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LABORATORY INVESTIGATION

Cardioprotection by sevoflurane against reperfusion injury after cardioplegic arrest in the rat is independent of three types of cardioplegia

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Background. Sevoflurane protects the heart against reperfusion injury even after cardioplegic arrest. This protection may depend on the cardioplegic solution. Therefore, we investigated the effect of sevoflurane on myocardial reperfusion injury after cardioplegic arrest with University of Wisconsin solution (UW), Bretschneider's cardioplegia (HTK), and St Thomas' Hospital solution (STH).

Methods. We used an isolated rat heart model where heart rate, ventricular volume, and perfusion pressure were constant. The hearts underwent 30 min of normothermic ischaemia followed by 60 min of reperfusion. Seven groups were studied (n=9 each). Three groups received 7°C cold cardioplegic solutions (UW, HTK, STH) during the first 2 min of ischaemia at a flow of 2 ml min^{-1}. In three groups (UW+Sevo, HTK+Sevo, STH+Sevo), sevoflurane was additionally added to the perfusion medium (membrane oxygenator) at 3.8% (1.5 MAC) during the first 15 min of reperfusion after cardioplegic arrest. Nine hearts served as untreated control group (control). We measured left ventricular developed pressure (LVDP) and infarct size.

Results. LVDP was similar in all groups during baseline (130 (SEM 2) mm Hg). HTK and STH improved recovery of LVDP during reperfusion from 5 (1) (control) to 67 (7) (HTK) and 52 (8) mm Hg (STH, both P<0.05), while UW had no effect on myocardial function (7 (2) mm Hg). In the sevoflurane-treated groups, LVDP at the end of the experiments was not significantly different from the respective group without anaesthetic treatment (UW+Sevo 11 (2); HTK+Sevo 83 (8); STH+Sevo 64 (8) mm Hg; P=ns). Infarct size was reduced in the HTK and STH groups (HTK 20 (4); STH 17 (3)%; P<0.05) compared with controls (39 (5)%; P<0.05), but not in the UW group (52 (4)%). Compared with cardioplegia alone, sevoflurane treatment during reperfusion reduced infarct size (UW+Sevo 31 (4); HTK+Sevo 8 (1); STH+Sevo 4 (1)%; P<0.05).

Conclusion. We conclude, that the protection against reperfusion injury offered by sevoflurane is independent of the three cardioplegic solutions used.

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In the setting of transient myocardial ischaemia, the resulting lethal cell injury is caused by both ischaemic injury and reperfusion injury. Reperfusion injury is defined as metabolic, functional, and structural consequences of restoring coronary arterial flow that can be avoided or reversed by modifications of the conditions of reperfusion.[1] Clinically, pharmacologic interventions to reduce reperfusion injury are not established, and current clinical concepts of cardioprotection focus on ischaemic injury by using cardioplegic solutions. Inhalation anaesthetics can reduce

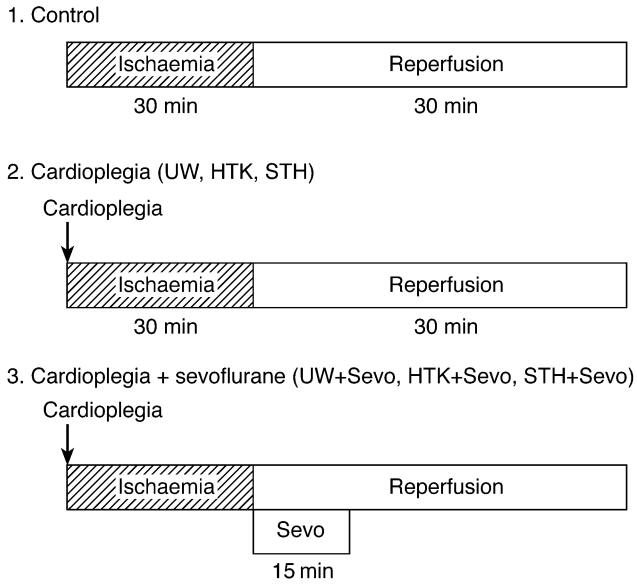

Fig 1 Experimental programme and treatment of the seven study groups (UW, University of Wisconsin solution; NTK, Bretschneider's cardioplegia; STH, St Thomas' Hospital solution).

reperfusion injury in various experimental settings[2–4] including the situation when the heart was already protected against the preceding ischaemic injury by cardioplegic arrest.[5 6] In this situation, the composition of the cardioplegic solution seems to be of importance. When halothane was given to isolated ischaemic reperfused rat hearts during early reperfusion, it provided additional cardioprotection in combination with a cardioplegic solution which contains calcium, but was not protective when the cardioplegic solution had a low calcium content.[5] Therefore, it is important to know what combination of cardioplegic solution and anaesthetic may provide additive protective effects against ischaemic and reperfusion injury.

In the present study, we investigated the effect of sevoflurane on myocardial reperfusion injury after protecting the heart against ischaemic injury with three different commonly used cardioplegic solutions. Sevoflurane was given during the early reperfusion period after 30 min of no flow ischaemia. Left ventricular (LV) developed pressure (LVDP) and infarct size were determined as variables of myocardial function and cellular injury, respectively.

Material and methods

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

The experimental preparation of the isolated rat heart model used in this study has been described in detail previously.[4] In brief, isolated hearts from male Wistar rats were perfused in a Langendorff apparatus with modified Krebs–Henseleit solution at a constant pressure of 100 cm H_2O. Heart rate was kept constant at 375 beats min^{-1}. For measurement of LV 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 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 resulting in an LV end-diastolic pressure (LVEDP) of 10–12 mm Hg, and this volume was kept constant throughout the experiment. Coronary flow (CF) 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. Following this preparation, the heart was placed in a water-jacketed chamber at 38°C, filled with humidified warm air. During ischaemia, the heart chamber was filled with isotonic sodium chloride solution, gassed with N_2. Myocardial temperature was kept constant at 38°C. Aliquots from the perfusion medium and the coronary venous effluent were sampled and processed further to determine myocardial oxygen consumption. At the end of each experiment, the heart was frozen and cut into transverse slices of 1 mm thickness. The slices were stained in buffered 0.75% triphenyltetrazolium chloride solution (TTC) at 37°C for 15 min and incubated in 4% formaldehyde for 24 h to identify viable and necrotic tissue. The basal side of each slice was scanned (StudioScan Iisi, AGFA, Leverkusen, Germany). Viable myocardium was then identified as red stained by TTC, whereas necrotic tissue appeared pale grey. The area at risk and the infarcted area were determined by planimetry on a personal computer (Sigma Scan Pro 5 computer software, SPSS Science Software, Chicago, IL, USA) and corrected for dry weight.

Experimental procedure

Figure 1 shows the experimental procedure of the different groups. After a stabilization period of 10 min, baseline measurements were performed. The hearts underwent 30 min of no-flow ischaemia and were then reperfused with the initial oxygenated medium for 60 min.

Seven groups (each n=9) were studied. Six groups received 7°C cold cardioplegic solutions (University of Wisconsin solution (UW), Bretschneider's cardioplegia (HTK), St Thomas' Hospital solution (STH)) during the first 2 min of ischaemia at a flow of 2 ml min^{-1} (infusion pump, Model 5003, Precidior Infors, Basel, Switzerland). In three of these groups (UW+Sevo, HTK+Sevo, STH+Sevo) sevoflurane was added to the perfusion medium (hollow fibre oxygenator D705 Midflow, Dideco, Mirandola, Italy) during the first 15 min of reperfusion (measured in the gas outlet of the oxygenator, Capnomac Ultima, Datex, Helsinki, Finland) at 3.8% corresponding to 1.5 minimum alveolar concentration (MAC) in the rat.[7] One further group served as a control and underwent the ischaemia reperfusion procedure without treatment.

Table 1 Dry weight, maximum ischaemic contracture, and time to maximum ischaemic contracture. *$P<0.05$ *vs* control

	Dry weight (g)	Maximum ischaemic contracture (mm Hg)	Time to maximum ischaemic contracture (min)
Control	0.16 (0.004)	88 (3)	14.9 (0.4)
UW	0.16 (0.01)	72 (8)	24.4 (1.1)*
UW+Sevo	0.15 (0.01)	69 (5)*	24.9 (0.5)*
HTK	0.16 (0.005)	69 (9)	29.1 (0.4)*
HTK+Sevo	0.16 (0.01)	74 (6)	29.3 (0.2)*
STH	0.15 (0.004)	67 (3)	27.4 (0.8)*
STH+Sevo	0.15 (0.004)	69 (3)*	28.3 (0.3)*

The UW solution was donated by DuPont Pharmaceuticals (Bad Homburg, Germany) and was composed of potassium lactobionate (100 mmol litre^{-1}), raffinose (30 mmol litre^{-1}), KH_2PO_4 (25 mmol litre^{-1}), $MgSO_4$ (5 mmol litre^{-1}), adenosine (5 mmol litre^{-1}), reduced glutathione (3 mmol litre^{-1}), insulin (40 unit litre^{-1}), dexamethasone (16 mg litre^{-1}), allopurinol (1 mmol litre^{-1}), and hydroxyethyl starch (50 mg litre^{-1}). The STH solution contained NaCl (110 mmol litre^{-1}), KCl (16 mmol litre^{-1}), $MgCl_2$ (16 mmol litre^{-1}), $CaCl_2$ (1.2 mmol litre^{-1}), and $NaHCO_3$ (10 mmol litre^{-1}). The HTK solution (HTK solution, Köhler, Alsbach, Germany) was composed of NaCl (15 mmol litre^{-1}), KCl (9 mmol litre^{-1}), K-ketoglutarate (1 mmol litre^{-1}), $MgCl_2$ (4 mmol litre^{-1}), histidine (180 mmol litre^{-1}), histidine–HCl (18 mmol litre^{-1}), tryptophan (2 mmol litre^{-1}), mannitol (30 mmol litre^{-1}), and $CaCl_2$ (0.015 mmol litre^{-1}).

In an additional set of experiments, we tested the effect of sevoflurane on reperfusion injury without preceding cardioplegic arrest. Eight hearts (Sevo group) received 1.5 MAC sevoflurane during the first 15 min of the reperfusion period after 30 min of ischaemia, and eight hearts underwent this procedure without sevoflurane administration to serve as controls.

Data analysis and statistics

LVP and d*P*/d*t* were continuously recorded on an ink recorder (Mark 260, Gould, Cleveland, OH, USA). All haemodynamic 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. LVDP was calculated by subtracting LVEDP from LV peak systolic pressure. Maximum LVEDP during ischaemia and the time from onset of ischaemia to this peak was assessed (maximum ischaemic contracture and time to maximum ischaemic contracture, Table 1). 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}) 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} (mm Hg), Pv_{O_2}=venous P_{O_2} (mm Hg) and CF=coronary flow (ml min^{-1}). Myocardial efficiency was calculated by dividing LVDP (mm Hg) by myocardial oxygen consumption (ml min^{-1} g^{-1} dry weight). All data are expressed as mean (SEM).

Statistical comparison (SPSS, SPSS Inc., USA) was performed between the groups that received sevoflurane and the respective groups that received the same cardioplegic solution (UW *vs* UW+Sevo, HTK *vs* HTK+Sevo, STH *vs* STH+Sevo). For haemodynamic variables and myocardial oxygen consumption, statistical analysis was performed using analysis of variance (ANOVA). If ANOVA showed a group effect, Student's *t*-test was used as a *post hoc* test at each measurement time. All other variables were compared using Student's *t*-test for unpaired observations followed by adjustment of the *P* values by Bonferroni correction.

To detect differences between the control group and the other groups (control *vs* UW, HTK, STH, and *vs* UW+Sevo, HTK+Sevo, STH+Sevo), Dunnett's test was used with the control group as the reference group. If the Dunnett's test showed a difference in haemodynamic variables, a Student's *t*-test was performed to detect differences at the different time points.

In the additional set of experiments, infarct size between the Sevo group and its control group was compared using Student's *t*-test. ANOVA was used to test for differences in the haemodynamic variables with Student's *t*-test as a *post hoc* test at each measurement time.

All statistical calculations were performed with the original data. Differences with a *P* value of <0.05 were regarded as significant.

Results

A total of 63 hearts fulfilling the predefined quality criteria (LVDP >95 mm Hg during baseline and no ventricular fibrillation during the stabilization period) were included into the study. Six hearts did not fulfil the quality criteria and were excluded after the stabilization period. Under baseline conditions, haemodynamic and metabolic variables were not different.

University of Wisconsin solution

Haemodynamic data of the UW and the UW+Sevo group are shown in Figure 2. LVEDP increased during ischaemia to similar values in all groups, but the time to maximum LVEDP was significantly delayed in the UW group compared with the control group ($P<0.001$, Table 1). LVEDP further increased during reperfusion after the onset of reperfusion, similar in all groups. LVDP decreased to zero with the onset of ischaemia and only recovered slightly

to 4–8% of baseline during reperfusion. In addition, CF, $\dot{V}O_2$, and myocardial efficiency were impaired after 60 min of reperfusion, with differences between the three groups (Fig. 2, Tables 2 and 3). The UW solution did not reduce infarct size (control 39 (4); UW 52 (4)%, P=0.60). However, sevoflurane administration during early reperfusion reduced infarct size after cardioplegic arrest with UW solution (UW+Sevo 31 (4)%, P=0.007).

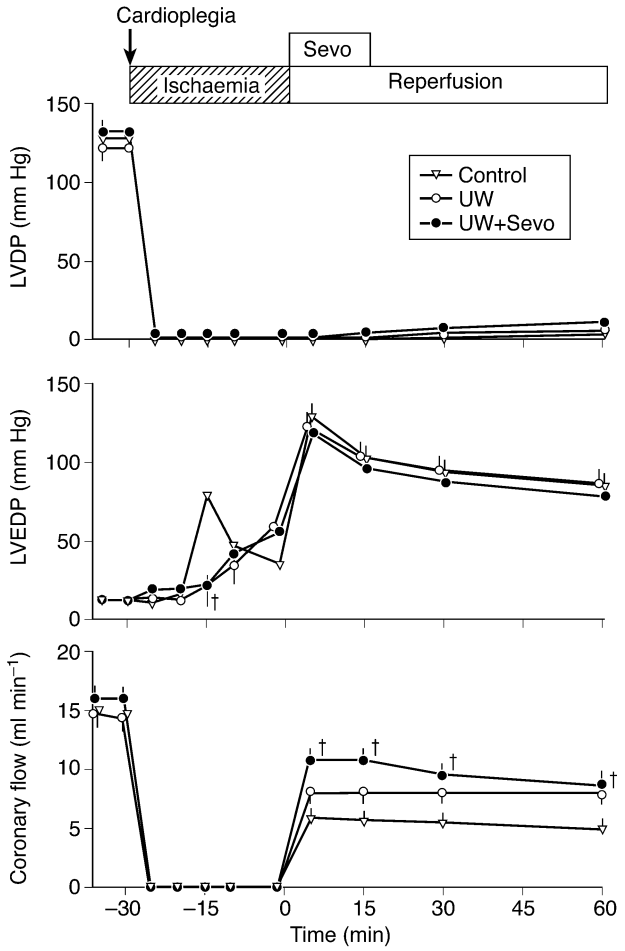

Fig 2 Left ventricular developed pressure (LVDP, top), left ventricular end-diastolic pressure (LVEDP, middle), and coronary flow (CF, bottom). In the UW group, the hearts were arrested with cold UW solution at the beginning of the 30 min ischaemia. The hearts in the UW+Sevo group additionally received sevoflurane during the first 15 min of reperfusion. Data are mean (SEM). †P<0.05 *vs* control.

Bretschneider's solution

Haemodynamic data of the control, HTK, and HTK+Sevo group are shown in Figure 3. During ischaemia, LVEDP increased to similar values in all groups, while time to maximum contracture was significantly delayed in the HTK group compared with the controls (Table 1). LVEDP during reperfusion was significantly lower in the HTK than control group and similar in the HTK and the HTK+Sevo group. LVDP in the HTK and the HTK+Sevo group recovered significantly better during reperfusion than in the control group. CF during reperfusion was higher in the HTK group (compared with CON) and was further increased in the HTK+Sevo group. $\dot{V}O_2$ during reperfusion remained impaired in the HTK group, whereas this approached baseline values during reperfusion after additional sevoflurane treatment (Table 2). Myocardial efficiency was similarly reduced in the HTK and the HTK+Sevo groups during reperfusion, but still was greater than the controls (Table 3). Infarct size (Fig. 5) was reduced in the HTK compared with the control group (control 39 (4)%; HTK 20 (4)%; P=0.003), and sevoflurane administration led to a further reduction of infarct size (HTK+Sevo 8 (1)%, P=0.03 *vs* HTK).

St Thomas' Hospital solution

LVDP, LVEDP, and CF of the control, the STH, and the STH+Sevo group are shown in Figure 4. LVEDP increased to similar values during ischaemia in the three groups, but time to maximum contracture was reduced in the STH group compared with the control (Table 1). During reperfusion, LVEDP was similar in the STH and the STH+Sevo groups, and there was no statistical difference between the STH and control group. During reperfusion, LVDP was improved in the STH and the STH+Sevo groups, and CF was higher in the STH+Sevo and lower in the control group compared with the STH group. $\dot{V}O_2$ and myocardial efficiency were similarly reduced during reperfusion in the STH and STH+Sevo groups but these were still greater than in the control group (Tables 2 and 3). Myocardial infarct size (Fig. 5) was smaller in the STH group compared with the control group (control 39 (4)%; STH 17 (3)%, P<0.001), and was

Table 2 Myocardial oxygen consumption (μl min^{-1}); *P<0.05 *vs* HTK; †P<0.05 *vs* control

	Baseline		Reperfusion			
	0 min	5 min	5 min	15 min	30 min	60 min
Control	245 (16)	252 (16)	99 (14)	99 (15)	85 (15)	72 (11)
UW	246 (22)	242 (24)	136 (21)	113 (24)	93 (17)	84 (15)
UW+Sevo	249 (27)	248 (26)	138 (17)	114 (14)	93 (14)	95 (14)
HTK	217 (6)	213 (7)†	176 (13)†	164 (16)†	168 (15)†	151 (13)†
HTK+Sevo	243 (6)*	238 (8)*	175 (16)†	211 (24)†	224 (9)*†	222 (14)*†
STH	230 (10)	228 (10)	139 (7)†	151 (7)†	150 (8)†	153 (16)†
STH+Sevo	257 (9)	244 (12)	162 (8)†	168 (11)†	174 (12)†	160 (17)†

further reduced in the STH+Sevo group (STH+Sevo 4 (1)%, P=0.002 *vs* STH).

Sevoflurane without cardioplegic arrest

Sixteen of the 18 hearts fulfilled the predefined quality criteria (both groups n=8). There were no differences in haemodynamic variables under baseline conditions, or in heart dry weight (Sevo 0.15 (0.007); control 0.15 (0.005), P=0.98).

LVEDP increased similarly in both groups from 12.8 (2.1) mm Hg in the Sevo group and 10.5 (2.1) mm Hg in its control group during baseline to 74.9 (5.6) and 75.4 (6.2) mm Hg during ischaemia (P=0.93), and was 50.5 (7.6) and 54.5 (10.3) mm Hg after 60 min reperfusion. Time to maximum contracture was also similar in both groups (Sevo 14.4 (0.9) min; control 14.3 (0.4) min; P=0.93). LVDP was 113.9 (7.6) mm Hg in the Sevo group and 114.4 (3.8) mm Hg in its control group, only marginally recovering in both groups after ischaemia and 60 min of reperfusion (4.9 (2.0) and 2.3 (1.4) mm Hg). CF and $\dot{V}O_2$ also did not differ, either during baseline conditions (CF, Sevo 16.9 (0.9) ml min^{-1}; control 16.2 (1.2) ml min^{-1}; $\dot{V}O_2$, Sevo 275 (14) µl min^{-1}; control 257 (25) µl min^{-1}) or after 60 min reperfusion (CF 8.7 (1.1) ml min^{-1}; 7.8 (1.2) ml min^{-1}; $\dot{V}O_2$ 117 (14) µl min^{-1}; 98 (14) µl min^{-1}). Infarct size was significantly lower in the Sevo group (25.1 (5.0)%) than in its control group (40.9 (3.1)%; P=0.018).

Discussion

We studied the effect of sevoflurane on myocardial reperfusion injury after cardioplegic arrest with three different cardioplegic solutions. The results show that the protection against reperfusion injury offered by sevoflurane after cardioplegic arrest is independent of the three cardioplegic solutions used.

Myocardial reperfusion injury may occur in multiple clinical settings, such as thrombolysis, percutaneous balloon angioplasty, and after periods of cardiac arrest during heart surgery with cardiopulmonary bypass. In cardiac surgery and heart transplantation, cardioplegic arrest is widely used to protect the myocardium against the consequences of ischaemia.[8]

In our study, the 'extracellular' solutions HTK and STH reduced the time to ischaemic contracture and myocardial infarct size by 50 and 57%, respectively. This again confirms the potent cardioprotective effect of these cardioplegic solutions against ischaemic damage, even under normothermic conditions. The 'intracellular' UW solution is safely used for heart transplantation[9] and may even have advantages compared with 'extracellular' cardioplegic solutions.[10–12] The key to the strong cardioprotective effect of the UW solution seems to be the high potassium content.[13] However, the advantage of such a high potassium concentration is highly temperature dependent, because UW solution leads to temperature-dependent endothelial dysfunction and a progressive increase in coronary vascular resistance at temperatures above 15°C.[14] This might explain the tendency to a greater infarct size in the UW group compared with the control group, as our experiments were carried out at 38°C. However, the maximum ischaemic contracture was delayed after cardioplegic arrest with UW solution. This delay indicates a reduction of ischaemic hazard. Therefore, the possible damage caused by UW solution at 38°C may largely occur at the onset of reperfusion.

Inhalation anaesthetics are known to reduce myocardial reperfusion injury[2–4] even if the heart is already protected against the ischaemic damage by cardioplegic arrest.[5 6] The protection provided by halothane against reperfusion injury after cardioplegic arrest depended on a high calcium content of the cardioplegic solution. This is not surprising because halothane reduces reperfusion injury by modulating calcium handling at the sarcoplasmic reticulum.[15] The mechanism of protection against reperfusion injury is known only for halothane, but not sevoflurane or other inhalation anaesthetics. As the calcium content of a cardioplegic solution can influence the cardioprotection provided by halothane,[5] different cardioplegic solutions may also affect the protection of sevoflurane against reperfusion injury. The cardioplegic solutions used are the most frequently used solutions for organ transplantation (UW) and cardiac surgery (HTK, STH) in Europe. Sevoflurane administration during early reperfusion reduced myocardial infarct size by 40% after cardioplegic arrest with UW, and by 60 and 76% after arrest with HTK and STH solution, and by 38% without cardioplegic arrest. Our data indicate that this protection

Table 3 Myocardial efficiency (mmHg min ml^{-1}); $^{\dagger}P$<0.05 *vs* control

	Baseline		Reperfusion			
	0 min	5 min	5 min	15 min	30 min	60 min
Control	533 (26)	518 (27)	15 (3)	18 (3)	29 (4)	62 (16)
UW	516 (39)	527 (5)	20 (6)	29 (9)	59 (16)	80 (23)
UW+Sevo	560 (51)	561 (56)	14 (3)	23 (7)	64 (13)	125 (23)
HTK	596 (30)	599 (37)	203 (45)†	297 (52)†	417 (60)†	439 (39)†
HTK+Sevo	548 (38)	551 (43)	314 (57)†	335 (62)†	426 (40)†	422 (40)†
STH	606 (29)	586 (27)	89 (32)†	175 (55)†	303 (56)†	357 (53)†
STH+Sevo	538 (23)	555 (21)	84 (39)	233 (58)†	351 (50)†	386 (27)†

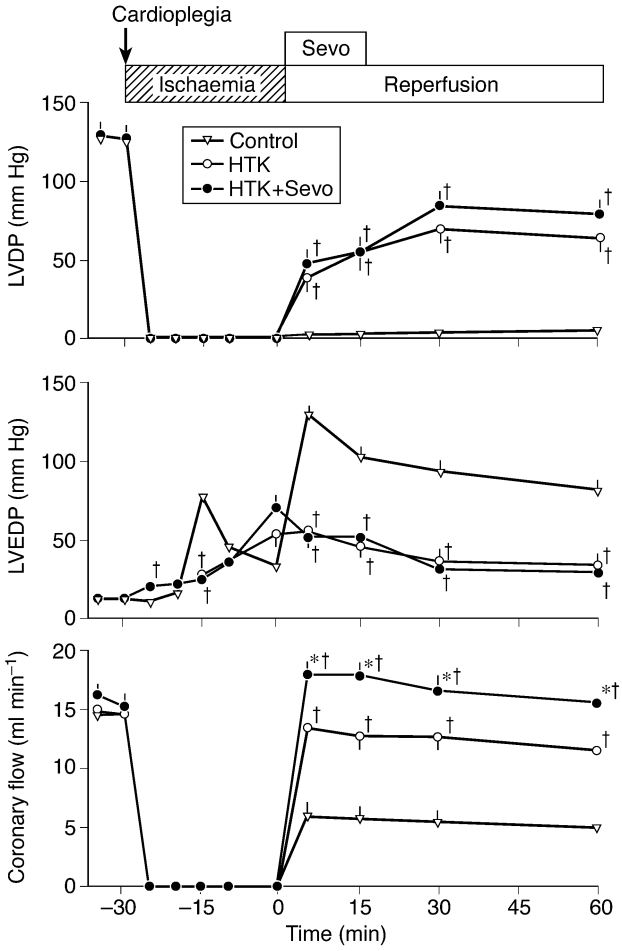

Fig 3 Left ventricular developed pressure (LVDP, top), left ventricular end-diastolic pressure (LVEDP, middle), and coronary flow (CF, bottom). The hearts in the HTK group were protected against ischaemic damage by cardioplegic arrest with Bretschneider's solution. In the HTK+Sevo group, sevoflurane was administered additionally during early reperfusion. Data are mean (SEM). **P*<0.05 HTK *vs* HTK+Sevo; †*P*<0.05 *vs* control.

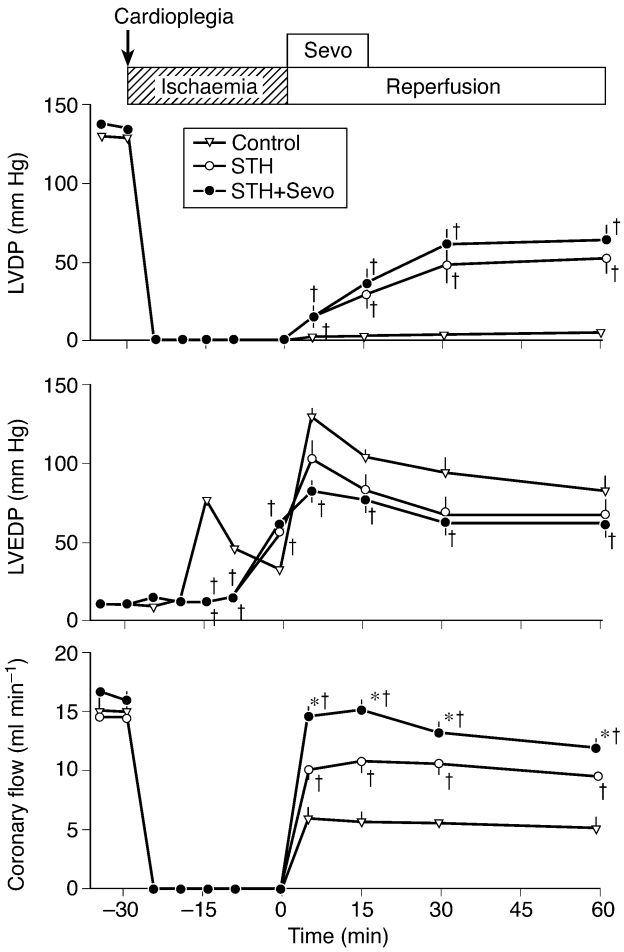

Fig 4 Left ventricular developed pressure (LVDP, top), left ventricular end-diastolic pressure (LVEDP, middle), and coronary flow (CF, bottom). In the STH group, hearts cardioplegic arrest was performed by administration of St Thomas' Hospital solution at the beginning of ischaemia. In the STH+Sevo group, the hearts additionally received sevoflurane during early reperfusion. Data are mean (SEM). **P*<0.05 STH *vs* STH+Sevo; †*P*<0.05 *vs* control.

is largely independent of intracellular calcium and sodium loading because UW solution is calcium free and has only a low sodium content. The similar protection afforded by sevoflurane administration after cardioplegic arrest with HTK and STH solution also supports this hypothesis because the calcium content in both solutions is very different (HTK 0.015 mmol litre^{-1}; STH 1.12 mmol litre^{-1}). A block of the contractile filaments can also reduce myocardial reperfusion injury[16] by preventing early cellular damage caused by reperfusion hypercontracture.[17] We cannot exclude that the negative inotropic effect of sevoflurane has contributed to the cardioprotective effect. However, for halothane it has been shown that the protective effect against myocardial reperfusion injury is independent of its negative inotropic effect.[3]

LVDP and myocardial efficiency (LVDP divided by $\dot{V}O_2$) was reduced during reperfusion compared with baseline values indicating a state of myocardial stunning.

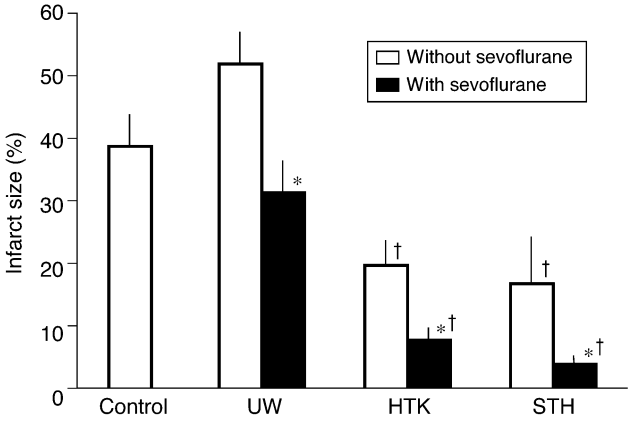

Fig 5 The infarct size in per cent of right and left ventricle. Data are mean (SEM). **P*<0.05 cardioplegia *vs* cardioplegia+sevoflurane; †*P*<0.05 *vs* control.

Independent of the cardioplegic solution, we could neither determine a better functional recovery nor an improved myocardial efficiency in the sevoflurane treated hearts. This indicates that sevoflurane, while protecting the myocardium against lethal reperfusion injury, has no effect on myocardial stunning (non-lethal reperfusion injury). This conclusion has to be restricted to the situation after cardioplegic arrest. The cardioprotective effects of sevoflurane against reperfusion injury have to be distinguished from preconditioning effects: given that before and during ischaemia, sevoflurane protects myocardium against stunning through activation of mitochondrial ATP-sensitive potassium channels.[18] This does not imply a direct effect of sevoflurane against myocardial stunning when given during early reperfusion.

An important limitation of this investigation results from the duration of the reperfusion period. With 60 min reperfusion, only the early reperfusion injury can be assessed, and later cell death as caused by apoptosis cannot be excluded. Although halothane and isoflurane can reduce apoptotic cell death,[19] nothing is known about an effect of sevoflurane on apoptosis.

Coetzee and colleagues[20] performed similar experiments with isolated rat hearts in working mode. They found a deleterious effect on aortic output and myocardial work with sevoflurane administration during early reperfusion after ischaemic cardioplegic arrest with STH solution. These findings cannot be explained by Coetzee and colleagues and are in contrast to our data and to previous studies.[4 6] In a recent study, we found that there is a threshold concentration of 1 MAC (2.4%) in the rat at which sevoflurane is protective against lethal reperfusion injury.[21] Coetzee and colleagues investigated a much lower sevoflurane concentration of 0.9% (*vs* 3.8% in our study) at which no effect against lethal reperfusion injury can be expected. However, they did not assess any variables of cellular damage so that no direct conclusion regarding an effect of sevoflurane on lethal reperfusion injury can be drawn from their study. However, their results are in accordance with our hypothesis that sevoflurane has no effect on myocardial stunning after cardioplegic arrest.

In summary, we have found that sevoflurane at a concentration of 1.5 MAC reduces lethal reperfusion injury after cardioplegic arrest with UW, HTK, and STH solutions in the isolated rat heart. Recovery of myocardial function ('stunning') was not affected. Administration of sevoflurane in an ischaemia-reperfusion situation appears to be advantageous even if the heart is protected against the consequences of ischaemia by cardioplegic arrest.

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