Effect of lidocaine on ischaemic preconditioning in isolated rat heart

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Background. Lidocaine is frequently used as an agent to treat ventricular arrhythmias associated with acute myocardial ischaemia. Lidocaine is a potent blocker not only of sodium channels, but also of ATP-sensitive potassium channels. The opening of these channels is a key mechanism of ischaemic preconditioning. We investigated the hypothesis that lidocaine blocks the cardioprotection induced by ischaemic preconditioning.

Methods. Isolated rat hearts (n=60) were subjected to 30 min of no-flow ischaemia and 60 min of reperfusion. Control hearts (CON) underwent no further intervention. Preconditioned hearts (PC) received two 5-min periods of ischaemia separated by 10 min of reflow before the 30 min ischaemia. In three groups, lidocaine was infused at concentrations of 2, 10 or 20 µg ml⁻¹ for 5 min before the preconditioning ischaemia. Left ventricular developed pressure (LVDP) and infarct size (IS) (triphenyltetrazolium chloride staining) were measured as variables of ventricular function and cellular injury, respectively.

Results. PC reduced IS from 24.8 (SEM 4.1) % to 4.0 (0.7) % of the area at risk (P<0.05). Adding 2 or 10 µg ml⁻¹ lidocaine had no effect on IS compared with PC alone (3.7 (0.7) %, 6.9 (1.8) %). Adding 20 µg ml⁻¹ lidocaine increased IS to 14.1 (2.5) % compared with PC (P<0.05). Baseline LVDP was similar in all groups (111.4 (2.1) mm Hg). Compared with CON, PC improved functional recovery (after 60 min of reperfusion; 52.3 (5.9) mm Hg vs 16.0 (4.0) mm Hg, P<0.01). The improved ventricular function was not influenced by addition of 2 or 10 µg ml⁻¹ lidocaine (47.3 (5.7) mm Hg, not significant; 45.3 (7.3) mm Hg, not significant), but was blocked by the infusion of 20 µg ml⁻¹ lidocaine (22.5 (8.0) mm Hg, P<0.01 vs PC).

Conclusions. Lidocaine blocks the cardioprotection induced by ischaemic preconditioning only at supratherapeutic concentrations.

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Brief periods of ischaemia have been shown to protect the heart against infarction produced by a subsequent long ischaemia. This manifestation of myocardial adaption is known as ischaemic preconditioning, and it leads not only to a limitation of necrosis, but also to a marked reduction in the severity of dysrhythmias and postischaemic contractile dysfunction. Various signalling pathways (G proteins, protein kinase C and phospholipase activation) and transmitters (bradykinin, endothelin or acetylcholine) are involved in the protective mechanism of preconditioning. It is known that ATP-sensitive potassium (K_ATP) channels play a key role in preconditioning, since it was found that K_ATP channel openers (such as cromakalin or bimakalin) mimic protection and that 5-hydroxydecanoate (5-HD), an ischaemia-selective K_ATP channel blocker, could abolish protection. K_ATP channels were first described on the sarcolemma of cardiac myocytes. The outward current of these channels might lead to shortening of the action potential, reduced calcium influx, preservation of ATP and reduced energy consumption during ischaemia. Another K_ATP channel is present at the mitochondrial inner membrane (mitoK_ATP). K_ATP channel openers which are selective for mitoK_ATP have strong cardioprotective properties, and activation of these channels produces myocardial preconditioning. Olschewski and colleagues found that lidocaine blocked the K_ATP channel of rat cardiomyocytes at the
therapeutic concentrations used for antiarrhythmic treatment. The action of lidocaine on these channels might block the beneficial effect of ischaemic preconditioning and thus could represent a potential risk for patients with coronary heart disease. This could help to explain why lidocaine prophylaxis increased the overall mortality among patients with myocardial infarction. Therefore we tested the hypothesis that lidocaine treatment before ischaemic preconditioning blocks this powerful endogenous defence system against myocardial injury.

Methods
The study was performed in accordance with the regulations of the German Animal Protection Law and local institutional regulations.

Experimental preparation
Male Wistar rats (body weight 350–400 g) were anaesthetized with S(+)-ketamine 250 mg kg$^{-1}$ i.p. The hearts were quickly excised and mounted on a Langendorff perfusion system. Retrograde perfusion via the aorta was initiated with an oxygenated modified Krebs–Henseleit solution containing (in mmol litre$^{-1}$) NaCl 116, KCl 4.7, MgSO$_4$ 1.1, KH$_2$PO$_4$ 1.17, NaHCO$_3$ 24.9, CaCl$_2$ 2.52, glucose 8.3 and pyruvate 2.2. The perfusion buffer was equilibrated with a gas mixture of 95% O$_2$–5% CO$_2$, which produced $P_{O_2}$ = 550–630 mmHg and pH 7.36–7.42 in the perfusion solution. The coronary perfusion pressure (CPP) was kept constant at 80 mm Hg. For measurements of left ventricular pressure (LVP), a latex balloon (size No. 5, Hugo Sachs Elektronik, March, Germany) was introduced into the left ventricle via the left atrium. The balloon was fixed at the tip of a stainless steel cannula which was directly connected to a pressure transducer (Gould P23, Cleveland, OH, USA). At the beginning of each experiment the balloon was filled with the perfusion buffer, free from air bubbles, to achieve a left ventricular end-diastolic pressure (LVEDP) of 5–10 mm Hg. The right ventricle was vented via the pulmonary artery with a Teflon catheter (OD 1.2 mm) for sampling of the coronary venous effluent. Heart rate was maintained at 380 beats min$^{-1}$ by right ventricular pacing (2V control, up to 12 V during reperfusion). After the experimental preparation, the heart was placed in a water-jacketed chamber filled with humidified warmed air. During ischaemia the chamber was filled with normal saline and gassed with nitrogen to prevent oxygen supply to the myocardium by diffusion. The myocardial temperature was kept constant at 38°C. Coronary flow (CF) was measured continuously using an ultrasonic flow probe (In-line-Flowprobe 2N, Transonic Systems Inc., Ithaca, NY) near the aortic cannula. A syringe pump (Model 5003, Precidior Infors, Basel, Switzerland) was used to infuse lidocaine into the perfusion system at a flow rate of CF/100 to achieve a final perfusate concentration of 2, 10 or 20 µg ml$^{-1}$.

Experimental protocol
After preparation, a stabilization period of 20 min was allowed before baseline measurements were performed. The hearts in all groups underwent 30 min of no-flow ischaemia followed by 60 min of reperfusion. The control group received no further treatment. In the preconditioning (PC) group, ischaemic preconditioning was induced by two 5-min periods of ischaemia interspersed with 10 min of reperfusion before 30 min of no-flow ischaemia. In three groups, lidocaine at concentrations of 2, 10 or 20 µg ml$^{-1}$ was added to the perfusate for 5 min before the preconditioning periods. This corresponds to concentrations in molar terms of 9, 43 or 86 µmol litre$^{-1}$. To test whether lidocaine itself had any effect on myocardial ischaemia in this experimental setting, it was administered at a concentration of 10 µg ml$^{-1}$ to unpreconditioned hearts using the same protocol. Figure 1 outlines the experimental protocol.

Measurement of infarct size
After experimentation, the hearts were frozen and cut into transverse slices 1 mm thick. The slices were stained in buffered 0.75% triphenyltetrazoliumchloride (TTC) solution and then incubated in 10% formalin to identify viable and necrotic tissue. The basal side of each slice was scanned and the infarcted area was determined by planimetry on a personal computer (SigmaScanPro, Image Analysis, Version 5.0, SPSS Inc., Richmond, CA).

Myocardial oxygen consumption
Aliquots of the perfusion medium and the coronary venous effluent were sampled anaerobically. Samples were immediately processed for $P_{O_2}$ measurements (ABL 30, Radiometer, Copenhagen, Denmark). Oxygen consumption ($V_{O_2}$) was calculated according to the Fick principle using the Bunsen absorption coefficient

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**Fig 1** Experimental protocol. After a stabilization period of 20 min (Stab.), all hearts were subjected to 30 min of ischaemia followed by 60 min of reperfusion. Ischaemic preconditioning (PC) was induced by two 5-min periods of ischaemia. In three groups, lidocaine (L) was administered in different concentrations for 5 min prior to the preconditioning ischaemia. In an additional group, lidocaine was administered to unpreconditioned hearts before the 30 min ischaemia in two 5-min intervals.
(α=0.036 μl mm Hg⁻¹ ml⁻¹) at 37°C:

$$\bar{V}O_2 (\mu l min^{-1}) = (P_{O_2} - P_{O_2} v) \alpha / CF$$

where $P_{O_2}$ is arterial $P_{O_2}$ (mm Hg), $P_{O_2} v$ is venous $P_{O_2}$ (mm Hg) and CF is coronary flow (ml min⁻¹).

**Data analysis and statistics**

LVP and CPP were continuously recorded on an ink recorder (Mark 260, Gould). Signals of LVP, its first derivative $dP/dt$, CPP and CF were digitized at a sampling rate of 500 Hz using an analogue-to-digital converter (Data Translation, Marlboro, MA) and further processed on a personal computer. Twenty sequential cardiac cycles were averaged to compensate for variations. Left ventricular developed pressure (LVDP) was calculated as a variable of myocardial contractility by subtracting LVEDP from the left ventricular (LV) systolic pressure. LV end-systole was defined as the point of minimum $dP/dt$ and LV end-diastole as the beginning of the sharp upslope of the $dP/dt$ tracing.

All data are expressed as mean (SEM). Statistical analysis was performed on infarct measurement using one-way analysis of variance (ANOVA). ANOVA for repeated measurements was used to test for differences in haemodynamics. Dunnett’s post hoc test with the PC group as a reference was used for further analysis. $P<0.05$ was regarded as significant.

**Results**

A total of 60 hearts were included in the statistical analysis (six groups of 10 hearts). Mean (SEM) heart wet weight was 1.1 (0.02) g and mean dry weight was 0.16 (0.003) g, and was similar in all groups.

**Haemodynamic function**

Haemodynamic variables are shown in Figure 2 and Table 1. Baseline LVDP was 111.4 (2.1) mm Hg, and was similar in all groups ($P=0.2–0.8$ vs PC). In the PC group, the two 5-min periods of ischaemia produced little effect on haemodynamic variables except for LVDP, which decreased from 108.4 (5.3) to 80.0 (4.4) mm Hg prior to the 30 min ischaemia ($P<0.05$ vs baseline). Lidocaine administration at all concentrations before ischaemic preconditioning had no influence on the LVDP reduction ($P=0.06–0.6$ vs PC).

During ischaemia, LVEDP increased in all groups, indicating the development of myocardial contracture (LVEDP peak value after 20 min ischaemia: control, 49 (7) mm Hg; PC, 38 (3) mm Hg; PC+lidocaine 2 μg ml⁻¹, 34 (5) mm Hg; PC+lidocaine 10 μg ml⁻¹, 42 (7) mm Hg; PC+lidocaine 20 μg ml⁻¹, 38 (7) mm Hg; lidocaine 10 μg ml⁻¹, 48 (6) mm Hg). With the onset of reperfusion, there was a further increase in LVEDP to values between 74 and 106 mm Hg (reperfusion contracture), which was significantly higher in unpreconditioned hearts compared with preconditioned hearts. After 60 min of reperfusion, LVEDP recovered to values of 37–63 mm Hg, and was lower in the PC group than in the other groups and significantly higher in the PC+lidocaine 20 μg ml⁻¹ and lidocaine 10 μg ml⁻¹ groups (Table 1).

LVDP recovered only slightly in the control group during the reperfusion period, reaching only 13 (3) % of baseline values at the end of the experiment in controls (Fig. 2). The preconditioning protocol resulted in an improved recovery of myocardial performance (LVDP 48 (5) % of baseline, $P<0.01$ vs control) after 60 min of reperfusion. In the groups pretreated with lidocaine 2 or 10 μg ml⁻¹ before preconditioning, recovery of LVDP was similar to that of the preconditioned hearts. Pretreatment with lidocaine 20 μg ml⁻¹ before preconditioning and lidocaine infusion to unpreconditioned hearts resulted in a functional recovery comparable with that of control hearts (21 (7) % and 17 (3) % of baseline values, respectively) (Fig. 2).

In all groups, the recovery of $dP/dt_{max}$ as a variable of myocardial contractility paralleled the recovery of LVDP. As a variable of diastolic function, $dP/dt_{min}$ changed similarly and recovery was improved by preconditioning (Table 1).

Coronary flow (Table 1) is a direct measure of coronary vascular resistance in this experimental model because perfusion pressure was kept constant. Infusion of lidocaine reduced coronary flow slightly in all groups (not statistically significant). Coronary flow was reduced in the control, PC+lidocaine 20 μg ml⁻¹ and lidocaine 10 μg ml⁻¹ groups during reperfusion (to 61 %, 71 % and 66 %, respectively, of the initial baseline flow at the end of reperfusion), indicating an increased vascular resistance. These differences did not reach statistical significance compared with the PC group.

**Myocardial oxygen consumption**

Under baseline conditions, there were no differences in $\bar{V}O_2$ between groups ($P>0.05$ vs preconditioning for all groups). With the onset of reperfusion, $\bar{V}O_2$ recovered in all groups.
Infarct size

Infarct size (Fig. 3), expressed as a percentage of the LV, was 24.8 (4.1) % in control hearts and was markedly reduced by preconditioning (4.0 (0.7) %, P<0.05). In the groups pretreated before preconditioning with lidocaine 2 or 10 μg ml⁻¹, infarct size was not different from preconditioning (P=1.0 and P=0.89, respectively). Pretreatment with lidocaine 20 μg ml⁻¹ before preconditioning increased infarct size to 14.1 (2.5) % compared with preconditioning (P=0.037). In unpreconditioned hearts, pretreatment with lidocaine had no effect on infarct size (27.1 (3.8) %) compared with controls.

**Discussion**

Lidocaine is often used for the treatment of ventricular arrhythmias. Although lidocaine clearly prevents the primary ventricular fibrillation that occurs during and shortly

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**Table 1** Haemodynamic variables during experiments. Data are mean (SEM), n=10 in each group. dP/dt max and dP/dt max peak positive and negative velocity of change of left ventricular pressure; VO₂, myocardial oxygen consumption; *P<0.05 vs baseline; †P<0.05 vs PC

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| LVEDP (mm Hg)     | Control   | PC           | PC+lidocaine| Control | PC | PC+lidocaine| PC+lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+lidocaine| Lidocaine| PC+li

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**Fig 3** Infarct size as a percentage of area at risk. Data are mean (SEM), n=10 in each group; *P<0.05 vs PC group. Lido, lidocaine.
after myocardial infarction, a significant effect on mortality could not be demonstrated. The results of a meta-analysis even suggested that prophylactic lidocaine administration might increase mortality due to pump failure or asystole.

Lidocaine is a potent blocker of sodium channels, but at concentrations of 10, 30, 100, 300 and 1000 μmol litre⁻¹ it also exerts blocking effects on K_ATP channels in rat cardiomyocytes. The half-maximum blocking concentration (IC₅₀=43 μmol litre⁻¹ or 10 μg ml⁻¹) corresponds to values reached by the application of lidocaine for the treatment of ventricular arrhythmias. Yoneda and colleagues reported a similar blocking effect on sarcolemmal K_ATP channels in Xenopus oocytes. The opening of K_ATP channels has been shown to be an important component of ischaemic preconditioning, which is the most potent mechanism of protection against myocardial ischaemia–reperfusion injury. This endogenous protective response has been demonstrated in several species including humans. Recent evidence reported by Pain and colleagues suggests that the mitochondrial K_ATP channel may not be the end effector of ischaemic preconditioning, but act as a trigger by generating oxygen-derived free radicals which activate intracellular kinases. We hypothesized that the K_ATP channel blocking properties of lidocaine might abolish the beneficial effect of ischaemic preconditioning. A blockade of this defence system by lidocaine may pose a risk to patients with coronary heart disease.

The main finding of the current study is that lidocaine at clinically relevant concentrations does not block the cardio-protective effects of ischaemic preconditioning. However, at a supratherapeutic concentration lidocaine abolished this protective effect. This suggests that lidocaine does not seem to be detrimental with regard to the maintenance of cardioprotection by ischaemic preconditioning.

Pretreatment of unpreconditioned hearts with lidocaine 10 μg ml⁻¹ resulted in similar infarct size and poor functional recovery to that in untreated controls. Therefore a direct effect of lidocaine 10 μg ml⁻¹ on ischaemia/reperfusion injury in this experimental setting can be excluded. It is often generalized that a decrease in the occurrence of arrhythmias translates into protection. However, this is not necessarily true, as supported by the present data demonstrating that the antiarrhythmic agent lidocaine (10 μg ml⁻¹) did not confer protection when administered alone. Modulation of the K_ATP channel during ischaemia represents a dilemma. It has been proposed that the inhibition of the K_ATP channel may contribute to the antiarrhythmic action noted for many drugs, including lidocaine, propafenone, amiodarone and verapamil, and thereby enhance cardiac electrical stability. On the other hand, this would antagonize the beneficial effect of reduced myocardial injury by ischaemic preconditioning.

Supratherapeutic concentrations of lidocaine may produce non-specific effects in the heart. Increased sodium channel blockade may affect cardioprotection. Blockade of these channels by lidocaine can reduce ischaemic sodium accumulation and sodium-dependent calcium loading. This would result in protection by a reduced activity of the energy-consuming Na⁺/K⁺-ATPase and reduced intracellular calcium overload. Lidocaine has a negative inotropic effect on the myocardium, which was also observed in a concentration-dependent manner in this study. Negative inotropy may reduce myocardial oxygen consumption and thereby ischaemic injury. Lidocaine can also cause direct contractile depression. This effect may only be relevant at higher lidocaine concentrations. In addition, lidocaine has been shown to protect the heart against ischaemic injury. However, treatment of unpreconditioned hearts with lidocaine had no effect on infarct size and functional recovery in the present study. The washout period before the 30 min ischaemia was long enough to exclude a possible anti-ischaemic effect of lidocaine, and a contribution of reduced myocardial contractile function to the effect on ischaemic preconditioning seems very unlikely.

Surprisingly, we observed a preservation of the cardioprotective effect of ischaemic preconditioning despite the administration of high concentrations of lidocaine over clinically relevant ranges, whereas lidocaine in supratherapeutic concentrations (20 μg ml⁻¹) had inhibitory effects on ischaemic preconditioning. Our hypothesis was based on the investigation by Olschewski and colleagues, who employed a patch–clamp technique on rat cardiomyocytes and found a concentration-dependent inhibition of the mean K_ATP channel current by lidocaine. This method can only assess action on the sarcolemmal K_ATP channel. One early hypothesis on the mechanism of ischaemic preconditioning was that opening of sarcolemmal K_ATP channels leads to a shortening of the action potential. This would result in a reduction in calcium overload during ischaemia and a decrease in cellular ATP consumption. However, it is now widely accepted that the K_ATP channel mediating cardioprotection is situated on the mitochondrial inner membrane. Therefore our results may indicate different activities of lidocaine on sarcolemmal and mitochondrial K_ATP channels. To explain this finding we might consider the presence of different K_ATP isoforms resulting in differential pharmacological properties of blocking agents on K_ATP channels. The molecular structure of the mitochondrial K_ATP channel is largely unknown. In contrast, sarcolemmal K_ATP channels are composed of four subunits (Kir6.1 or Kir6.2), forming an inward-rectifying K⁺ channel, and four sulfonylurea receptors (SUR1, SUR2A or SUR2B). Recent studies demonstrate that mitochondrial K_ATP channels resemble the Kir6.1/SUR1 isoform, while the Kir6.2/SUR2A isoform is located in the surface membrane of the cardiomyocytes. The existence of different K_ATP isoforms in the heart for sensitivity, conductance and regulation might explain why our findings regarding the two lower concentrations do not correspond to the results obtained in cardiomyocytes by Olschewski and coworkers.

The concentration-dependent action of lidocaine on mitochondrial K_ATP channels was also observed by Tsutsumi and colleagues. They found that lidocaine inhibits flavoprotein
fluorescence induced by diazoxide (a mitochondrial K$_{ATP}$ channel opener). A reduced flavoprotein fluorescence correlates with impaired mitochondrial oxidation and depolarization. Both are possible mechanisms for cardioprotection via reduced calcium influx and conservation of ATP during ischaemia. These findings suggest that lidocaine may attenuate the cardioprotective effect of mitochondrial K$_{ATP}$ channel opening. The IC$_{50}$ of lidocaine found in this study is 98 µmol litre$^{-1}$, which is more than twice as high as that obtained by Olschewski and colleagues$^7$ on sarcolemmal K$_{ATP}$ channels and is much higher than clinical concentrations. These observations are in line with our findings that cardioprotection is attenuated by infusion of 20 µg ml$^{-1}$ (86 µmol litre$^{-1}$) of lidocaine.

The present study used an isolated buffer perfused rat heart model. This experimental setting excludes systemic haemodynamic and most humoral effects of lidocaine, and was chosen to examine direct myocardial effects on ischaemic preconditioning. Consequently, the effects of lidocaine in vivo may be different from our in vitro results.

Different anaesthetics have differential actions on the K$_{ATP}$ channel.$^{27,28}$ Rats were anaesthetized with S(+)-ketamine because it has been shown that the S-enantiomer of ketamine does not effect ischaemic preconditioning.$^{29,30}$

Three different concentrations of lidocaine were used in this study. The highest concentration (20 µg ml$^{-1}$) has no clinical relevance. Therapeutic plasma concentrations are 1–5 µg ml$^{-1}$ after a single injection of 1 mg kg$^{-1}$, with 60–80% protein bound.$^{31}$ Peak plasma levels may exceed 30 µg ml$^{-1}$ but begin to fall into the therapeutic range after 2 min.$^{10}$ These values correspond to the previously described IC$_{50}$ of 10 µg ml$^{-1}$.7

In summary, lidocaine blocks cardioprotection produced in isolated rat hearts by ischaemic preconditioning only at supratherapeutic concentrations, as indicated by a preserved reduction of infarct size and improved functional recovery in the groups that received lidocaine at lower, but clinically relevant, concentrations.

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