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Conductance Catheter Measurement and Effect of Different Anesthetics in a Rat Model of Postresuscitation Myocardial Dysfunction

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We demonstrate the usefulness of left ventricular pressure–volume (PV) loops generated by the use of conductance catheter measurements and investigate the influence of the type of general anesthesia on postresuscitation myocardial dysfunction in a rat model of cardiac arrest (CA) and subsequent cardiopulmonary resuscitation. A total of 42 Wistar-Han rats were randomized to receive general anesthesia with sevoflurane and resuscitation after CA, general anesthesia with pentobarbital intraperitoneally and resuscitation after CA, or general anesthesia with pentobarbital without CA (sham group). Myocardial function, assessed by analysis of PV loops, was measured continuously and in real-time by using a PV–conductance catheter. Rats were monitored for 3 h after restoration of spontaneous circulation (ROSC). The use of PV–conductance catheters supported objective and reliable evaluation of myocardial function and proved feasible in this rat model of CA. End-diastolic volume increased in rats anesthetized with pentobarbital after ROSC (before CA, 237 ± 45 µL; after ROSC, 402 ± 64 µL). Preload-adjusted maximal power before CA was the same in all groups but decreased in both resuscitated groups. The decrease was less pronounced in rats anesthetized with sevoflurane compared with pentobarbital (11.8 ± 4.9 mW/µL^2 compared with 4.8 ± 1.9 mW/µL^2 at 3 h after ROSC). This finding indicates that the type of general anesthesia influences postresuscitation myocardial dysfunction in this rat model of experimentally induced CA and cardiopulmonary resuscitation. Rats that were anesthetized with sevoflurane exhibited less postresuscitation myocardial dysfunction than did those anesthetized with pentobarbital.

Abbreviations: CA, cardiac arrest; $\delta p/\delta t_{max}$, maximal slope of systolic pressure increment; EDV, end-diastolic volume; EF, ejection fraction; MAP, mean arterial pressure; PAMP, preload adjusted maximal power; PRMD, postresuscitation myocardial dysfunction; PV, pressure–volume; ROSC, restoration of spontaneous circulation.

Return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest (CA) can be achieved in 30% to 50% of subjects,[40] but only 5% to 15% of patients can be discharged from hospital.[5,6,19,23,38] One of the reasons for this marked discrepancy is so-called postresuscitation myocardial dysfunction (PRMD).[12,27] This situation justifies the need for animal models analyzing this complex clinical picture. Several studies investigated PRMD.[14,26,46] However, these studies are limited by various weaknesses, including differences in target variables and monitoring units. Echocardiographic measurements are used routinely to assess myocardial function in humans but are unreliable in small laboratory animals such as mice and rats. The accuracy of these measurements primarily depends on the experience of the investigator, especially with regard to stroke volume and left ventricular performance.[28,50] Conductance catheter measurement enables objective and real-time measurement of heart rate, mean arterial pressure (MAP), ejection fraction (EF), maximal slope of systolic pressure increment ($\delta p/\delta t_{max}$), and preload-adjusted maximal power (PAMP). Whereas $\delta p/\delta t_{max}$ depends on preload and to a lesser extent on afterload, PAMP is a measure of contractility that is independent of preload conditions.[24,30,45] Therefore, pressure–volume (PV)–conductance catheters are well suited to monitoring PRMD in a rat model of CA and resuscitation but have not previously been used for this purpose. One study measured left ventricular function by using a self-constructed conductance catheter in pigs[14] and thus far represents the only published application of this method in a setting of experimental CA.

Because rodent models have several advantages over models involving pigs or dogs (for example, availability of knockout mice, increased cost effectiveness),[36] the first aim of our study was to prove feasibility of the PV–conductance catheter in a small animal model of experimentally induced CA and CPR. The second aim was to analyze the effect of 2 general anesthetics commonly used in animal experiments (sevoflurane and pentobarbital) on PRMD at 3 h after ROSC. Because volatile anesthetics are known to have cardioprotective effects in regional myocardial ischemia in rats and dogs, we hypothesize that sevoflurane anesthesia during surgical procedure prior to CA attenuates PRMD.[13,42,49]

Materials and Methods

Healthy adult male Wistar rats (Janvier, Saint Berthevin Cedex, France) were obtained at 6 wk of age and maintained in our animal colony on a 12:12-h light:dark cycle and at 22 °C for 2 to 3 wk prior to experimentation. Two rats were housed per cage on cottonwood chips (PK3, LASvendi, Soest, Germany) and given food (ROD 16A, LASvendi) and water ad libitum. After institutional approval by the Governmental Animal Care Committee (Regierungspraesidium Karlsruhe, 35-91825.81/G-112/06), 42 male Wistar rats (age, 8 to 9 wk; body weight, 320

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to 380 g; international strain nomenclature, RjHan:Wi) were studied.

All animals were handled in accordance with the European Council Directive of 22 September 2010 (2010/63/EU) and the investigation conformed to the *Guide for the Care and Use of Laboratory Animals*.[22,48] The animals were randomized into the following groups: Sevo group, induction of anesthesia and maintenance with sevoflurane ($n = 15$); Pento group, induction of anesthesia with one single injection of pentobarbital intraperitoneally ($n = 15$); and Sham group, induction and maintenance with pentobarbital and surgical preparation only (no CA; $n = 12$).

Anesthesia was induced either by inhalation of 3 to 4 $Vol\%_{endtidal}$ of sevoflurane or with administration of pentobarbital (60 mg/kg IP). Thereafter rats were intubated and mechanically ventilated (Rodent Ventilator, Harvard Apparatus, Holliston, MA). A conventional single-lead ECG was established by using subcutaneous needle electrodes. Tympanic temperature was monitored throughout preparation, CA, CPR, and the ROSC phase (Thermistor YSI 400 series, Mon-a-therm Tympanic, Mallinckrodt, Griesheim, Germany). The left femoral artery and vein were cannulated with a 2-French catheter (Polythene Tubing, SIMS Portex, Hythe, Kent, UK).

Generating PV loops by using conductance catheter technique. The PV–conductance catheter (SPR 838, Millar Instruments, Houston, TX) was inserted via the right carotid artery into the left ventricle by online measuring of pressure and volume signals. Catheter signals were recorded (Chart 5.5.3 software, AD Instruments, Colorado Springs, CO) and analyzed with the PV-analysis software (PVAN 3.6, Millar Instruments). Figures 1 and 2 show representative examples of pressure–volume loops (PV loops) before induction of CA and 3 h after ROSC.

The conductance catheter system was calibrated at the beginning of each experiment by using a 3-fold injection (10 µL each) of a 30% saline solution.[34] Calibration measurements were performed after stopping ventilation in the expiratory phase and waiting for 1 to 2 s, to stabilize the PV loop.

Arterial blood gas analysis (Rapidlab 348; Bayer Healthcare, Leverkusen, Germany) was performed to achieve steady-state conditions and to fulfil the Utstein Style guidelines for uniform reporting of laboratory CPR research.[21] Mean arterial blood pressure in the abdominal aorta was measured continuously (TBD-122, FMI GmbH, Seeheim, Germany) and recorded by using the Chart 5.5.3 software. Each catheter insertion site was infiltrated with 0.5 mL lidocaine 2%. To evaluate the depth of general anesthesia accurately, we did not administer neuromuscular blocking agents. Adequacy of anesthesia was confirmed by the absence of spontaneous limb movements.

CA was induced through ventricular fibrillation by using 12 V/50 Hz alternating current through a transesophageal electrode, as described previously.[39] After 6 min of CA, CPR was started: 60 breaths per minute (100% oxygen), external manual chest compression at a rate of 200/min, duty cycle of 50%, and compression depth of 25% of the anterior–posterior chest diameter. After 2 min of CPR without ROSC, defibrillation was attempted by using a single biphasic shock of 1 Joule (M series, Zoll Corporation, Cologne, Germany). CPR was continued and adrenaline was administered (epinephrine, 20 µg/kg) if ROSC could not be achieved within 30 s after the first defibrillation attempt. Defibrillation procedures were repeated every 30 s. If CPR was not successful after 6 min, resuscitation was terminated, and the rat was excluded from further analysis. ROSC was defined as the maintenance of an unassisted mean arterial blood pressure (MAP) above 50 mm Hg for at least 10 consecutive minutes, according to the Utstein-style guidelines.[21]

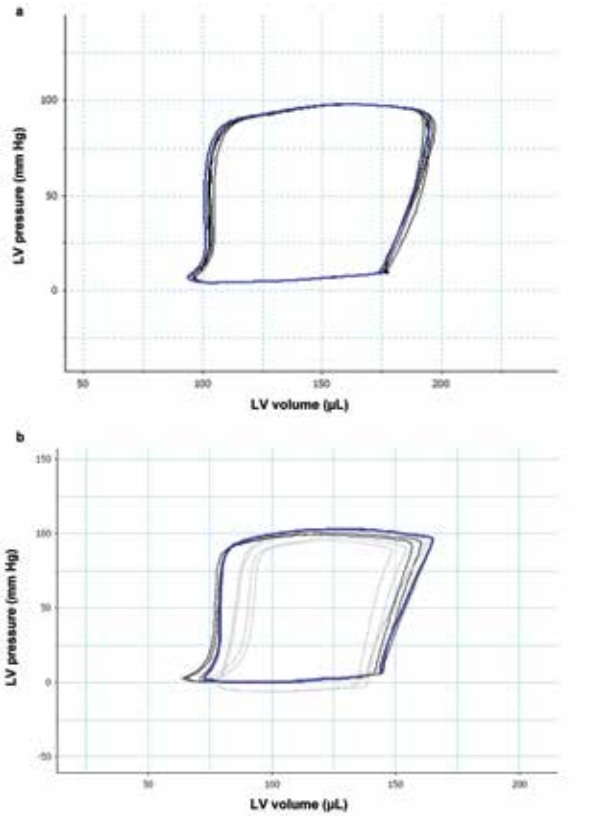

Figure 1. Example PV loops of a rat anesthetized with sevoflurane (a) during baseline and (b) 3 h after restoration of spontaneous circulation. LV, left ventricular.

Once ROSC was achieved, no further steps such as defibrillation, cardioversion, and administration of vasopressors or antiarrhythmic drugs were taken. The ventilation rate was adjusted to reach and maintain normocapnia, and sodium bicarbonate was titrated according to blood gas analyses, aiming for a base excess of 0 to –5 at 20 min after ROSC.

Rats were monitored for 3 h. Within this period, the PV–conductance catheter remained in the left ventricular position, and analyses were conducted at baseline and every 30 min after ROSC. Rats were extubated as soon as adequate spontaneous breathing was observed. The experiment was stopped by using an injection of KCl at the predefined endpoint of 3 h after ROSC.

We analyzed heart rate, MAP, left ventricular EDV, EF, $\delta p/\delta t_{max}$, and PAMP.

Statistical analysis. Data was analyzed by one-way ANOVA with post hoc Bonferroni correction. All data followed a normal distribution as tested by the Shapiro–Wilk test. For statistical analysis, SPSS 15 (SPSS, Chicago, IL) was used. All data are presented as means ± 1 SD, and a of P value of less than 0.05 was set to define significance.

Results

Baseline characteristics. A total of 42 rats were randomized into the Sevo ($n = 15$), Pento ($n = 15$), and sham ($n = 12$) groups. In both the Sevo and Pento groups, 12 of 15 animals were resuscitated successfully. None of the physiologic parameters including weight, arterial blood gas analysis, core body temperature, and MAP showed any pathologic findings or differences between the interventional and control groups before induction of CA. Neither did the placement of the conductance catheter cause any technical problems. The time needed to induce stable ventricular

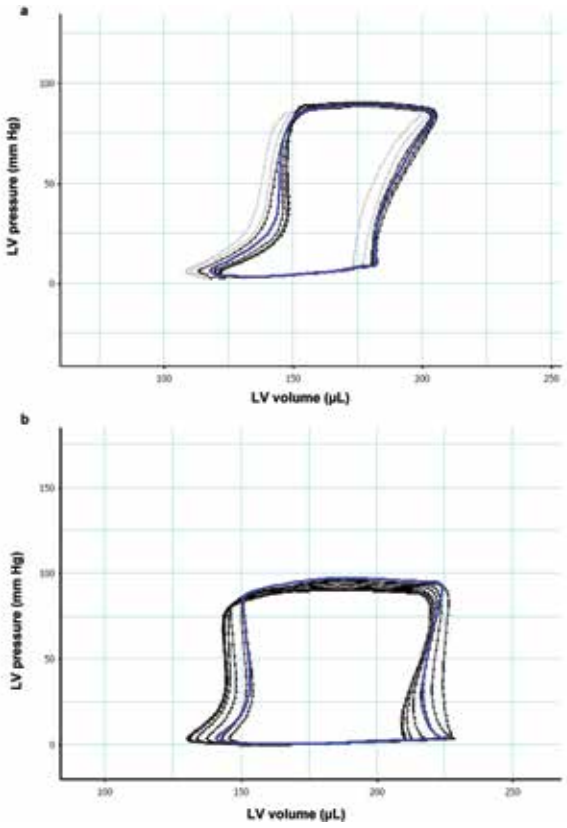

Figure 2. Example PV loops of a rat anesthetized with pentobarbital (a) during baseline and (b) 3 h after restoration of spontaneous circulation. LV, left ventricular

fibrillation was shorter in the Sevo group than in the Pento group (65 ± 6 s compared with 202 ± 18 s, $P < 0.001$). Furthermore, duration of CPR was longer (4:21 ± 0:51 min compared with 3:00 ± 0:44, $P < 0.01$) and number of defibrillations (4.8 ± 1.2 compared with 2.4 ± 0.9, $P < 0.01$) and dose of epinephrine (11 ± 2 µg compared with 8 ± 1 µg, $P < 0.01$) were higher in the Sevo group than in the Pento group. However, all but one rat in the Sevo group could be extubated within the first hour after ROSC, whereas none of the rats in the Pento group could be extubated after ROSC ($P < 0.01$). All rats remained in a comatose state during the post-ROSC phase, and it was not necessary to administer any additional anesthetic (Table 1).

Example PV loops. Figure 1 shows example PV loops before CA and at 3 h after ROSC of a rat in the Sevo group. Figure 2 illustrates PV loops measured at baseline and at 3 h after ROSC in a rat anesthetized with pentobarbital.

Pentobarbital reduces MAP in the early postresuscitation phase. MAP decreased after ROSC in both resuscitated groups as compared with the sham group and remained decreased throughout the entire recording time (Figure 3). However, compared with that in the Pento group, MAP during the first 2 h after ROSC was higher ($P < 0.05$) in the Sevo group. No difference in MAP was observed 2 h and more after ROSC.

Pentobarbital increases postresuscitation EDV. EDV before CA was higher in the Sevo group (279 ± 26 µL) compared with the Sham group (237 ± 45 µL, $P < 0.05$) and the Pento group (225 ± 40 µL, $P < 0.01$). Although EDV remained fairly constant in the Sevo group, a time-dependent increase of EDV occurred in the Pento group over a period of 3 h. No significant difference in EDV was revealed between the Sevo and Sham groups throughout the entire postresuscitation period. However EDV was reduced in these 2 groups compared with the Pento group (Figure 4).

Table 1. Baseline characteristics (mean ± 1 SD)

	Sevo group	Pento group	*P*
Body weight (g)	366 ± 22	373 ± 25	0.77
Time to induction time of ventricular fibrillation (s)	65 ± 6	202 ± 18	<0.001
Epinephrine (µg)	11 ± 2	8 ± 2	<0.01
$NaHCO_3^-$ (8.4%, mL)	1.4 ± 0.2	1.6 ± 0.3	0.58
No. of defibrillations	4.8 ± 1.2	2.4 ± 0.9	<0.01
Duration of CPR (min)	4:21 ± 0:51	3:00 ± 0:44	<0.01
No. of rats extubated after ROSC	11 of 12	0 of 12	<0.01

Body weight of rats in sham group: 370 ± 25 g.

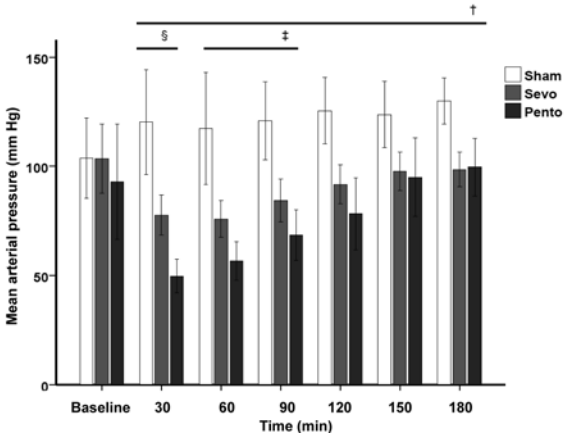

Figure 3. Time course of arterial pressure (mean ± 1 SD). For the sham group, time is given as minutes after achieving steady state; for the resuscitated groups, time is given as minutes after ROSC. †, $P < 0.01$ compared with sham group; ‡, $P < 0.05$ between the sevoflurane (Sevo) and pentobarbital (Pento) groups; §, $P < 0.01$ between the Sevo and Pento groups.

Reduction of EF is most pronounced after pentobarbital. Postresuscitation EF was reduced in both groups and only partially recovered over a period of 3 h (Figure 5). The observed decrease in EF was more pronounced in the Pento group (53% ± 4% at baseline compared with 24% ± 6% at 30 min after ROSC) than in the Sevo group (47% ± 7% at baseline compared with 32% ± 15% 30 min after ROSC, $P < 0.05$). Furthermore, EF recovery did not differ significantly between the Sevo and Pento groups at 3 h after ROSC (32% ± 9% compared with 23% ± 9%).

Pentobarbital reduces $\delta p/\delta t_{max}$ in the early postresuscitation period. The drop in $\delta p/\delta t_{max}$ was sharper in the Pento group, achieving a minimal value of 2622 ± 574 mm Hg/s at 30 min after ROSC (baseline, 4908 ± 1176 mm Hg/s; $P < 0.01$), compared with the Sevo group, in which $\delta p/\delta t_{max}$ was decreased only slightly at 30 min after ROSC (4737 ± 545 mm Hg/s; baseline, 5843 ± 1060 mm Hg/s; $P < 0.05$). Therefore, for 2 h after ROSC, $\delta p/\delta t_{max}$ was significantly lower in the Pento group than in the Sevo group (Figure 6).

Pentobarbital results in a lack of recovery of PAMP. In the sham group, PAMP increased during 3 h, from 13.7 ± 4.4 mW/µL^2 at baseline to 20.6 ± 7.0 mW/µL^2 at 3 h ($P < 0.01$). However, although PAMP remained strongly impaired in the Pento group (3.4 ± 1.7 mW/µL^2 at 30 min after ROSC compared with 4.8 ± 1.9 mW/µL^2 at 3 h), PAMP significantly increased during the post-ROSC phase (6.4 ± 3.1 mW/µL^2 at 30 min after ROSC to 11.8 ± 4.9 mW/µL^2 at 3 h after ROSC; $P < 0.01$) in the Sevo group (Figure 7). At 2.5 h after ROSC, PAMP was higher in the Sevo

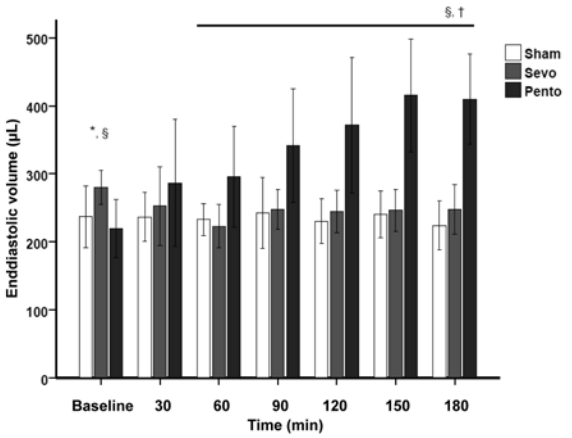

Figure 4. Time course of end-diastolic volume. For the sham group, time is given as minutes after achieving steady state; for the resuscitated groups, time is given as minutes after ROSC. *, $P < 0.05$ compared with the sham group; †, $P < 0.01$ compared with the sham group; §, $P < 0.01$ between the sevoflurane (Sevo) and pentobarbital (Pento) groups.

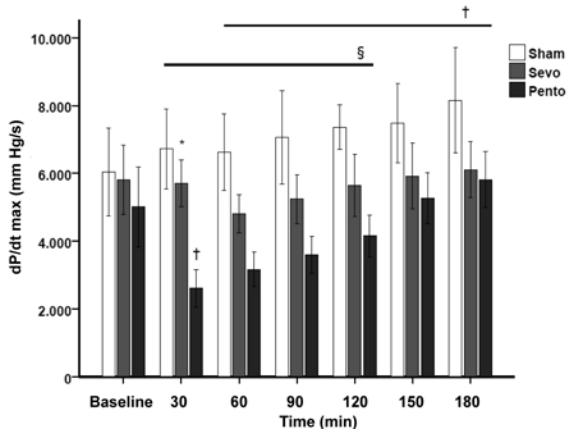

Figure 6. Time course of δp/δp max. For the sham group, time is given as minutes after achieving steady state; for the resuscitated groups, time is given as minutes after ROSC. *, $P < 0.05$ compared with the sham group; †, $P < 0.01$ compared with the sham group; ‡, $P < 0.05$ between the sevoflurane (Sevo) and pentobarbital (Pento) groups; §, $P < 0.01$ between the Sevo and Pento groups.

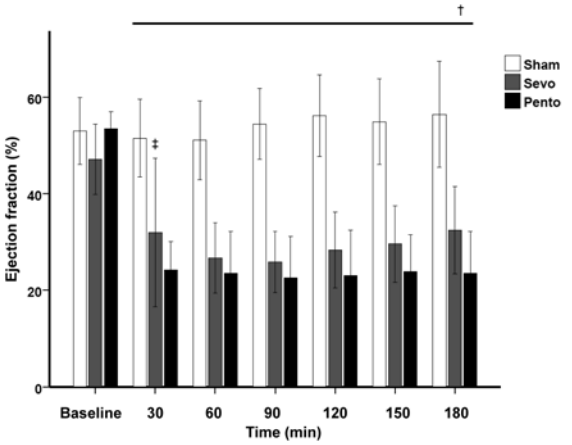

Figure 5. Time course of ejection fraction. For the sham group, time is given as minutes after achieving steady state; for the resuscitated groups, time is given as minutes after ROSC. †, $P < 0.01$ compared with the sham group; ‡, $P < 0.05$ between the sevoflurane (Sevo) and pentobarbital (Pento) groups.

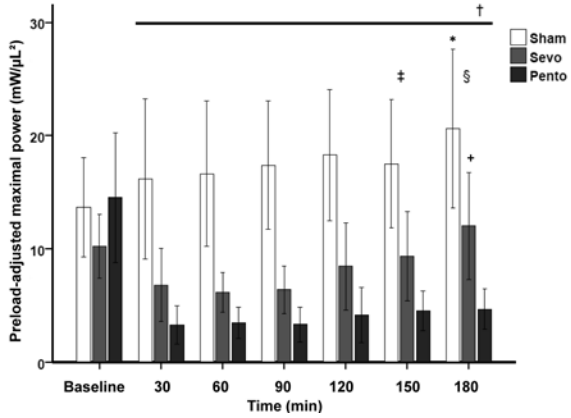

Figure 7. Time course of preload-adjusted maximal power. For the sham group, time is given as minutes after achieving steady state; for the resuscitated groups, time is given as minutes after ROSC. *, $P < 0.01$ compared with baseline; +, compared with 30 min after ROSC; †, $P < 0.01$ compared with sham group; ‡, $P < 0.05$ between the sevoflurane (Sevo) and pentobarbital (Pento) groups; §, $P < 0.01$ between the Sevo and Pento groups.

group than in the Pento group (9.4 ± 3.9 compared with 4.6 ± 1.8 mW/µL^2, $P < 0.05$). This difference became even more obvious at 3 h after ROSC, with a PAMP of 11.8 ± 4.9 mW/µL^2 in the Sevo group and 4.8 ± 1.9 mW/µL^2 in the Pento group ($P < 0.01$).

Discussion

The use of PV loops in assessing myocardial dysfunction after regional or global myocardial ischemia is becoming increasingly important. Most of these studies have been performed by using canine and porcine models. PV loop measurement in a porcine model revealed that infusion of adenosine and lidocaine improves postresuscitation cardiac function.[15] Cardiac diseases other than myocardial ischemia also are being investigated by using PV-loop measurements. For example, a piglet model showed improved left ventricular function when left ventricular apical pacing was used instead of right ventricular free wall pacing.[41] In human studies, PV-loop measurements are used for evaluating myocardial function in patients with hypertrophic cardiomyopathy or pulmonary hypertension.[25,47]

The effect of volatile anesthetics on myocardial ischemia–reperfusion injury has garnered increasing interest recently. A clinical benefit of volatile anesthetics on ischemia–reperfusion injury in patients undergoing heart surgery has been clearly demonstrated.[10] A pig model of CA showed that sevoflurane reduces myocardial damage in the early postresuscitation period.[31] Therefore, a model for evaluating myocardial dysfunction after CA by using PV-loop measurement and for assessing the influence of various anesthetics ought to be established.

Our results demonstrate that the use of PV–conductance catheters is feasible and that PV-loop measurements can be used to assess PRMD in models of CA and CPR in small laboratory animals, such as rats, objectively and reliably. Compared with established imaging techniques, such as ultrasonography and MRI, PV–conductance catheters yield data that are accurate and highly reproducible. In the current study, rats were monitored for 3 h after ROSC. During this period, no major problems developed during invasive measurements through the carotid artery, even with the catheter in place during CPR. By using sonomicrometer crystals, it is possible to generate PV loops continually for several days or even months.[29,32]

Measuring PV loops for studies on myocardial function in rats is a well-established technique.[1,3,4] We report here that

such a device is also well suited for the analysis of myocardial dysfunction after CPR in a small animal model. Rodent models have several advantages over models in pigs or dogs.[36] First, the conductance catheter technique could be used in genetically modified animals, such as knockout mice, to evaluate the effect of expression of specific genes after myocardial infarction or cardiorespiratory arrest, for example. Second, in small animals it is possible to analyze the whole brain histologically, which is not feasible in larger animals, like pigs. For this reason, our model supports studies that use outcome parameters of myocardial function and neuronal damage simultaneously. This characteristic might reduce the number of animals needed, because more information can be obtained from the same population. Third, rodent models are more cost effective and easier to handle (for example, housing) than are models using pigs or dogs.[36] Finally, the use of mice or rats over pigs or dogs as phylogenetically higher animals likely is preferable in animal studies.

In the present study, different cardiocirculatory baseline conditions existed among the groups before CA. For instance, EDV was higher in the Sevo group than in the other groups. This might be due to the reported negative inotropic effects of sevoflurane.[8,17] Furthermore, induction of ventricular fibrillation was significantly delayed in the Pento group, which can be explained by myocardial molecular mechanisms of action of sevoflurane. It has been suggested that volatile anesthetics exert cardiac side effects by inhibiting cardiac ion channels.[20] Interaction with cardiac Ca^{2+}-channels is a well-known side effect of sevoflurane.[2,37] Indeed, such a decrease in calcium influx has been shown to shorten the action potentials and decrease the refractory period. Furthermore, sevoflurane has been shown to inhibit cardiac Na^{+}-channels, which reduces cardiac conduction velocity.[52] Therefore, the effects observed in the Sevo group can at least in part be explained by the known effects of volatile anesthetics, that is, sevoflurane at the myocardial receptor and cellular levels.

Despite the duration of CPR and consequently the period of low-flow conditions in the Sevo group were significantly longer, important parameters of myocardial dysfunction such as EDV, $\delta p/\delta t$ max, and PAMP improved within 3 h after ROSC compared with those in the Pento group.

The EDV was found to be stable over the entire 3 h after ROSC in the Sevo group in contrast to the Pento group, in which the EDV increased continuously after ROSC. This increase in EDV is an indicator of serious ischemic myocardial damage caused by CA, which leads to acute heart failure. MAP was decreased after resuscitation in both groups, which correlates with results from other studies.[43,44] In the Sevo group MAP did not drop as sharply as in the Pento group and recovered earlier, which might be explained by a faster recovery of myocardial function.

One indicator of contractility is $\delta p/\delta t_{max}$, which is the first derivative of the native pressure curve. This parameter showed the expected decreasing course in the Sevo and Pento groups but, again, the Sevo group performed significantly better than did the Pento group. This finding also points to improved recovery of myocardial function in rats anesthetized by sevoflurane compared with pentobarbital. Whereas $\delta p/\delta t_{max}$ depends on preload conditions, PAMP is a more valid parameter of myocardial contractility. This measure was first described in 1991 and can be used to compare contractility even under different preload conditions.[24] PAMP at 3 h after ROSC was more than twice as high in the Sevo group as in the Pento group. Even the lowest value after ROSC in the Sevo group was higher than the best value in the Pento group (6.0 ± 1.7 mW/μL^2 1 h after ROSC compared with 4.8 ± 1.9 mW/μL^2 3 h after ROSC).

Together, these findings lead to the conclusion that the type of anesthesia used influences myocardial parameters after resuscitation of CA. When sevoflurane was used for preparing the animals before induction of CA, postresuscitation myocardial function was better than in the Pento group. These findings are even more interesting as the duration of CPR, the number of defibrillations, and the amount of epinephrine administered were higher in the Sevo group. Although volatile anesthetics are known to depress myocardial contractility,[35] parameters of myocardial contractility were significantly better during the first 3 h after CA and resuscitation in the Sevo group than in the Pento group.

It is well known from studies of regional ischemia that volatile anesthetics such as sevoflurane can contribute to a reduction of myocardial damage after ischemia–reperfusion injury.[9,10,51] This phenomenon is called anesthetic-induced pre- or postconditioning. This conditioning effect exists regardless of whether the volatile anesthetic was administered before regional ischemia or during the reperfusion phase.[16,42] There are several underlying molecular mechanisms. Ischemic and anesthetic preconditioning may release small concentrations of reactive oxygen species, which might activate intracellular protein kinases. This activation lowers the opening threshold for mitochondrial ATP-dependent K^{+} channels, thus reducing oxidative phosphorylation during ischemia and reperfusion by lowering the mitochondrial membrane potential.[11,33] In addition, volatile anesthetics activate the phosphatidylinositol-3-kinase signal transduction pathway, which stimulates nitric oxide synthase.[7] Nitric oxide mediates the ischemic postconditioning effect.[53] Volatile anesthetics reduce the adhesion of neutrophils in reperfused myocardium, and the application of sevoflurane in pigs after cardiopulmonary resuscitation reduced the expression of FAS ligand, an important mediator of apoptosis.[18,31]

In conclusion, we established a rat model of PV-loop measurement for assessing postresuscitation myocardial dysfunction. This model seems particularly suitable for the growing field of pre- and postconditioning research. Furthermore, our results demonstrate that when compared with pentobarbital anesthesia, sevoflurane anesthesia is associated with significantly improved postresuscitation myocardial function. Therefore, we recommend a standardized type of anesthesia in animal models for resuscitation research to improve the comparability of future studies on PRMD.

Acknowledgments

The authors state that there is no conflict of interest.

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