG. Proper reperfusion was verified by the disappearance of ECG changes and by hyperemia over the surface of the previously ischemic-cyanotic segment. Ventricular fibrillation during coronary artery occlusion and reperfusion was treated by electrical defibrillation (5 J, DCS261 Defibrillator; Piekser, Ratingen, Germany).

After 2 h of reperfusion, the heart was arrested by injection of potassium chloride solution (16 mmol/L) into the left atrium, quickly excised, and mounted on a modified Langendorff apparatus. The size of the "area at risk" was then determined by Evans blue staining, which identifies the ischemic-reperfused, i.e., the nonischemic area, as unstained. The infarct size within the area at risk was determined by triphenyl-tetrazolium chloride staining. The procedure has been described in detail previously (10).

Rabbits were randomly assigned to one of the four groups (each $n = 9$), and all animals were subjected to 30 min of sustained ischemia followed by 120 min of reperfusion. Animals in the Control group underwent the ischemia-reperfusion procedure without LPC. In the LPC group, LPC was elicited in awake animals by one 5-min period of coronary artery occlusion 24 h before to the sustained ischemia. In the Ketamine groups, ketamine 10 mg/kg (LPC/Ketamine group)

or S(+)-ketamine 10 mg/kg (LPC/S(+)-Ketamine group) was given by IV bolus injection 10 min before the 30 min ischemia. Animals in the Control and the LPC groups received benzethoniumchloride 0.1 mg/kg, the vehicle of ketamine, at the corresponding time.

LV pressure, its first derivative dP/dt , aortic pressure, and CO were recorded continuously on an ink recorder (Recorder 2800; Gould, Cleveland, OH). The data were digitized using an analog-to-digital converter (Data Translation, Marlboro, MA) at a sampling rate of 500 Hz and processed later on a personal computer.

Global systolic function was measured in terms of LV systolic pressure (LVSP) and maximum rate of pressure increase (dP/dt_{max}). Global LV end-systole was defined as the point of minimum dP/dt (dP/dt_{min}), and LV end-diastole as the beginning of the sharp upslope of the LV dP/dt tracing. The time constant of decrease in LV isovolumic pressure (τ) was used as an index of LV diastolic function. Rate pressure product (RPP) was calculated from heart rate and LVSP, and systemic vascular resistance was calculated from mean aortic pressure and CO, assuming a right atrial pressure of 0 mm Hg in the open-chest preparation.

Statistical analysis was performed by two-way analysis of variance for time and treatment (Experimental group) effects. If an overall significance between groups was found, comparison was done for each time point using one-way analysis of variance followed by the Dunnett's *post hoc* test with the LPC group as the reference group. If an overall significance within a group (time effect) was found, one-way analysis of variance followed by the Dunnett's *post hoc* test with the baseline value as the reference time point was used for the assessment of time effects in that group. Changes were considered significant when the *P* value was <0.05 . Data are presented as mean $\pm$ SEM.

Results

Forty-three animals were used. Seven animals died from ventricular fibrillation during the preconditioning ischemia. In the remaining 36 animals, complete data sets were obtained. The hemodynamic variables are summarized in Figure 1 and Table 1. During baseline recordings, LVSP, CO, heart rate, and consequently, RPP, a major determinant of myocardial oxygen consumption, did not differ significantly among groups. Hemodynamic variables remained unchanged after administration of ketamine or S(+)-ketamine.

In all groups, coronary artery occlusion was accompanied by a reduction of LVSP ($7\% \pm 4\%$), dP/dt_{max} ($15\% \pm 5\%$) and CO ($16\% \pm 4\%$) (Table 1, Fig. 1). With regard to LV diastolic function, τ increased by a mean of $32\% \pm 6\%$ and LV end-diastolic pressure from 4 ± 1 mm Hg during baseline conditions to 9 ± 1 mm Hg

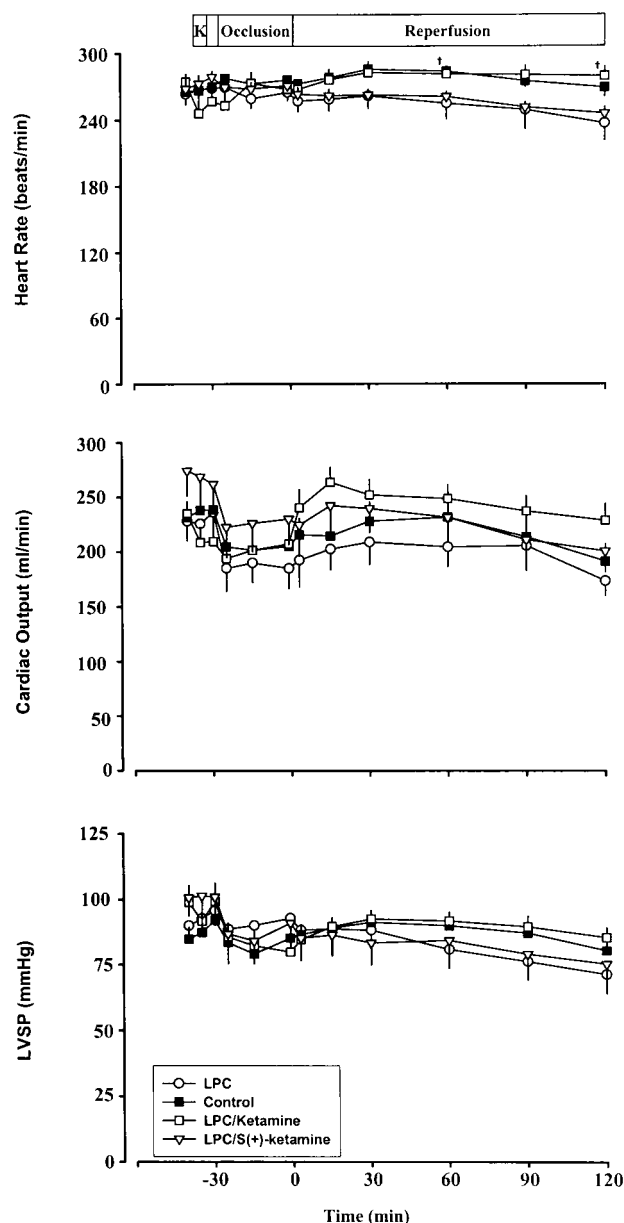


Figure 1. Line plot showing the time course of heart rate, cardiac output, and left ventricular systolic pressure (LVSP) during experiments in the late preconditioning (LPC), control, LPC/Ketamine, and LPC/S(+)-Ketamine group. Data are mean $\pm$ SEM, $n = 9$ in each group. K = ketamine or vehicle application. $\dagger P < 0.05$ compared with LPC group.

during coronary artery occlusion (all values at 25 min of coronary artery occlusion). RPP did not significantly differ among the groups during the 30-min period of coronary artery occlusion.

After 2 h of reperfusion, LVSP was reduced by $15\% \pm 4\%$ and dP/dt_{max} by $28\% \pm 5\%$ of baseline values in all groups, still reflecting an impaired myocardial contractile function. RPP was reduced by a mean of $16\% \pm 5\%$. Diastolic function also remained depressed during the reperfusion period; τ was prolonged by a

Table 1. Hemodynamic Variables

	Baseline	Intervention period		Occlusion		Reperfusion		
		Ket./Vehic.	10 min	5 min	25 min	5 min	30 min	120 min
LVEDP (mmHg)								
Control	3.3 ± 0.9	3.5 ± 0.9	4.0 ± 1.0	6.6 ± 1.4	8.7 ± 2.3	9.7 ± 2.2	7.6 ± 1.9	6.7 ± 2.0
LPC	4.8 ± 0.7	5.1 ± 0.9	5.4 ± 1.0	6.3 ± 1.9	9.2 ± 2.1	9.5 ± 1.8	8.1 ± 1.4	6.8 ± 1.8
LPC/Ketamine	4.7 ± 1.5	5.4 ± 1.4	5.4 ± 1.1	8.9 ± 1.9	9.4 ± 1.3	10.6 ± 1.5	10.1 ± 1.5	9.7 ± 1.6
LPC/S(+)-ketamine	3.3 ± 0.5	3.4 ± 0.5	3.5 ± 0.5	7.1 ± 1.1	9.6 ± 1.8	10.6 ± 2.4	7.9 ± 2.1	6.2 ± 1.7
dP/dtmax (mmHg/s)								
Control	3843 ± 419	4066 ± 413	4413 ± 386	3559 ± 185	3530 ± 237	2954 ± 276	3817 ± 297	2951 ± 352
LPC	3927 ± 401	4088 ± 409	4234 ± 400	3754 ± 422	3532 ± 388	3394 ± 395	3953 ± 451	2795 ± 413
LPC/Ketamine	4382 ± 633	3337 ± 562	3401 ± 466	3172 ± 386	3246 ± 523	3372 ± 411	3882 ± 311	3154 ± 253
LPC/S(+)-ketamine	4801 ± 502	4787 ± 676	4876 ± 702	3567 ± 631	3526 ± 556	2602 ± 318*	3191 ± 464	2762 ± 472
SVR (mmHg min l ⁻¹)								
Control	307 ± 24	311 ± 26	331 ± 28	355 ± 30	344 ± 31	318 ± 31	330 ± 22	326 ± 17
LPC	375 ± 31	387 ± 33	380 ± 27	464 ± 41	445 ± 40	437 ± 39	378 ± 25	341 ± 28
LPC/Ketamine	354 ± 25	386 ± 24	425 ± 29	403 ± 33	311 ± 29†	299 ± 16†	314 ± 18	317 ± 23
LPC/S(+)-ketamine	350 ± 36	356 ± 44	358 ± 40	355 ± 42	366 ± 33	316 ± 31†	302 ± 29	315 ± 38
RPP (mmHg min ⁻¹ 10 ³)								
Control	22.6 ± 1.2	23.3 ± 1.2	24.9 ± 1.2	23.3 ± 1.1	23.2 ± 1.1	23.4 ± 1.4	26.2 ± 1.4	21.9 ± 2.0
LPC	24.1 ± 2.3	25.2 ± 2.2	26.0 ± 2.1	24.2 ± 2.2	24.5 ± 2.6	23.5 ± 2.3	23.4 ± 2.5	17.3 ± 2.6
LPC/Ketamine	27.4 ± 2.2	22.7 ± 2.2	25.9 ± 2.8	21.8 ± 1.7	21.1 ± 2.3	23.3 ± 1.7	26.3 ± 1.5	24.1 ± 1.7
LPC/S(+)-ketamine	27.2 ± 2.2	27.7 ± 3.0	28.3 ± 3.2	23.5 ± 3.1	22.6 ± 2.8	22.1 ± 2.1	21.8 ± 2.1	18.8 ± 2.6
τ (ms)								
Control	14.1 ± 1.2	13.8 ± 1.0	13.8 ± 0.9	15.9 ± 1.1	16.3 ± 1.4	16.5 ± 1.6	14.4 ± 1.2	15.4 ± 1.6
LPC	15.1 ± 0.6	15.4 ± 0.8	15.1 ± 1.1	17.4 ± 1.1	18.9 ± 1.4	17.7 ± 1.6	17.0 ± 2.2	20.8 ± 2.8
LPC/Ketamine	14.6 ± 1.6	16.4 ± 1.4	16.2 ± 1.7	19.0 ± 2.2	19.7 ± 2.4	18.6 ± 2.4	16.8 ± 2.1	18.3 ± 2.3
LPC/S(+)-ketamine	12.6 ± 0.6	13.9 ± 0.9	13.1 ± 0.6	18.3 ± 1.2*	18.2 ± 1.2*	16.9 ± 1.2	16.4 ± 1.0	20.3 ± 3.3*

Data given as mean ± SEM; *n* = 9 in each group.

LPC = ischemic late preconditioning; LVEDP = left ventricular end-diastolic pressure; dP/dtmax = maximum rate of increase in left ventricular pressure; SVR = systemic vascular resistance; RPP = rate pressure product; τ = time constant of decrease in isovolumic left ventricular pressure. Ket./Vehic. = ketamine or vehicle administration.

* *P* < 0.05 compared with baseline; † *P* < 0.05 compared with LPC group.

mean of 34% ± 8% and LV end-diastolic pressure remained increased by a mean of 3 ± 1 mm Hg at the end of the experiment.

Mean LV dry weight was 0.74 ± 0.02 g with no significant differences among groups (data from individual groups are given in Table 2). The ischemic-reperfused area (area at risk) was 0.47 ± 0.03 g and constituted 62% ± 3% of the left ventricle with no significant differences among groups. LPC significantly reduced infarct size from 44% ± 3% of the area at risk in controls to 22% ± 3% (LPC; *P* = 0.002) (Fig. 2). Pretreatment with ketamine blocked LPC, as evidenced by an infarct size of 44% ± 3% in the LPC/Ketamine group (*P* = 0.002 vs LPC). In contrast, S(+)-ketamine had no effect on infarct size reduction induced by LPC (26% ± 6%; *P* = 0.88 vs LPC).

Discussion

The main finding of our study is that a single dose of ketamine blocks the cardioprotective effects of LPC in the rabbit heart *in vivo*, but that S(+)-ketamine does not. Thus, the influence of ketamine on LPC is most likely enantiomer specific.

Ketamine or S(+)-ketamine 10 mg/kg were administered by IV bolus injection 10 minutes before the sustained ischemia. The plasma levels of ketamine in the present study can be assumed to be in the same range as those achieved in patients after administration of 2 mg/kg of ketamine (11,12). We hypothesized that the inhibitory effect of ketamine and S(+)-ketamine on the signal transduction pathway of LPC is concentration dependent. Therefore, we did not use "equianesthetic" concentrations, but the same dose of both drugs to achieve identical plasma concentrations. The anesthetic potency of ketamine and S(+)-ketamine is different, and differences in anesthetic depth might have influenced the severity of myocardial ischemia. However, RPP and dP/dtmax as major determinants of myocardial oxygen consumption were similar in all groups during ischemia.

LPC was induced by one five-minute period of myocardial ischemia in awake animals to avoid the confounding effects of anesthesia and surgical trauma on the signal transduction cascade of LPC. Baxter et al. (13) reported that the threshold for eliciting LPC in this model is as low as one five-minute period of coronary artery occlusion.

Table 2. Weights and Area at Risk Size

	Control	LPC	LPC/Ketamine	LPC/S(+)-ketamine
Body weight (kg)	2848 ± 42	2905 ± 84	2874 ± 45	2847 ± 50
LV weight (g)	0.73 ± 0.04	0.71 ± 0.04	0.70 ± 0.02	0.81 ± 0.03
Area at risk (g)	0.44 ± 0.07	0.46 ± 0.06	0.43 ± 0.06	0.57 ± 0.08
Area at risk/LV (%)	57 ± 7	64 ± 6	61 ± 7	68 ± 8
Infarct size (g)	0.18 ± 0.03	0.10 ± 0.02	0.19 ± 0.03*	0.13 ± 0.02

Data given as mean ± SEM; n = 9 in each group.

LPC = ischemic late preconditioning; LV = left ventricle.

*P < 0.05 compared with LPC group.

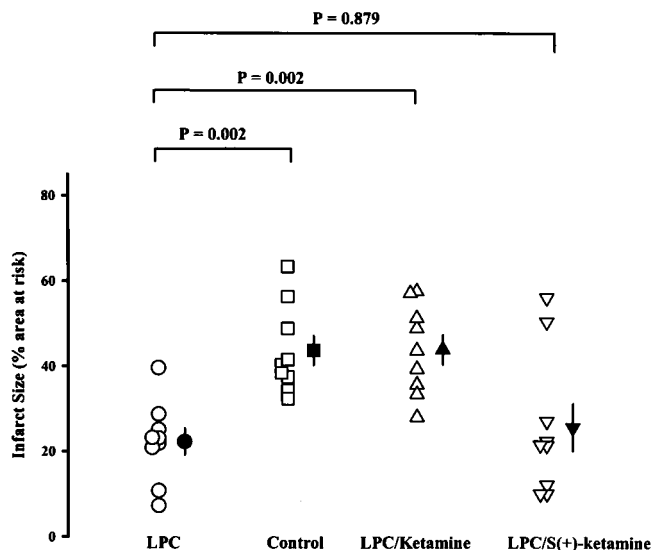


Figure 2. Infarct size as a percentage of the area at risk in the late preconditioning (LPC), control, LPC/Ketamine, and LPC/S(+)-Ketamine group. Open symbols = single data points, filled symbols = mean ± SEM, n = 9 in each group.

Although the signal transduction pathway of LPC is still not fully understood, the NO hypothesis proposed by Bolli et al. (3) is now well accepted. The preconditioning ischemia induces increased production of NO and reactive oxygen species that in turn activates a signal transduction cascade that involves protein kinase C, tyrosine kinases (and probably other kinases), and the transcription factor NF- κ B, thus resulting in increased transcription of the inducible NO-synthase gene. Increased NO production during the sustained ischemia activates K_{ATP} channels (14), thereby inducing cardioprotection by an unknown mechanism (15).

Ketamine may interfere with several parts of this signal transduction cascade. Ketamine inhibits NO synthase in lipopolysaccharide-treated alveolar macrophages (8) and decreases its activity in human leukocytes (16). Ketamine inhibits endotoxin-induced NF- κ B activity (9). Ketamine exerts a concentration dependent inhibitory effect on K_{ATP} channel activity in isolated cardiomyocytes (17). On the basis of these findings, we hypothesized that ketamine might block LPC. In fact, a single bolus dose of ketamine was

sufficient to block the protective effects of LPC in the rabbit heart *in vivo*. The stereoselective effects of the two optically active isomers on cardiac receptors (18) suggest that the blockade of LPC by ketamine may also be stereospecific. Indeed, administration of S(+)-ketamine before the 30-minute ischemia did not alter the protective effect of LPC *in vivo* as infarct size in this group was not different from the LPC group. The differences in infarct size were not caused by differences in area at risk sizes, temperature, or hemodynamic variables during ischemia and reperfusion.

On the basis of these findings, it is not possible to determine the exact site of action of ketamine on LPC. However, it seems unlikely that the inhibitory effect of ketamine on NO synthase and NF- κ B activity contributes to the blocking effect of ketamine on LPC, because proteins are already expressed 24 hours after the preconditioning ischemia (19) at the time when ketamine is given. Therefore, the later steps of the signal transduction are most likely involved in ketamine's effects on LPC. Ketamine blocks sarcolemmal K_{ATP} channels of isolated cells (17). Opening of mitochondrial and/or sarcolemmal K_{ATP} channels is involved in the cardioprotection induced by LPC (7,15), which can be blocked by ligands of a sulfonylurea-receptor of this channel (20). Thus, the K_{ATP} channel is most likely involved in the effects of ketamine on LPC. The stereoselectivity of this effect indicates a receptor-mediated mechanism, and as the sulfonylurea-receptor is the only receptor known to block K_{ATP} channels, it may be a possible target for R(-)-ketamine.

This is in accordance with a recent study from our laboratory, in which ketamine blocked the cardioprotective effects of EPC in isolated rat hearts (5). The improved functional recovery and reduced creatine kinase release seen in that model after EPC was blocked by a clinically relevant concentration of ketamine. The blockade was attributable to the R(-)-enantiomer, whereas S(+)-ketamine had no effect on EPC. These findings have also been confirmed in rabbit hearts *in vivo*, where EPC was elicited by one five-minute period of coronary artery occlusion followed by 10 minutes of reperfusion before the 30-minute period of myocardial ischemia (6). The present study now extends these findings to the clinically

more important situation of LPC. We did not test any effect of ketamine on infarct size in the absence of LPC. However, we can exclude the possibility that an increase of infarct size resulting from a proischemic effect of ketamine is counteracted by the cardioprotection induced by LPC because we have previously shown that administration of ketamine 10 mg/kg before ischemia had no effect on infarct size in the absence of a preconditioning stimulus (6).

The significant reduction in infarct size induced by LPC was not accompanied by a better functional recovery. Thus, we did not observe a protective effect of LPC against myocardial stunning in the reperfusion period of two hours as it was described by Bolli et al. (21). However, our result is in accordance with a study performed by Cohen et al. (22) in which the enhanced functional recovery as a result of infarct size reduction by LPC becomes apparent only one to three days later.

LPC is still a laboratory-based phenomenon that has not been conclusively documented in patients. However, there is some *in vitro* evidence of LPC in humans (2), and it appears that patients with prodromal angina before myocardial infarction, when rapidly reperfused, have a better postinfarction clinical outcome (4). It may, therefore, be of great practical interest to avoid the use of anesthetics that block this strongest endogenous cardioprotective mechanism against myocardial ischemia, especially during the perioperative period when patients are more prone to myocardial ischemia and infarction. In contrast to the negative effects of K_{ATP} channel blockade, it has been suggested that K_{ATP} agonists, including anesthetics such as isoflurane (23), sevoflurane (24), or opioids (25) may provide perioperative organ protection during cardiac surgery, vascular surgery, or neurosurgery. However, clinical evidence for the role of anesthetics in improving morbidity and mortality in patients at risk for ischemic or hypoxic injury is still lacking.

In summary, the present data indicate that a single bolus dose of ketamine blocks the cardioprotective effect of LPC *in vivo*, but S(+)-ketamine does not. Thus, the influence of ketamine on LPC is most likely enantiomer specific.

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