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Effect of propofol on reperfusion injury after regional ischaemia in the isolated rat heart

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Free oxygen radicals and intracellular calcium homeostasis play important roles in the development of myocardial reperfusion injury. Propofol is a radical scavenger with calcium channel blocking properties. We have investigated the effects of propofol on myocardial reperfusion injury. We used an isolated rat heart model where heart rate, ventricular volume and perfusion pressure were constant. The left anterior descending coronary artery (LAD) was occluded for 30 min and reperfused for 2 h. We studied an untreated control group, an Intralipid group (1 μl ml^{-1}) and a propofol group (Intralipid 1 μl ml^{-1} and propofol 1 μg ml^{-1}) (n=12 each). Drugs were infused for 20 min starting 5 min before reperfusion. We measured left ventricular developed pressure (LVDP), coronary flow and infarct size. LAD occlusion reduced mean LVDP from 129 (SEM 4) to 36 (3) mm Hg and mean coronary flow from 12.2 (0.3) to 5.2 (0.2) ml min^{-1}. During reperfusion, LVDP recovered to 98 (4) mm Hg and coronary flow to 11.9 (0.4) ml min^{-1}. Haemodynamic variables were similar in all groups. Propofol had no effect on infarct size compared with the Intralipid group (25.0 (3.7) *vs* 26.9 (3.3)% of the area at risk; P=0.89). Infarct size in the Intralipid group tended to be smaller compared with the control group (34.8 (3.2)%; P=0.19). We conclude that propofol, at a clinically relevant concentration, provided no protective effect against myocardial reperfusion injury in the rat heart *in vitro*.

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Reperfusion is the therapy of choice in myocardial ischaemia. The only effective means of limiting myocardial injury requires restoration of coronary blood flow to the ischaemic area.[1] However, reperfusion can initiate additional cell damage which limits the amount of potentially salvageable myocardium. This phenomenon is known as 'lethal reperfusion injury' and can be reduced by modification of the conditions of reperfusion.[2] Free oxygen radicals, generated particularly in the first few minutes of reperfusion, play an important role in the development of reperfusion injury.[1 3] Free oxygen radical scavenging drugs such as superoxide dismutase, given at the onset of reperfusion, can reduce myocardial infarct size.[4–6] Another important factor involved in the development of myocardial reperfusion injury is cellular calcium overload. With the re-supply of oxygen, disturbance in cytoplasmic calcium homeostasis contributes to the development of hypercontracture leading to disruption of the cytoskeleton and finally to cell death.[7] Propofol may interfere with the mechanisms of myocardial reperfusion injury. It is known as a free oxygen radical scavenger.[8] Propofol also inhibits calcium influx across plasma membranes[9–11] and it has been suggested that it acts as a calcium channel blocker.[12–14] The beneficial effects of calcium channel blockers on myocardial reperfusion injury are well established.[15 16]

Propofol is being used increasingly in cardiac anaesthesia[17] in which the heart is subjected to periods of ischaemia and reperfusion. Under these conditions, a cardioprotective effect of the anaesthetic may have some clinical relevance. Therefore, we have investigated if propofol, at clinically relevant concentrations, provides specific protection against lethal reperfusion injury. We used an isolated rat heart model so that extrinsic humoral and autonomic nervous system influences in addition to the effect of propofol on peripheral vascular tone could be excluded. Regional ischaemia was achieved by occlusion of the left anterior descending coronary artery. Propofol or its solvent Intralipid was administered during the last minutes of ischaemia and

the initial reperfusion period so that it was possible to investigate only the effects on reperfusion injury and not on ischaemic injury. Cellular lethal damage was assessed by measuring infarct size.

Material and methods

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

Experimental preparation

We excised hearts from male Wistar rats, weighing 300–350 g, anaesthetized with enflurane, and mounted on a Langendorff perfusion system. Retrograde perfusion was initiated with an oxygenated modified Krebs–Henseleit buffer containing (mmol litre^{-1}): NaCl 116, KCl 4.7, $MgSO_4$ 1.1, KH_2PO_4 1.17, $NaHCO_3$ 24.9, $CaCl_2$ 2.52, glucose 8.3 and pyruvate 2.0, and was gassed with 95% oxygen – 5% carbon dioxide, which produced a P_{O_2} of 80–100 kPa and a pH of 7.38–7.44. Perfusion pressure was maintained constant at 100 cm H_2O. The right ventricle was vented via the pulmonary artery with a Teflon catheter (1.2 mm od). In hearts used for the ischaemia–reperfusion experiments, the left anterior descending coronary artery (LAD) was encircled with a suture (6–0 Prolene, Ethicon, Norderstedt, Germany) for later occlusion. Heart rate was maintained at 370 beat min^{-1} by left ventricular pacing (2–6 V, 1 ms). Myocardial temperature was measured (GTH 1160, Geisinger-Elektronik, Germany) and kept constant at 38°C. 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 cut mitral valve. The balloon was fixed at the tip of a stainless steel cannula (length 5.9 cm) which was connected directly to a pressure transducer (Gould P23, Cleveland, OH, USA). At the beginning of each experiment, the Latex balloon was filled, air-bubble free, with Krebs–Henseleit buffer to achieve an end-diastolic left ventricular pressure of 8 mm Hg. Coronary flow was measured using an ultrasonic flow probe (In-Line-Flowprobe 2N, Transonic Systems Inc., Ithaca, NY, USA) placed in the perfusion system near the aortic cannula. The perfusing system consisted of glass, metal and Teflon only and therefore loss of infused substances in the system could be excluded.

Dose–effect experiments

Six hearts received different concentrations of propofol by infusing an emulsion of a commercial propofol preparation in an Intralipid–Krebs–Henseleit mixture using a perfusion pump (Model 5003, Precidior Infors, Basel, Switzerland). The infusion rate was set to one-hundredth of coronary flow to achieve propofol concentrations of 0.1, 0.5, 1, 2, 4, 6, 8 and 10 μg ml^{-1} together with 10% Intralipid 1 μl ml^{-1}. Immediately before starting each infusion, baseline measurements of haemodynamic variables (LVP, coronary flow) were performed. Five minutes after starting the infusion, measurements were repeated. Fifteen minutes was allowed between administration of each concentration to allow haemodynamic variables to recover to baseline.

In five additional hearts, different doses of Intralipid were infused in the same manner to achieve concentrations of 0.1, 1, 5 and 10 μl ml^{-1}.

Ischaemia–reperfusion experiments

Three groups (n=12 each) were studied: propofol, Intralipid and control groups. After preparation, a stabilization period of 20 min was allowed. Baseline measurements were then performed. To initiate regional ischaemia, the LAD was occluded by tightening the Prolene suture over 5 mm of vinyl tubing (1 mm od). After 30 min of regional ischaemia, LAD occlusion was released, followed by 2 h of reperfusion. In the propofol group, a mixture containing propofol 0.1 mg and Intralipid 0.1 ml per millilitre of Krebs–Henseleit buffer was infused during the last 5 min of regional ischaemia and the first 15 min of reperfusion. The infusion rate was one-hundredth of coronary flow to achieve a final perfusate concentration of propofol 1 μg ml^{-1} and Intralipid 1 μl ml^{-1}. In the Intralipid group, only Intralipid 0.1 ml per millilitre of Krebs–Henseleit was given with the same infusion rate. The control group was untreated.

Myocardial oxygen consumption

Aliquots from the perfusion medium and the coronary venous effluent perfusate were sampled anaerobically. Samples were processed immediately for P_{O_2} measurements (ABL 30, Radiometer, Copenhagen, Denmark). Oxygen consumption ($\dot{V}_{O_2}$) was calculated according to Fick's principle with the use of Bunsen's absorption coefficient (α'= 0.036 μl×mm Hg^{-1} ×ml^{-1}) at 37°C as follows:

$$\dot{V}_{O_2}(\mu l\ min^{-1}) = (Pa_{O_2} - Pv_{O_2})\ \alpha'\ CF$$

where Pa_{O_2}= arterial P_{O_2} (kPa), Pv_{O_2}=venous P_{O_2} (kPa) and CF=coronary flow (ml min^{-1}).

Measurement of infarct size

After 2 h of reperfusion, the hearts were arrested in diastole by perfusion with a cardioplegic solution. The LAD was then re-occluded and the hearts perfused with 0.2% Evans blue and 1% dextran in normal saline. This treatment identifies the area at risk as unstained. The hearts were then frozen and cut into transverse slices of 1 mm thickness. The slides were stained in buffered 0.75% triphenyltetrazolium chloride solution (TTC) and incubated in 10% formalin to identify viable and necrotic tissue within the area at risk. The basal side of each slice was scanned (StudioScan IIsi, AGFA, Leverkusen, Germany) and the area at risk in addition to the infarcted area were determined by planimetry on a personal computer.

Data analysis and statistics

LVP, its first derivative dP/dt and coronary flow were recorded continuously on an ink recorder (Mark 260, Gould,

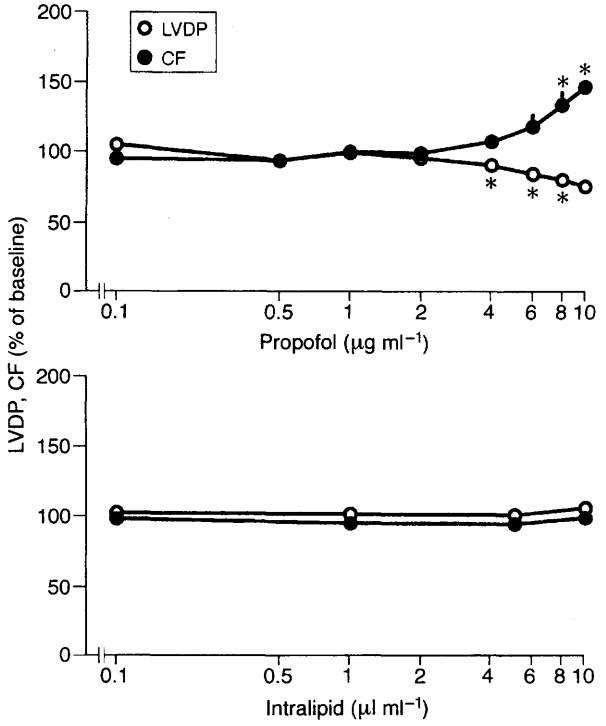

Fig 1 Effect of propofol with Intralipid 1 μl ml^{-1} (top) and Intralipid alone (bottom) at different concentrations on left ventricular developed pressure (LVDP) and coronary flow (CF) in normal myocardium (mean (SEM)). *$P<0.05$ compared with baseline values.

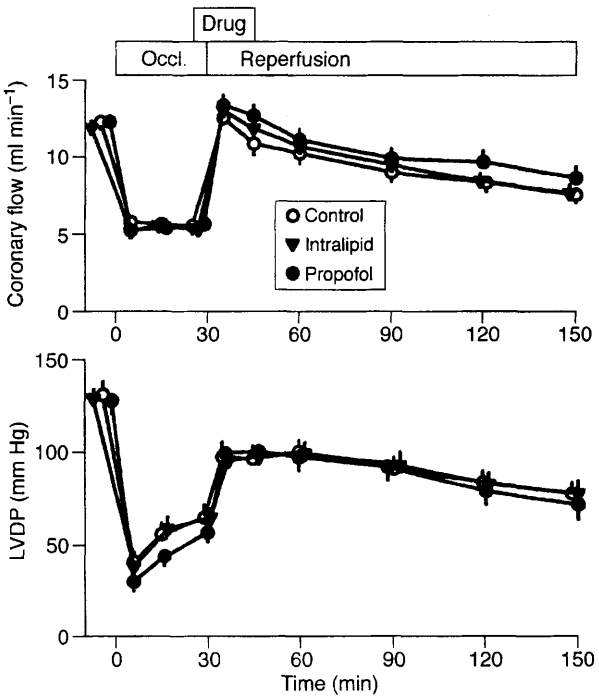

Fig 2 Coronary flow (CF, top) and left ventricular developed pressure (LVDP, bottom) in the control, Intralipid and propofol groups. Occlusion of the left anterior descending coronary artery led to reduction in CF and LVDP. CF recovered fully after release of the occlusion. LVDP was still reduced at the end of the reperfusion period. Neither CF nor LVDP were different between the three groups. Data are mean (SEM).

Cleveland, OH, USA). 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 left ventricular (LV) end-diastolic pressure from LV systolic pressure. All data are expressed as mean (SEM) and 95% confidence intervals (CI) if indicated. In the ischaemia–reperfusion experiments, statistical analysis was performed using ANOVA with Dunnett's *post hoc* test comparing the control and propofol groups with the Intralipid group. If ANOVA showed a time effect within a group, Dunnett's test was used as a *post hoc* test to compare each recorded value of the variable with its baseline value. In the dose–effect experiments, each control was compared with the respective intervention (drug administration) using the Student's *t* test for paired observations. Differences with $P<0.05$ were regarded as significant.

Results

Effect of propofol and Intralipid on normal myocardium

Figure 1 shows the effect of propofol and Intralipid on haemodynamic variables in the normal myocardium. Propofol produced a concentration-dependent decrease in the variables of contractility, LVDP and d*P*/d*t*max, and an increase in coronary flow. However, propofol 1 μg ml^{-1} in the ischaemia–reperfusion experiments had no effect on LVDP, d*P*/d*t*max or coronary flow. In contrast, Intralipid had no effect on these variables at any concentration.

Ischaemia–reperfusion experiments

A total of 47 hearts were used in the study: 11 did not fulfil the predefined quality criteria (LVDP >95 mm Hg at a coronary flow of 10–16 ml min^{-1} and no ventricular fibrillation during the stabilization period). These hearts were excluded. Mean heart wet weight was comparable in all groups (control group 1.16 (0.05) g; Intralipid group 1.07 (0.05) g; propofol group 1.07 (0.07) g).

Haemodynamic function

Under baseline conditions, haemodynamic variables were similar in all groups. Figure 2 shows LVDP and coronary flow during the course of the experiment. In the control, Intralipid and propofol groups, LAD occlusion caused similar decreases in coronary flow to 45 (2)% of baseline ($P<0.001$). After release of LAD occlusion, coronary flow returned to baseline in all groups (97 (2)% of baseline after 15 min of reperfusion; $P=1.0$), and then decreased slowly to 66 (2)% of baseline at the end of the reperfusion period. During LAD occlusion, LVDP decreased to 28 (2)% of baseline ($P<0.001$) with recovery to 78 (3)% of baseline after 15 min of reperfusion. LVDP did not return to baseline

Table 1 Left ventricular d*P*/d*t*max and d*P*/d*t*min in the control, Intralipid and propofol groups (mean (SEM)). *$P<0.05$, **$P<0.01$, ***$P<0.001$ compared with baseline values

	d*P*/d*t*max (mm Hg s^{-1})			d*P*/d*t*min (mm Hg s^{-1})		
	Control	**Intralipid**	**Propofol**	**Control**	**Intralipid**	**Propofol**
Baseline	4139 (259)	4343 (215)	4200 (270)	−3376 (186)	−3263 (215)	−3322 (235)
Occlusion						
5 min	1629 (151)***	1592 (137)***	1342 (169)***	−1174 (103)***	−1183 (118)***	−1038 (140)***
15 min	2001 (179)***	2197 (189)***	1764 (150)***	−1497 (152)***	−1657 (144)***	−1334 (140)***
29 min	2309 (236)***	2409 (206)***	2156 (159)***	−1788 (197)***	−1783 (160)***	−1669 (158)***
Reperfusion						
5 min	3050 (216)*	3106 (245)**	3193 (222)*	−2533 (178)*	−2716 (229)	−2723 (220)
15 min	3125 (225)*	3267 (219)*	3428 (231)	−2435 (194)**	−2653 (231)	−2689 (235)
30 min	3428 (244)	3456 (226)	3411 (209)	−2524 (173)*	−2638 (216)	−2463 (202)*
45 min	3406 (186)	3454 (253)	3427 (256)	−2530 (155)*	−2626 (207)	−2560 (265)
60 min	3297 (277)	3343 (274)*	3328 (251)	−2439 (204)**	−2452 (222)*	−2420 (230)*
90 min	3037 (232)*	3117 (274)**	2900 (234)**	−2253 (179)***	−2281 (230)**	−2161 (205)**
120 min	2840 (224)**	2917 (280)***	2744 (272)***	−2131 (181)***	−2089 (209)**	−1999 (225)***

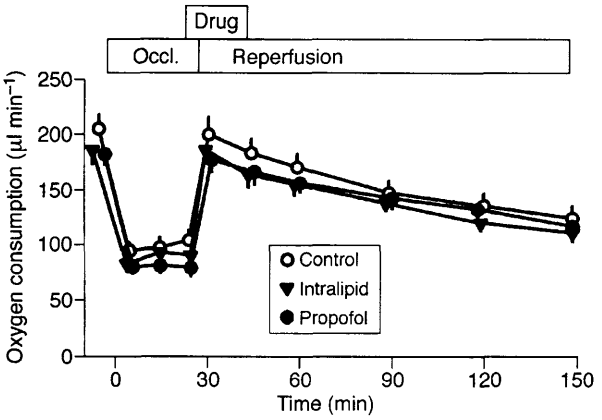

Fig 3 Myocardial oxygen consumption in the control, Intralipid and propofol groups. Occlusion of the left anterior descending coronary artery led to a decrease in myocardial oxygen consumption. After release of the occlusion, myocardial oxygen consumption returned to baseline values during early reperfusion, but then successively decreased during the late reperfusion period. There were no significant differences between groups. Data are mean (SEM).

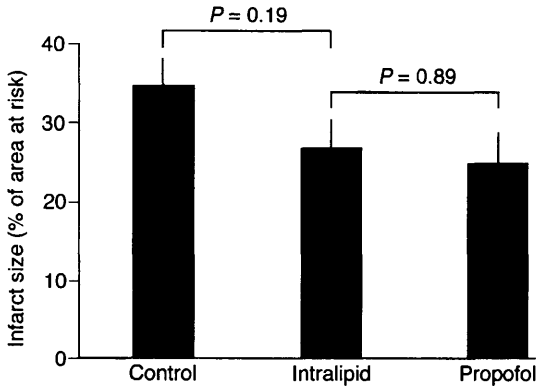

Fig 4 Infarct size as a percentage of the area at risk in the control, Intralipid and propofol groups. While infarct size in the Intralipid group tended to be smaller than in the control group, administration of propofol 1 µg ml^{-1} did not lead to a reduction in infarct size compared with its solvent Intralipid. Data are mean (SEM).

values ($P<0.001$) and was impaired further at the end of the reperfusion period (60 (3)% of baseline). This effect was similar in all groups. Table 1 shows LV d*P*/d*t*max and d*P*/d*t*min. d*P*/d*t*max, a variable of myocardial contractility, was reduced after LAD occlusion to 36 (2)% of baseline ($P<0.001$), recovered to 78 (3)% of baseline ($P<0.001$) and remained reduced compared with baseline until the end of the reperfusion period (67 (3)% of baseline; $P<0.001$). As a variable of diastolic function, d*P*/d*t*min changed similarly during occlusion ($P<0.001$) and reperfusion ($P<0.001$). There were no significant differences between the three groups for any haemodynamic variable.

Myocardial oxygen consumption

Under baseline conditions, $\dot{V}_{O_2}$ was similar in all groups (Fig. 3). LAD occlusion impaired $\dot{V}_{O_2}$ to 46 (2)% of baseline ($P<0.001$) which recovered to 91 (3)% of baseline ($P=0.15$) 15 min after release of LAD occlusion. $\dot{V}_{O_2}$ slowly decreased (61 (3)% of baseline; $P<0.001$) to the end of the reperfusion period. There were no differences between the three groups during occlusion or reperfusion.

Infarct size

Infarct size (Fig. 4) in the Intralipid group, expressed as a percentage of the area at risk, tended to be smaller than that in the control group (26.9 (3.3; CI 20.5–33.3)% in the Intralipid group, 34.8 (3.2; CI 28.5–41.1)% in the control group; $P=0.19$). However, compared with its solvent Intralipid, administration of propofol did not result in a further reduction in infarct size (25.0 (3.7; CI 17.8–32.2)% in the propofol group, 26.9 (3.3; CI 20.5–33.3)% in the Intralipid group; $P=0.89$).

Discussion

We have examined the effects of propofol on myocardial lethal reperfusion injury, defined as myocyte cell death caused by reperfusion itself rather than by the preceding ischaemia.[18]

There is a burst of free oxygen radicals within the first few minutes of reperfusion,[3] attacking lipids that constitute

the cell membrane and membrane proteins involved in the transport of ions and maintenance of cellular ionic homeostasis.[19] Several studies showed a reduction of lethal reperfusion injury by administration of oxygen radical scavengers.[4–6] The calcium overload phenomenon is another important factor in myocardial reperfusion injury and calcium antagonists are known to reduce myocardial reoxygenation damage.[15 16] Propofol may interfere with both mechanisms, suggesting a cardioprotective effect in myocardial reperfusion.

Plasma concentrations of propofol during clinical use are 0.7–20 μg ml^{-1}.[12] Considering that 97–99% of propofol is protein bound,[20] effective free plasma concentrations are 0.6 μg ml^{-1} or less.[21] Thus our concentration of propofol 1 μg ml^{-1} is comparable with clinically achieved free plasma concentrations. Administration of higher concentrations of propofol would not have allowed conclusions of clinical relevance. In our study, this would have affected myocardial contractility, and the beneficial effect of partial and complete contractile block on lethal reperfusion injury is already known.[22 23] Therefore, administration of propofol at higher concentrations may show an effect on lethal reperfusion injury but it would be difficult to distinguish a specific cardioprotective effect caused by antioxidant and calcium channel blocking effects from a general effect caused by a reduction in preload, afterload and inotropy.

In our study, propofol at a clinically relevant concentration of 1 μg ml^{-1} did not cause a reduction in infarct size. There were no differences between groups in LV systolic performance (LVDP, dP/dtmax), LV diastolic properties (dP/dtmin), coronary flow or myocardial oxygen consumption. This is similar to the findings of other studies which examined non-lethal reperfusion injury (myocardial stunning). These studies failed to show a beneficial effect of propofol on post-ischaemic functional recovery.[24 25]

One can speculate why propofol did not provide protection against lethal reperfusion injury in our study. Apart from the fact that propofol may not produce such an effect, a concentration of 1 μg ml^{-1} may not have been large enough to exert this effect. Propofol, at this concentration, does not appear to scavenge a sufficient number of free oxygen radicals to reduce myocardial damage significantly. Also, the calcium channel blocking property may not have been powerful enough at a concentration that had no effect on inotropy. Nevertheless, studies have shown a reduction in lethal reperfusion injury by diltiazem in concentrations that had no effect on haemodynamic state, including variables of contractility.[15 16] Absence of reperfusion injury in this study as a possible cause for the lack of protection is unlikely as the isolated rat heart is used commonly to investigate reperfusion injury and several studies showed a reduction in myocardial reperfusion damage using this model.[26–28]

Ko and colleagues reported a cardioprotective effect of propofol on myocardial ischaemia–reperfusion injury in the isolated rat heart.[29] They used 5–17 times higher concentrations than us and therefore their findings may be explained by the cardiodepressant effect of propofol which caused markedly decreased oxygen demand during occlusion, modulating the severity of ischaemia. The importance of inotropy and heart rate in the extent of ischaemia–reperfusion injury is well known and explains the cardioprotective effect of cardiodepressant drugs such as β blockers,[30] calcium antagonists[31] and bradycardic agents[32] given before and during ischaemia. However, no conclusion on reperfusion injury can be drawn from their study because propofol was given before global ischaemia and not during reperfusion.

The tendency of a smaller infarct size in the Intralipid group compared with the control group may reflect a small cardioprotective effect of Intralipid. Some interaction between Intralipid and H_2O_2 has been suggested.[8] Kamikawa and Yamazaki showed that Intralipid and heparin administration decreased free radical formation in mitochondria isolated from normal and ischaemic dog hearts,[33] and mitochondria are an important source of free oxygen radicals in the ischaemic and reperfused myocardium.[19] If Intralipid itself reduced the amount of free oxygen radicals, this could explain the lack of an additional cardioprotective effect of propofol in our study. However, our study was not designed to investigate the influence of Intralipid on the formation of or effects on free oxygen radicals in reperfused myocardium, and does not have the statistical power to prove or disprove such a small protective effect. Our power analysis showed that we would have detected a difference in infarct size of less then 15% of the area at risk. Therefore, it is unlikely that we missed an effect of clinical relevance, particularly as Intralipid did not increase myocardial oxygen consumption or contractile function during reperfusion, which would be expected after a significant reduction in myocardial damage.

In summary, we found that a clinically relevant concentration of propofol, given during early reperfusion, did not reduce cellular damage in the isolated rat heart and did not lead to better functional recovery. Thus propofol seems to have no specific effect on lethal myocardial reperfusion injury. In contrast, some volatile anaesthetics protect the myocardium against reperfusion injury,[34–36] and may possibly be beneficial in ischaemia–reperfusion situations compared with total i.v. anaesthesia with propofol.

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