

## Lidocaine reduces ischaemic but not reperfusion injury in isolated rat heart

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The local anaesthetic lidocaine protects the myocardium in ischaemia–reperfusion situations. It is not known if this is the consequence of an anti-ischaemic effect or an effect on reperfusion injury. Therefore, we investigated the effect of two concentrations of lidocaine on myocardial ischaemia–reperfusion injury and on reperfusion injury alone. We used an isolated rat heart model where heart rate, ventricular volume and coronary flow were kept constant. Hearts underwent 45 min of low-flow ischaemia followed by 90 min reperfusion. Two groups received lidocaine 1.7 or 17  $\mu\text{g ml}^{-1}$  starting 5 min before the onset of reperfusion. In two additional groups, lidocaine infusion started 5 min before low-flow ischaemia. In all groups, lidocaine administration was stopped after 15 min of reperfusion. One group served as an untreated control ( $n=11$  in each group). Left ventricular developed pressure (LVDP) and total creatine kinase release (CKR) were measured. Lidocaine administration during ischaemia and reperfusion led to an improved recovery of LVDP during reperfusion (1.7  $\mu\text{g ml}^{-1}$ , 54 (SEM 10) mm Hg; 17  $\mu\text{g ml}^{-1}$ , 71 (9) mm Hg at 30 min of reperfusion; both significantly different from control (21 (4) mm Hg) ( $P<0.05$ )) and a reduced CKR (1.7  $\mu\text{g ml}^{-1}$ , 79 (13) IU; 17  $\mu\text{g ml}^{-1}$ , 52 (8) IU at 30 min of reperfusion; both significantly different from control (130 (8) IU ( $P<0.05$ )). Lidocaine given during early reperfusion only, affected neither LVDP during reperfusion (1.7  $\mu\text{g ml}^{-1}$ , 19 (6) mm Hg ( $P=1.0$ ); 17  $\mu\text{g ml}^{-1}$ , 36 (8) mm Hg ( $P=0.46$ )) nor CKR (156 (21) IU ( $P=0.50$ ) and 106 (14) IU ( $P=0.57$ )). We conclude that lidocaine protects the myocardium against ischaemic but not against reperfusion injury in the isolated rat heart.

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Myocardial ischaemia can lead to cellular damage, not only during ischaemia itself, but also during subsequent reperfusion. Reperfusion injury can be reduced by modifying conditions of reperfusion.<sup>1</sup> One major aim of therapy for myocardial ischaemia is to limit infarct size by restoring coronary blood flow.<sup>2</sup> Several drugs reduce myocardial ischaemia–reperfusion injury further. When administering these drugs, it is important to know if they are protective only when given during ischaemia or if they are still protective when given after ischaemia during reperfusion. An example is the volatile anaesthetic halothane, which has greater protective effect against reperfusion injury than against ischaemic injury in isolated hearts.<sup>3</sup>

Lidocaine is often used as an anti-arrhythmic drug in ischaemia–reperfusion situations. Besides having anti-arrhythmic effects, lidocaine may protect myocardium not only against ischaemic but also against reperfusion injury by affecting intracellular concentrations of sodium<sup>4,5</sup> and calcium<sup>6,7</sup> during ischaemia and reperfusion, by protecting cellular membranes against long-chain acylcarnitines<sup>8</sup> and reactive oxygen species,<sup>9</sup> and perhaps by blocking calcium channels.<sup>10,11</sup> Lidocaine reduces myocardial ischaemia–reperfusion injury in isolated rat heart<sup>12–14</sup> and *in vivo* (in rabbit,<sup>15</sup> cat,<sup>16</sup> pig,<sup>17,18</sup> and dog<sup>19–22</sup>).

In all these studies, lidocaine administration started before or early during ischaemia. The question whether the cardioprotective effect of lidocaine is a consequence of

anti-ischaemic properties or whether lidocaine can reduce myocardial reperfusion injury could not be answered by these studies. The present study was designed to determine if lidocaine reduces ischaemic or reperfusion injury, or both.

We used an isolated rat heart model with 45 min of low-flow ischaemia and 90 min of reperfusion. A clinically relevant concentration of lidocaine and a 10-fold higher concentration were administered either during ischaemia and early reperfusion or during early reperfusion alone.

## Methods

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

Preparation of the isolated rat heart model used in this study has been described in detail previously.<sup>3</sup> In brief, isolated hearts from male Wistar rats were perfused in a Langendorff preparation with Krebs–Ringer solution at a constant flow rate of 14 ml min<sup>-1</sup>. Heart rate was maintained at 374 beats min<sup>-1</sup>. For measurement of left ventricular pressure (LVP), a latex balloon (size no. 5; 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 which was connected directly to a P23 pressure transducer (Gould, Cleveland, OH, USA). At the beginning of each experiment, the latex balloon was filled, air-bubble free, with Krebs–Henseleit buffer resulting in a left ventricular end-diastolic pressure (LVEDP) of 10–12 mm Hg, and the volume was kept constant throughout the experiment. Coronary perfusion pressure (CPP) was also measured using a Gould P23 pressure transducer. Aliquots from the perfusion medium and the coronary venous effluent perfusate were sampled and further processed in order to determine myocardial oxygen consumption and creatine kinase (CK) activity at different times during the experimental course, as markers of cellular damage. Total cumulative CK release was assessed by determining area under the curve.

## Experimental protocol

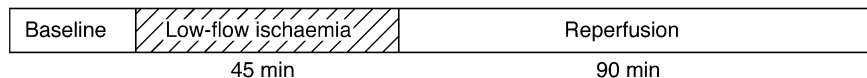
Figure 1 shows the experimental protocol used for the different groups. After preparation, a stabilization period of 20 min was allowed. Baseline measurements were then performed. Low-flow ischaemia was initiated by reducing coronary flow from 14 to 0.5 ml min<sup>-1</sup> and maintained for 45 min; 90 min of reperfusion (14 ml min<sup>-1</sup>) followed. Samples for measurement of CK activity were collected 5 min before low-flow ischaemia, immediately before low-flow ischaemia, after 20, 30 and 40 min of ischaemia, and 1, 3, 5, 10, 15, 20, 30, 45, 60 and 90 min after the onset of reperfusion.

Five groups ( $n=11$  in each) and two lidocaine concentrations (1.7 and 17 µg ml<sup>-1</sup>) were studied. To achieve lidocaine concentrations of 1.7 or 17 µg ml<sup>-1</sup> in the perfusate of lidocaine-treated hearts, a 100-fold higher concentration (0.17 or 1.7 mg ml<sup>-1</sup>) was infused with a hundredth of the total flow (Model 5003 infusion pump; Precidior Infors, Basel, Switzerland). In two groups, the two lidocaine concentrations were administered during the last 5 min of low-flow ischaemia and during the first 15 min of reperfusion. In two further groups, lidocaine infusion was started 5 min before low-flow ischaemia and stopped after 15 min of reperfusion. One group served as an untreated control.

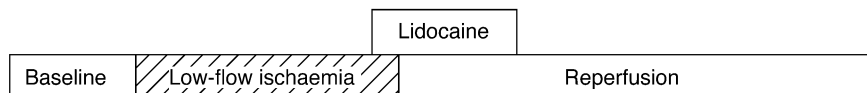
## Data analysis and statistics

LVP and CPP were continuously recorded on an ink recorder (Mark 260; Gould). The data were digitized using an analogue-to-digital converter (Data Translation, Marlboro, MA, USA) at a sampling rate of 500 Hz and processed on a personal computer. Twenty sequential cardiac cycles were averaged to compensate for variations. Left ventricular developed pressure (LVDP) as a variable of myocardial contractility was calculated by subtracting LVEDP from left ventricular systolic pressure. All data are expressed as mean (SEM).

### 1. Control



### 2. Lidocaine during early reperfusion, 1.7 or 17 µg ml<sup>-1</sup>



### 3. Lidocaine during ischaemia and early reperfusion, 1.7 or 17 µg ml<sup>-1</sup>



**Fig 1** Experimental protocol.

For haemodynamic variables and myocardial oxygen consumption, statistical analysis was performed using analysis of variance (ANOVA). If ANOVA showed a group effect, Dunnett's test was used as a *post hoc* test at each measurement time. To detect group differences in cumulative CK release, ANOVA and Dunnett's *post hoc* test were performed. In the groups that received lidocaine during ischaemia and reperfusion, the pre-ischaemic effect of lidocaine was assessed using Student's *t*-test for paired values. All statistical calculations were performed with the original data; *P*-values of <0.05 were regarded as significant.

## Results

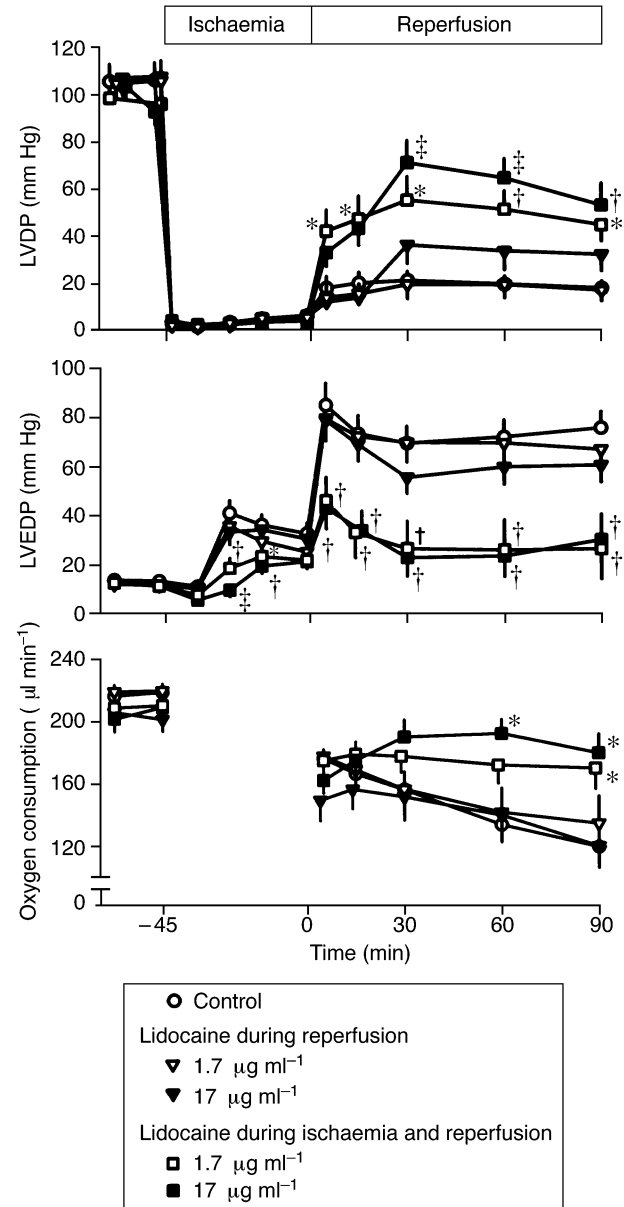
A total of 55 hearts, fulfilling predefined quality criteria (LVDP >80 mm Hg at CPP <100 mm Hg, and no ventricular fibrillation during the stabilization period), were included. CK samples for one heart in the control group were lost; all other data sets were complete. Heart weight was similar in all groups (1.14 (0.02) g, *P*=0.47–1.0 *vs* control).

### Haemodynamic function

Under baseline conditions, haemodynamic variables were similar in all groups. Figure 2 shows LVDP (top), LVEDP (middle) and oxygen consumption during the course of the experiment. Tables 1–3 show CPP and left ventricular  $dP/dt$ .

Administration of lidocaine  $1.7 \mu\text{g ml}^{-1}$  before ischaemia had no significant effect on any haemodynamic variable, while lidocaine  $17 \mu\text{g ml}^{-1}$  reduced LVDP and  $dP/dt_{\text{max}}$  by 11 (2)% (*P*<0.01) and increased  $dP/dt_{\text{min}}$  by 9 (1)% (*P*<0.05) and CPP by 19 (6)% (not statistically significant, *P*=0.17).

During low-flow ischaemia, LVDP was similarly reduced in all groups, to 4.2 (0.3)% of baseline (*P*<0.001 *vs* baseline). In the control group and the groups that received lidocaine only during early reperfusion, LVDP recovered only slightly during reperfusion (control, 19.7 (3.4)% of baseline;  $1.7 \mu\text{g ml}^{-1}$ , 18.2 (6.4)% of baseline;  $17 \mu\text{g ml}^{-1}$ , 31.7 (6.7) % of baseline; after 30 min of reperfusion). Recovery of LVDP in the groups receiving lidocaine during ischaemia and reperfusion was significantly improved ( $1.7 \mu\text{g ml}^{-1}$ , 60.3 (11.8)% of baseline, *P*=0.012;  $17 \mu\text{g ml}^{-1}$ , 69.6 (10.3)% of baseline, *P*<0.001 *vs* control; after 30 min reperfusion). LVEDP increased during low-flow ischaemia in the control group and the groups that received lidocaine only during reperfusion (control, 272 (34)% of baseline;  $1.7 \mu\text{g ml}^{-1}$ , 251 (23)% of baseline;  $17 \mu\text{g ml}^{-1}$ , 320 (55)% of baseline). This increase was smaller in the groups that had received lidocaine during ischaemia and reperfusion ( $1.7 \mu\text{g ml}^{-1}$ , 221 (44)% of baseline, *P*=0.001;  $17 \mu\text{g ml}^{-1}$ , 153 (26)% of baseline, *P*<0.001 *vs* control). During reperfusion, LVEDP in the groups that received lidocaine during ischaemia and early reperfusion was smaller than that in the control group (control, 528 (65)% of baseline; lidocaine during reperfusion:  $1.7 \mu\text{g ml}^{-1}$ , 605 (91)% of baseline,



**Fig 2** Left ventricular developed pressure (LVDP, top), left ventricular end-diastolic pressure (LVEDP, middle), and myocardial oxygen consumption (bottom) in the five groups. Low-flow ischaemia led to a marked reduction in LVDP and an increase in LVEDP. During reperfusion, LVDP recovered more in the groups that received lidocaine during ischaemia and early reperfusion. In these groups, myocardial oxygen consumption was also higher during reperfusion than in the control group. Data are mean (SEM). \**P*<0.05, †*P*<0.01, ‡*P*<0.001 *vs* control. *n*=11 in each group.

*P*=1.0;  $17 \mu\text{g ml}^{-1}$ , 505 (76)% of baseline, *P*=0.57; lidocaine during ischaemia and reperfusion:  $1.7 \mu\text{g ml}^{-1}$ , 194 (98)% of baseline, *P*=0.002;  $17 \mu\text{g ml}^{-1}$ , 180 (61)% of baseline, *P*<0.001 *vs* control; after 30 min reperfusion).

### Myocardial oxygen consumption

Myocardial oxygen consumption is shown in Figure 2 (bottom). After 90 min reperfusion, it was similar in the

**Table 1** Coronary perfusion pressure (CPP) during the experimental course. Data are mean (SEM).  $n=11$  in each group.  $*P<0.05$  vs control. Coronary flow was  $14 \text{ ml min}^{-1}$  during baseline and reperfusion, and  $0.5 \text{ ml min}^{-1}$  during ischaemia

	Control	Lidocaine during reperfusion		Lidocaine during ischaemia and reperfusion	
		$1.7 \mu\text{g ml}^{-1}$	$17 \mu\text{g ml}^{-1}$	$1.7 \mu\text{g ml}^{-1}$	$17 \mu\text{g ml}^{-1}$
Baseline					
0 min	77 (3)	80 (3)	78 (3)	72 (3)	75 (3)
5 min	80 (4)	81 (3)	81 (4)	76 (3)	90 (7)
Ischaemia					
10 min	9 (1)	10 (1)	8 (1)	10 (2)	9 (1)
20 min	13 (1)	13 (1)	13 (2)	13 (4)	8 (1)
30 min	14 (2)	14 (2)	14 (1)	14 (4)	11 (2)
44 min	13 (2)	14 (2)	15 (1)	14 (4)	12 (1)
Reperfusion					
5 min	100 (5)	106 (7)	100 (4)	85 (5)	85 (5)
15 min	113 (9)	123 (10)	118 (4)	91 (6)	104 (7)
30 min	124 (9)	144 (10)	115 (6)	98 (7)	101 (6)
45 min	140 (10)	161 (11)	128 (9)	105 (9)*	109 (8)
60 min	150 (9)	171 (11)	141 (11)	113 (10)*	117 (9)
90 min	162 (10)	184 (10)	153 (13)	122 (11)*	130 (9)

**Table 2** Left ventricular  $dP/dt_{\text{max}}$  during the experimental course. Data are mean (SEM).  $n=11$  in each group.  $*P<0.05$ ,  $\dagger P<0.01$  vs control;  $\ddagger P<0.05$  vs baseline

	Control	Lidocaine during reperfusion		Lidocaine during ischaemia and reperfusion	
		$1.7 \mu\text{g ml}^{-1}$	$17 \mu\text{g ml}^{-1}$	$1.7 \mu\text{g ml}^{-1}$	$17 \mu\text{g ml}^{-1}$
Baseline					
0 min	3965 (318)	3767 (204)	3877 (257)	3848 (212)	3923 (190)
5 min	3983 (323)	3808 (212)	3847 (222) $\ddagger$	3960 (209)	3447 (162)
Ischaemia					
10 min	738 (194)	439 (71)	807 (53)	1176 (285)	889 (88)
20 min	774 (182)	460 (61)	831 (56)	1213 (265)	896 (90)
30 min	804 (195)	528 (58)	837 (57)	1252 (259)	898 (86)
44 min	814 (180)	519 (70)	870 (53)	1254 (252)	922 (91)
Reperfusion					
5 min	1133 (190)	760 (142)	1020 (132)	2248 (431) $\dagger$	1573 (180)
10 min	1184 (192)	799 (124)	1027 (141)	2394 (468) $\dagger$	1691 (205)
15 min	1219 (194)	883 (125)	1066 (153)	2576 (509) $\dagger$	1925 (243)
30 min	1219 (187)	1048 (210)	1693 (258)	2919 (567) $\dagger$	3172 (380) $\dagger$
60 min	1204 (218)	991 (191)	1696 (286)	2747 (512) $\dagger$	2997 (341) $\dagger$
90 min	1084 (230)	902 (168)	1604 (253)	2585 (470) $\dagger$	2503 (403)*

control group and the groups that received lidocaine only during early reperfusion (control 54 (6)% of baseline;  $1.7 \mu\text{g ml}^{-1}$ , 61 (8),  $P=0.86$ ;  $17 \mu\text{g ml}^{-1}$ , 58 (7)% of baseline;  $P=1.0$  vs control). In the groups that received lidocaine during ischaemia and reperfusion, myocardial oxygen consumption was significantly higher at the end of the reperfusion period ( $1.7 \mu\text{g ml}^{-1}$ , 85 (5)% of baseline,  $P=0.049$ ;  $17 \mu\text{g ml}^{-1}$ , 85 (5)% of baseline,  $P=0.014$  vs control)

### Creatine kinase release

Figure 3 shows cumulative CK release as variable of cellular damage. Administration of lidocaine only during early reperfusion had no significant effect on CK release ( $1.7 \mu\text{g ml}^{-1}$ ,  $P=0.50$ ;  $17 \mu\text{g ml}^{-1}$ ,  $P=0.57$  vs control). Lidocaine during ischaemia and early reperfusion reduced CK release by 39.4% ( $1.7 \mu\text{g ml}^{-1}$ ,  $P=0.042$ ) and

60.2% ( $17 \mu\text{g ml}^{-1}$ ,  $P=0.001$ ) compared with the control group.

### Discussion

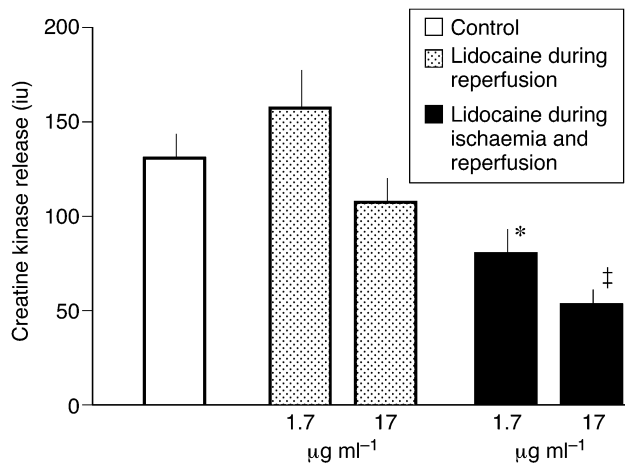
The cardioprotective effect of lidocaine in ischaemia–reperfusion situations has been demonstrated in several studies. The present study shows that cardioprotection by lidocaine is the consequence of an anti-ischaemic effect, but that lidocaine has no effect on reperfusion injury. Several mechanisms are discussed in the literature that may be responsible for this protective effect:

#### Reduction of intracellular sodium concentration

Myocardial ischaemia is accompanied by an increase in intracellular sodium concentration ( $[\text{Na}^+]_i$ ). Sodium influx

**Table 3** Left ventricular  $dP/dt_{\min}$  during the experimental course. Data are mean (SEM).  $n=11$  in each group. \* $P<0.05$ , † $P<0.01$ , ‡  $P<0.001$  vs control; § $P<0.01$  vs baseline

	Control	Lidocaine during reperfusion		Lidocaine during ischaemia and reperfusion	
		1.7 $\mu\text{g ml}^{-1}$	17 $\mu\text{g ml}^{-1}$	1.7 $\mu\text{g ml}^{-1}$	17 $\mu\text{g ml}^{-1}$
Baseline					
0 min	-3071 (264)	-2917 (150)	-2888 (163)	-2917 (174)	-2852 (129)
5 min	-3077 (252)	-2959 (152)	-2912 (140)	-2966 (184)	-2592 (143)§
Ischaemia					
5 min	-647 (153)	-427 (72)	-754 (21)	-989 (198)	-845 (47)
20 min	-641 (146)	-450 (69)	-758 (27)	-1028 (209)	-859 (59)
30 min	-664 (154)	-463 (67)	-769 (24)	-1023 (200)	-848 (49)
44 min	-682 (147)	-465 (71)	-790 (22)	-1048 (191)	-849 (44)
Reperfusion					
5 min	-993 (159)	-705 (119)	-926 (82)	-1737 (292)*	-1348 (137)
15 min	-1030 (156)	-845 (101)	-931 (85)	-1882 (322)†	-1552 (170)
30 min	-1000 (149)	-896 (147)	-1384 (144)	-2057 (348)†	-2150 (208)‡
60 min	-1002 (172)	-876 (129)	-1301 (143)	-1905 (300)†	-2046 (176)‡
90 min	-906 (175)	-798 (118)	-1255 (125)	-1841 (293)†	-1704 (215)*

**Fig 3** Cumulative creatine kinase release in the five groups. Lidocaine administered during ischaemia and early reperfusion reduced creatine kinase release. Lidocaine administration during reperfusion only had no effect on this marker of cellular damage. Data are mean (SEM). \* $P=0.042$ , ‡ $P=0.001$  vs control.  $n=10$  in control group;  $n=11$  in all other groups.

through sodium channels is an important route of hypoxic sodium loading,<sup>7,23</sup> and blockade of these channels by lidocaine can reduce and delay ischaemic sodium accumulation.<sup>45</sup> This may result in protection via two pathways. First, lidocaine leads to adenosine triphosphate preservation, probably as a consequence of a reduced activity of the energy-consuming  $\text{Na}^+/\text{K}^+$ -ATPase because of impaired sodium loading.<sup>4</sup> Second, the increase in  $[\text{Na}^+]_i$  is known to be closely connected to an increase in intracellular calcium via  $\text{Na}^+/\text{Ca}^{2+}$  exchange.<sup>24</sup> It has also been shown that lidocaine reduces ischaemic calcium loading.<sup>6,7</sup> Calcium overload is thought to be a major factor in reperfusion injury,<sup>25</sup> and lidocaine may reduce calcium overload by attenuating intracellular sodium overload.

### Lidocaine as a calcium channel blocker

Calcium channel blockers are known to reduce ischaemic injury and myocardial reperfusion injury.<sup>26,27</sup> There is evidence that lidocaine acts as a calcium channel blocker,<sup>10,11</sup> and this may be another way in which it reduces calcium overload.

### Protection of the cellular membrane

Destruction of the cellular membrane by reactive compounds generated during ischaemia and reperfusion is another important factor in ischaemia-reperfusion injury. Long-chain acylcarnitines participate in the production of ischaemia-reperfusion injury.<sup>28,29</sup> Oxygen free radicals generated particularly during the first few minutes of reperfusion play an important role in the development of reperfusion injury by attacking fatty acids, which lead to lipid peroxidation of the cellular membrane.<sup>2,30</sup> Lidocaine protects myocardium from long-chain acylcarnitine-induced mechanical and metabolic derangement,<sup>8</sup> and is a powerful antioxidant which can scavenge oxygen free radicals.<sup>9</sup>

### Negative inotropic effect of lidocaine

Negative inotropy may reduce myocardial oxygen consumption and, thereby, ischaemic injury. In addition, a complete or a partial contractile blockade at the onset of reperfusion can also reduce reperfusion injury.<sup>31,32</sup> These effects may only be relevant at higher concentrations of lidocaine at which it has negative inotropic effects.<sup>33</sup>

Calcium overload and the destruction of cellular membrane by reactive oxygen species play a role in the development not only of ischaemic injury but also of myocardial reperfusion injury. Together with the known effects of lidocaine, these findings indicate that the cardioprotection produced by lidocaine may at least in

part be caused by an effect on myocardial reperfusion injury.

In all studies showing cardioprotection by lidocaine against ischaemia–reperfusion injury, lidocaine was administered in a manner that did not allow effects on ischaemic injury to be distinguished from effects on reperfusion injury.<sup>12–22</sup> Therefore, it is unclear if late administration of lidocaine at the beginning of reperfusion can still be protective.

In the present study, lidocaine was administered at two concentrations during ischaemia and maintained during early reperfusion. In these two groups, functional recovery during reperfusion was improved (LVDP,  $dP/dt_{\max}$ ) accompanied by a smaller contracture (LVEDP) and a higher myocardial oxygen consumption, indicating a greater amount of viable myocardial tissue. CK release as a variable of cellular damage was reduced. These results demonstrate that lidocaine protects the myocardium from ischaemia–reperfusion injury in our model. The question of whether reduction of reperfusion injury contributes to this protective effect can be answered by looking at the two groups of our study which received lidocaine only during early reperfusion. While lidocaine administration during ischaemia and reperfusion was clearly cardioprotective, no protection was observed when lidocaine was given only during reperfusion: there was no improvement of functional recovery (LVDP,  $dP/dt_{\max}$ ), myocardial oxygen consumption was similar to that in the control group, myocardial contracture (LVEDP) was unchanged, and no reduction in cellular damage was detected (as assessed by CK release). In the group that received lidocaine at the higher concentration during reperfusion, there was a tendency to better functional recovery, lower contracture and reduced CK release. This effect was not statistically significant and occurred at a very high lidocaine concentration. However, if there is an effect of lidocaine at this high concentration on myocardial reperfusion injury, this effect is very small and of little clinical relevance.

Our study shows that lidocaine protects the isolated rat heart in an ischaemia–reperfusion situation, but reduction of reperfusion injury does not contribute to this protective effect. While lidocaine given during ischaemia with the resulting reduction in  $[Na^+]_i$  probably protected myocardium from ischaemic injury, the antioxidant effect of lidocaine, and its effect on intracellular calcium concentration—either indirect (by reduction of  $Na^+/Ca^{2+}$  exchange) or direct (by its possible calcium channel blocking properties)—were not sufficient to protect the hearts against reperfusion injury.

### Critique of methods

We used lidocaine at concentrations of 1.7 and 17  $\mu\text{g ml}^{-1}$ . Therapeutic plasma concentrations of lidocaine are approximately 1.5–5  $\text{mg l}^{-1}$ , while 60–80% of lidocaine is protein bound.<sup>34</sup> Therefore, the therapeutic free plasma concentra-

tion of lidocaine is not higher than 2  $\mu\text{g ml}^{-1}$  (range: 0.3–2  $\mu\text{g ml}^{-1}$ ); 1.7  $\mu\text{g ml}^{-1}$  lidocaine thus corresponds to high clinically achievable plasma concentrations, while the higher concentration of 17  $\mu\text{g ml}^{-1}$  is in the clinically toxic range. It could be argued that plasma-bound lidocaine in a blood-perfused model could still exert its antioxidant properties, but having studied a concentration of 17  $\mu\text{g ml}^{-1}$ , we can now exclude the possibility that this could have had an effect on reperfusion injury.

Lidocaine reduces neutrophil adherence *in vitro*<sup>35</sup> and *in vivo*.<sup>36</sup> It also reduces lysosomal enzyme release and superoxide anion production by these inflammatory cells.<sup>37</sup> A role for infiltrating leucocytes has been proposed in the development of reperfusion injury.<sup>38</sup> As we used cell-free saline perfusion, an effect of lidocaine on reperfusion injury in a blood-perfused heart cannot be completely excluded.

In summary, we found that lidocaine at a clinically relevant concentration (and a 10-fold higher concentration) protects the myocardium from ischaemic injury, but not from myocardial reperfusion injury. The known cardioprotective effects of lidocaine in ischaemia–reperfusion situations appear to be a consequence of anti-ischaemic properties only and not of reduction in myocardial reperfusion injury. Therefore, we suggest that post-ischaemic lidocaine treatment does not seem to be advantageous in terms of reduction of myocardial necrosis and improvement of recovery after ischaemia.

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