

Milrinone Combined with Vasopressin Improves Cardiac Index after Cardiopulmonary Resuscitation in a Pig Model of Myocardial Infarction

Thomas Palmaers, M.D., Sven Albrecht, M.D.,† Fabian Heuser, M.D.* Christian Leuthold,* Juergen Schuettler, M.D.,‡ Bernd Schmitz, M.D.§*

Background: **Milrinone used for acute cardiac insufficiency could be of interest during cardiopulmonary resuscitation because of its positive inotropic effects. In this study, the combination of milrinone–vasopressin was compared with epinephrine and vasopressin, as well as with the combination of epinephrine–vasopressin, in reference to hemodynamics.**

Methods: **Thirty-two pigs underwent ligation of the circumflex coronary artery and induction of ventricular fibrillation lasting for 4 min. Cardiopulmonary resuscitation was performed after randomization to one of four groups: epinephrine (30-μg/kg bolus), vasopressin (0.4-U/kg bolus), epinephrine–vasopressin (15-μg/kg epinephrine bolus, 0.2-U/kg vasopressin bolus), or milrinone–vasopressin (0.4-U/kg vasopressin bolus, 50-μg/kg milrinone bolus over 5 min and a continuous infusion of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The hemodynamic variables were measured before cardiopulmonary resuscitation as well as 4, 8, 15, and 30 min after return of spontaneous circulation.**

Results: **All animals were resuscitated successfully. The animals of the milrinone–vasopressin group displayed significantly ($P < 0.05$) higher cardiac index values (30 min after return of spontaneous circulation: epinephrine, 65.8 ± 13.2; vasopressin, 70.7 ± 18.3; epinephrine–vasopressin, 69.1 ± 36.2; milrinone–vasopressin, 120.7 ± 34.8 $ml \cdot min^{-1} \cdot kg^{-1}$) without a decrease in mean arterial pressure or coronary perfusion pressure.**

Conclusions: **The combination of vasopressin–milrinone as compared with epinephrine during cardiopulmonary resuscitation leads to an improved cardiac index without relevant decrease of mean arterial pressure or coronary perfusion pressure.**

EPINEPHRINE is the first-line drug for cardiopulmonary resuscitation (CPR).[1,2] The essential therapeutic effect of epinephrine during CPR is mediated by its α-sympathomimetic, vasoconstrictive component. Resulting from the increased systemic vascular resistance, improved diastolic perfusion of the coronary arteries is achieved during cardiac massage. The question of the best possible dosage of epinephrine has been the subject of many experimental and clinical studies and is still discussed controversially.[3–8] In addition, therapy with epinephrine alone has been critically questioned during the past years because the substance itself shows unwanted side effects due to its β-sympathomimetic actions: Epinephrine increases the degree of cerebral and myocardial oxygen consumption during CPR,[9] it influences the degree of myocardial dysfunction negatively,[10–12] and it worsens pulmonary gas exchange.[13] Pure vasopressors, such as methoxamine or vasopressin, both exhibiting no β-sympathomimetic acting component, were tested within the scope of experimental and clinical resuscitation studies.[14–17] On account of the resulting positive findings, vasopressin was recommended in the 2000 guidelines of the International Liaison Committee on Resuscitation as an alternative to epinephrine during CPR for ventricular fibrillation.[1] However, the 2005 International Liaison Committee on Resuscitation guidelines—published after achievement of this study—no longer recommend vasopressin, but do also not refute its use.[2]

In a resuscitation model without myocardial infarction in pigs, vasopressin reduced cardiac index (CI) during the postresuscitation period.[18] Therefore, it is conceivable that the administration of vasopressin in damaged myocardium could lead to a critical reduction in cardiac output followed by insufficient organ perfusion.

Selective phosphodiesterase III inhibitors are essential in the therapy of acute heart failure.[19–22] These drugs achieve the important improvement of myocardial contractility by increasing the intracellular concentration of cyclic adenosine monophosphate within the myocardial cells, as well as by vasodilation. An increase of cardiac output is achieved, independently of the stimulation of the adrenergic receptors, and does not lead to extensive tachycardia with a consecutive increase of myocardial oxygen consumption.[23] Therefore, phosphodiesterase III inhibitors could be of advantage for post-CPR cardiac insufficiency.

It was the aim of this study to investigate whether, in the scope of CPR, the vasoconstrictive effect of vasopressin and the subsequent decrease of cardiac output, especially in the immediate postresuscitation phase, can be reversed by phosphodiesterase III inhibitors. The second endpoint was to find out whether vasopressin administered together with milrinone causes a deterio-

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

* Staff Anesthesiologist, † Professor of Anesthesiology, ‡ Professor of Anesthesiology, Chairman, Department of Anesthesiology, University Hospital Erlangen. § Associate Professor of Anesthesiology, Chairman, Department of Anesthesiology and Intensive Care, Centre Hospitalier de Luxembourg, Luxembourg.

Received from the Department of Anesthesiology, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany. Submitted for publication December 13, 2005. Accepted for publication August 3, 2006. Support was provided solely from institutional and/or departmental sources. Presented in part at the Annual Meeting of the European Society of Anesthesiology, Vienna, Austria, May 29, 2005. Drs. Palmaers and Albrecht contributed equally to this work.

Address correspondence to Dr. Palmaers: Department of Anesthesiology, University Hospital Erlangen, Krankenhausstrasse 12, D-91054-Erlangen, Germany. palmaers@kfa.imed.uni-erlangen.de.

ration of mean arterial pressure (MAP) or coronary perfusion pressure (CPP) compared with the single or combined use of epinephrine and vasopressin. Because myocardial infarction based on coronary heart disease is the main cause of cardiocirculatory arrest, we decided to perform this study in an animal model of myocardial infarction.[24]

Materials and Methods

After the permission was granted by the responsible animal protection authority (Tierschutzkommission Würzburg, Würzburg, Germany), 32 male pigs were included in the study. Mean body weight was 28.3 ± 3.6 kg. The animals were premedicated intramuscularly with 15 mg/kg ketamine (Ketavet; Pfizer Pharma GmbH, Karlsruhe, Germany) and 0.5 mg/kg midazolam (Dormicum; Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany) followed by cannulation of an ear vein and an infusion of Ringer's solution at 10 $ml \cdot kg^{-1} \cdot h^{-1}$. Vital signs during the induction were monitored using a five-lead electrocardiogram and transcutaneous pulse oximetry (SC 9000XL; Siemens AG, Erlangen, Germany). After induction of general anesthesia with 3 mg/kg propofol (2% Disoprivan; AstraZeneca GmbH, Wedel, Germany), 30 μg/kg fentanyl (Fentanyl-Janssen; Janssen-Cilag GmbH, Neuss, Germany), and 0.2 mg/kg pancuronium (Pancuronium-Organon; Organon GmbH, Oberschleissheim, Germany), the animals were intubated orotracheally (Magill 7.0 mm ID; Mallinckrodt, Athlone, Ireland), and a volume-controlled ventilation was started with an inspiratory oxygen concentration of 30% (Servo 300 Ventilator; Siemens AG). The respiratory minute volume was adjusted to an end-tidal carbon dioxide concentration between 35 and 40 mmHg. Maintenance of general anesthesia was achieved with 5 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol (2% Disoprivan), 40 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl (Fentanyl-Janssen), and 0.4 $mg \cdot kg^{-1} \cdot h^{-1}$ pancuronium (Pancuronium-Organon). Depth of anesthesia was adjusted according to clinical and hemodynamic variables. After surgical exposure, the right femoral artery was cannulated using a 7-French catheter (110 cm; Arrow International Inc., Reading, PA). This catheter was advanced up into the descending aorta (at the level of the diaphragm) to measure MAP and diastolic arterial pressure. The right internal jugular vein was cannulated with a triluminal central venous catheter (7 French; Arrow International Inc.) for the administration of drugs and to measure the right ventricular end-diastolic pressure. All pressures were measured continuously during the entire experiment (SC 9000XL; Siemens AG). CPP was obtained by subtracting right ventricular end-diastolic pressure from diastolic aortic pressure. After median sternotomy, a pericardiotomy was performed to gain access to the heart. For continuous measurement of left atrial pressure, a catheter was advanced through the left auricular appendix into the left atrium. A thermodilution catheter (7 French; Arrow International Inc.) was inserted into the pulmonary artery to determinate the mean pulmonary arterial pressure (MPAP) and the cardiac output (CI = cardiac output/weight; SC 9000XL; Siemens AG). To assess CI, three single measurements, each with a bolus of 10 ml Ringer's solution (5°–10°C), were performed, and the results were averaged. A catheter was inserted through the apex of the heart into the left ventricle for continuous measurement of left ventricular pressure and to allow online calculations of the maximal velocity of the pressure increase (dP/dt_{max}) (DasyLab Software 5.0; Moenchengladbach, Germany). The correct position of all intravascular catheters was verified using fluoroscopy. All animals were then assigned to one of four therapeutic groups in a blinded and randomized manner using closed envelopes, each containing one of the four group numbers (eight envelopes for each group). Before the beginning of the experiment (32 days, 1 experiment/day), one of the 32 envelopes was taken out of a pot and opened, and the animal was assigned to its group:

- Epinephrine group (n = 8): CPR with 30 μg/kg epinephrine (Suprarenin; Sanofi-Aventis Germany, Frankfurt-Hoechst, Germany)
- Vasopressin group (n = 8): CPR with 0.4 U/kg arginine vasopressin (Pitressin; Pfizer Pharma Gmbh)
- Epinephrine–vasopressin group (n = 8): CPR with 15 μg/kg epinephrine (Suprarenin) in combination with 0.2 U/kg arginine vasopressin (Pitressin)
- Milrinone–vasopressin group (n = 8): CPR with 50 μg/kg milrinone (Corotrop; Sanofi-Synthelabo, Berlin, Germany) as a bolus over 5 min, followed by milrinone infusion with 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Arginine vasopressin (Pitressin) 0.4 U/kg was given at the start of the milrinone bolus.

Before CPR (baseline) and 4, 8, 15, and 30 min after return of spontaneous circulation (ROSC), the following measurements were taken: heart rate (beats/min), MAP (mmHg), MPAP (mmHg), left atrial pressure (mmHg), systemic vascular resistance index ($dyn \cdot s \cdot cm^{-5} \cdot kg$), maximal rate of change of left ventricular pressure (dP/dt_{max}; mmHg/s), CI ($l \cdot min^{-1} \cdot kg^{-1}$), and CPP (mmHg). After the 30-min assessment period, the animals were killed with an infusion of 20 mmol potassium chloride.

Subsequent to the preparation of the animals and a 20-min equilibration time, ventricular fibrillation (VF) and cardiac arrest were induced by placing a 9-V direct current on the heart. Immediately after onset of VF, the circumflex coronary artery was prepped directly at its origin from the left coronary artery and closed by clipping it with two vessel clips within 1–2 min from the beginning of VF. After a 4-min cardiocirculatory arrest, CPR was commenced. During cardiac arrest, ventilation was stopped, the ventilator disconnected from the en-

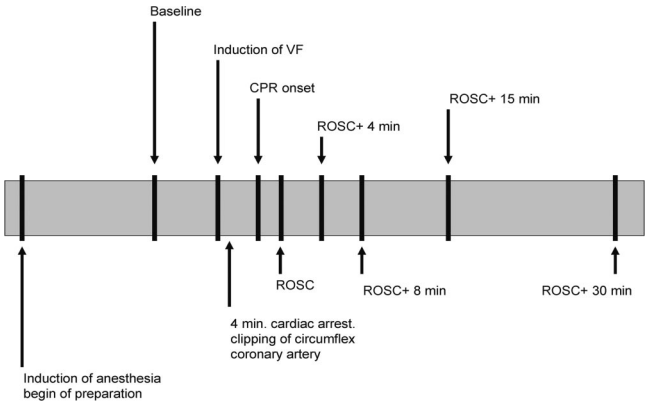

Fig. 1. Flowchart indicating the time course of the experiment. CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation; VF = ventricular fibrillation.

dotracheal tube, and sedation was discontinued. With the onset of CPR, volume-controlled ventilation was restarted with an inspiratory oxygen concentration of 100%, and general anesthesia was achieved with continuous infusion of 2.5 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} propofol (2% Disoprivan), 20 μg $\cdot$ kg^{-1} $\cdot$ h^{-1} fentanyl (Fentanyl-Janssen), and 0.2 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} pancuronium (Pancuronium-Organon). Open cardiac massage was always performed by the same examiner who was blinded to the pharmacologic therapy regimen and MAP gained by cardiac massage. At the beginning of cardiac massage, the drugs for CPR were administered according to the study protocol *via* the distal lumen of the triluminal central venous catheter. One minute after drug application, defibrillation occurred with 30 J for all shocks, which were delivered internally (transmyocardially) until termination of ventricular fibrillation. After a series of three unsuccessful defibrillations applied without time delay, cardiac massage was reperformed for 2 min, followed by another drug application and a new defibrillation series. The following values were measured and documented during the CPR phase: duration of CPR until ROSC, number of the applied defibrillations, and highest MAP during CPR and after ROSC. CPR was considered successful if spontaneous circulation (MAP $>$ 50 mmHg) was maintained for at least 3 min. A detailed timeline of the experiment is shown in figure 1.

Statistical Analysis

All variables were tested for normality using the Shapiro-Wilks W test. Normally distributed data are expressed as mean $\pm$ SD, and nonnormally distributed data are expressed as median and interquartile range (25–75%).

To determine the baseline differences between the therapeutic groups considering data surveyed only once, analysis of variance was used for normally distributed data. Nonnormally distributed data were tested using the Kruskal-Wallis test. Statistical differences of hemodynamic data between the respective groups were determined using analysis of variance. *Post hoc* testing of differences within the groups was performed using the Newman-Keuls test. The level of significance was defined as $P < 0.05$ (two-tailed). All statistical calculations were performed using Statistica 6.0 software (Stat-Soft, Tulsa, OK).

Results

All animals were successfully resuscitated. Table 1 shows the CPR-relevant data. There were no significant differences among the four study groups. One animal in the epinephrine group and one in the milrinone–vasopressin group died approximately halfway through the 30-min observation period after successful CPR due to VF. Regarding the CI values, the milrinone–vasopressin group differed significantly ($P < 0.05$) over time from the other groups during the postresuscitation phase. A significant increase of CI after ROSC compared with baseline levels could be seen only in this group. Even during the following postresuscitation phase, the CI values did not decrease below those measured before CPR (fig. 2A).

In the immediate postresuscitation period, MAP values significantly increased in all animals compared with baseline levels (fig. 2B), followed by a constant decrease to values lower than baseline 15 min after ROSC. Animals in the vasopressin group displayed the highest MAP values after ROSC. However, significant differences over time between the groups were not found (fig. 2B).

Similar to the MAP, the CPP values increased signifi-

Table 1. Cardiopulmonary Resuscitation–relevant Variables

	EPI (n = 8)	VP (n = 8)	EPI–VP (n = 8)	MIL–VP (n = 8)
Defibrillations until ROSC, n	4.5 (3.5–12.5)	5.0 (2.0–10.5)	6.0 (3.0–9.0)	2.0 (1.0–3.5)
CPR duration, s	102 (78–270)	110 (70–260)	130 (70–240)	79 (72–120)
MAP_{max} during CPR, mmHg	80 $\pm$ 19	66 $\pm$ 18	68 $\pm$ 7	68 $\pm$ 36
MAP_{max} after ROSC, mmHg	171 $\pm$ 32	162 $\pm$ 28	172 $\pm$ 21	141 $\pm$ 41

Nonnormally distributed data (number of defibrillations and cardiopulmonary resuscitation [CPR] duration) are presented as median (interquartile range). Normal distributed data (maximum mean arterial pressure [MAP_{max}] during CPR and MAP_{max} after return of spontaneous circulation [ROSC]) are presented as mean $\pm$ SD. No significant differences between groups.

EPI = epinephrine group (n = 8); EPI–VP = epinephrine–vasopressin group (n = 8); MIL–VP = milrinone–vasopressin group (n = 8); VP = vasopressin group (n = 8).

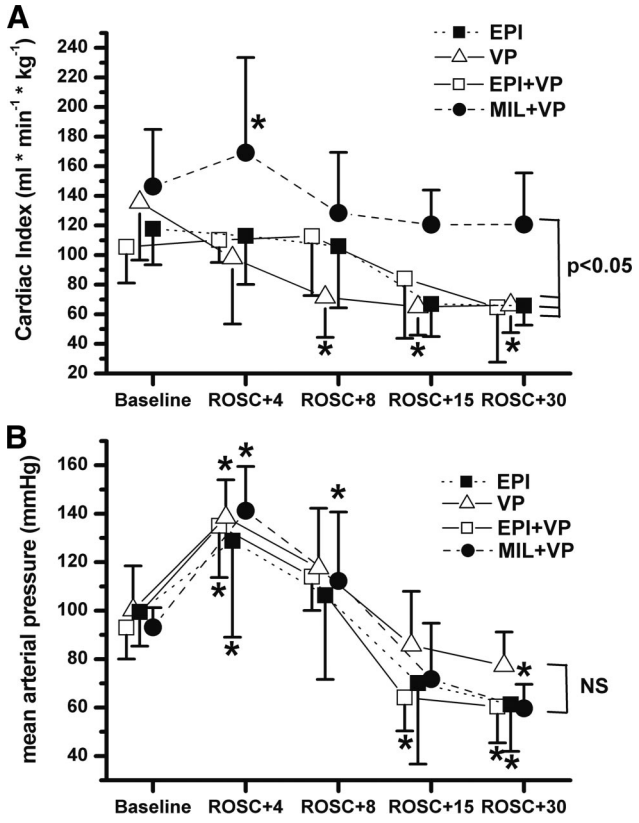

Fig. 2. Time course of cardiac index (*A*) and time course of mean arterial pressure (*B*) at different time points: baseline (before the beginning of resuscitation) and 4, 8, 15, and 30 min after return of spontaneous circulation (ROSC) in the different groups: epinephrine group (EPI; n = 8), vasopressin group (VP; n = 8), epinephrine–vasopressin group (EPI–VP; n = 8), and milrinone–vasopressin group (MIL–VP; n = 8). * indicates a significant difference ($P < 0.05$) from baseline value; $P < 0.05$ indicates a significant difference over time between the MIL–VP group and the EPI, VP, and EPI–VP group; NS indicates no significant difference over time among the four groups.

cantly in all study groups 4 min after ROSC. Subsequently, the CPP steadily decreased in all groups, reaching values below baseline levels 15 min after ROSC. Animals in the vasopressin group consistently exhibited the highest CPP values after ROSC. Significant differences between the groups over time were not found (table 2).

The time courses of the MPAP values after ROSC roughly paralleled those of the MAP values. Compared with the baseline levels, the MPAP values significantly increased during the first 4 min after CPR and thereafter decreased constantly. Contrary to the MAP values, the MPAP, except for the milrinone–vasopressin group, did not decrease below the baseline values. Those animals resuscitated with epinephrine (epinephrine and epinephrine–vasopressin groups) showed the highest MPAP values 30 min after ROSC and were significantly different over time compared with the vasopressin and epinephrine–vasopressin groups (table 2). Compared with the baseline values, heart rate significantly ($P < 0.05$) increased in all four groups at all time points after ROSC. No differences could be seen between the groups over time (table 2). In all groups, compared with the baseline level, the pressure within the left atrium increased significantly ($P < 0.05$) 4 min after ROSC, reaching baseline levels again during the following postresuscitation phase (table 2). Significant differences between the study groups were not found.

As for most of the other hemodynamic variables, the maximum velocity of the pressure increase of the left ventricle (dP/dt_{max}) was significantly increased in the immediate postresuscitation phase, except in the vasopressin group. No significant differences between the groups were found (table 2).

An increase of the systemic vascular resistance index compared with the baseline was only observed in the vasopressin group, whereas vasopressin compared with milrinone–vasopressin group was significantly different over time (table 2).

Discussion

Our study demonstrates that CPR during myocardial infarction in an animal model can be successfully performed using a combination of milrinone and vasopressin. Moreover, resuscitation—after 4 min of cardiac arrest—in terms of ROSC and maintenance of adequate circulation for more than 3 min was achieved in all animals of each group.

The allocation of the investigated drug regimen to one of the four groups was determined according to the recent research on CPR and the International Liaison Committee on Resuscitation Guidelines 2000.[1] Since vasopressin was strongly recommended by the International Liaison Committee on Resuscitation as an alternative drug in patients with VF, many studies have been published, including studies using a combination of vasopressin and epinephrine.[15,17,25–28] Because vasopressin is known to have severe adverse effects, such as a decrease in myocardial and renal medullary blood flow,[29,30] a partner drug suitable for combination with vasopressin is still missing. Lurie *et al.*[31] used nitroglycerine in combination with epinephrine and vasopressin and found a significant increase in vital organ blood flow compared with epinephrine alone. However, they did not compare nitroglycerine combined with epinephrine or vasopressin alone.

Niemann *et al.*[32] used milrinone during CPR for the first time. They showed that if using milrinone, systemic vascular resistance index was significantly lower after CPR, compared with placebo, without a significant reduction of MAP. Stimulated by the promising results of Niemann *et al.*, we decided to introduce milrinone–vasopressin as new comparator in our study.

The dosages of the drugs were chosen according to the usual dosage in humans or experimental settings. The

Table 2. Time Course of Hemodynamic Variables

Variable	Baseline	ROSC + 4	ROSC + 8	ROSC + 15	ROSC + 30	Between-group Comparison
DAP, mmHg						
EPI	76 ± 15	106 ± 38*	83 ± 32	50 ± 27	44 ± 17	NS
VP	79 ± 15	111 ± 19*	97 ± 24	68 ± 20	56 ± 15	
EPI–VP	69 ± 10	109 ± 23*	90 ± 18	49 ± 13	45 ± 12	
MIL–VP	70 ± 7	111 ± 21*	84 ± 29	53 ± 17	46 ± 7	
RVEDP, mmHg						
EPI	5 ± 2	9 ± 3*	8 ± 4	7 ± 3	7 ± 3	NS
VP	5 ± 2	7 ± 3	8 ± 4*	8 ± 3	8 ± 3	
EPI–VP	4 ± 1	5 ± 3	5 ± 4	5 ± 3	5 ± 3	
MIL–VP	6 ± 1	5 ± 3	4 ± 2	5 ± 1	6 ± 2	
CPP, mmHg						
EPI	71 ± 15	97 ± 40*	76 ± 35	44 ± 28	37 ± 17*	NS
VP	74 ± 16	103 ± 21*	89 ± 25	61 ± 19	49 ± 13	
EPI–VP	65 ± 10	104 ± 24*	85 ± 18	43 ± 12	40 ± 10	
MIL–VP	65 ± 7	107 ± 20*	80 ± 29	47 ± 17	40 ± 6	
MPAP, mmHg						
EPI	21 ± 4	45 ± 21*	41 ± 18*	32 ± 16*	26. ± 5	EPI, EPI–VP ≠ VP, MIL–VP
VP	20 ± 3	33 ± 10	27 ± 5	25 ± 5	22 ± 3	
EPI–VP	17 ± 7	38 ± 10*	35 ± 8*	28 ± 10	27 ± 10	
MIL–VP	19 ± 5	36 ± 11*	27 ± 7	23 ± 3	17 ± 4	
LAP, mmHg						
EPI	9 ± 2	29 ± 14*	21 ± 9*	18 ± 9	19 ± 5	NS
VP	9 ± 2	25 ± 7*	19 ± 6	19 ± 5	15 ± 3	
EPI–VP	8 ± 2	25 ± 12*	22 ± 9*	15 ± 5	15 ± 5	
MIL–VP	10 ± 3	28 ± 13*	17 ± 8	13 ± 2	11 ± 3	
HR, beats/min						
EPI	95 ± 10	193 ± 22*	175 ± 29*	149 ± 34*	136 ± 38*	NS
VP	91 ± 12	159 ± 22*	143 ± 30*	142 ± 32*	137 ± 31*	
EPI–VP	88 ± 6	187 ± 25*	156 ± 21*	147 ± 15*	127 ± 17*	
MIL–VP	95 ± 12	183 ± 17*	166 ± 14*	152 ± 13*	134 ± 13*	
SVRI, dyn · s · cm^{-5} · kg						
EPI	673 ± 181	894 ± 174	786 ± 211	700 ± 297	662 ± 165	VP ≠ MIL–VP
VP	592 ± 230	1167 ± 428*	1321 ± 668*	928 ± 244	819 ± 226	
EPI–VP	668 ± 110	922 ± 190	880 ± 461	611 ± 266	764 ± 335	
MIL–VP	507 ± 123	848 ± 671	759 ± 431	465 ± 232	389 ± 173	
dP/dt_{max}, mmHg/s						
EPI	1,287 ± 239	2,128 ± 635*	1,866 ± 731*	970 ± 381	721 ± 205	NS
VP	1,490 ± 251	1,937 ± 523	1,663 ± 657	1,164 ± 365	1,049 ± 224	
EPI–VP	1,409 ± 464	2,265 ± 864*	1,851 ± 743	994 ± 317	1,007 ± 568	
MIL–VP	1,412 ± 294	2,422 ± 887*	2,131 ± 875*	1,360 ± 615	1,158 ± 270	

Data are expressed as mean ± SD. Time points: baseline (before the beginning of resuscitation) and 4, 8, 15, and 30 min after return of spontaneous circulation (ROSC) in the different groups: epinephrine group (EPI; n = 8), vasopressin group (VP; n = 8), epinephrine–vasopressin group (EPI–VP; n = 8), and milrinone–vasopressin group (MIL–VP; n = 8). Between-group comparisons: NS indicates not significant; ≠ indicates a significant difference ($P < 0.05$) between groups over time; * indicates a significant difference ($P < 0.05$) *vs.* baseline value.

CPP = coronary perfusion pressure; DAP = diastolic aortic pressure; dP/dt_{max} = velocity increase of left ventricular pressure; HR = heart rate; LAP = left arterial pressure; MPAP = mean pulmonary arterial pressure; RVEDP = right ventricular end-diastolic pressure; SVRI = systemic vascular resistance index.

epinephrine dosage in the epinephrine group was 30 μg/kg. This is the most commonly used dosage in pig studies. The dosages range from 15 to 45 μg/kg.[15,25–28] However, the normal dosage in humans is 10 μg/kg. The vasopressin dosage (0.4 U/kg) in the vasopressin and milrinone–vasopressin groups resulted from the recommendations for humans and is also the typically used amount in CPR studies with pigs.[1,15,17,25–28] In the epinephrine–vasopressin group, we reduced the dosage of epinephrine and vasopressin by one half compared with the epinephrine and vasopressin groups. The reason for this dose reduction is the synergistic effect of the two drugs as vasopressors and the lack of an explicit dosing recommendation for this drug combination. However, our dosage of 15 μg/kg epinephrine plus 0.2 U/kg vasopressin was empirically chosen. The dosing regimen of milrinone followed the recommendations for humans with acute heart failure and the one used by Niemann *et al.*[32]

Because the majority of patients experience cardiac arrest due to myocardial infarction, acute heart failure, or severe cardiac arrhythmias[17,33] and because these pathophysiologic entities are usually not exhibited in animal models, our study is based on an experimental animal infarction model developed by this work group.[24]

Looking at the required number of defibrillations, we could not find any differences between the epinephrine, vasopressin, and epinephrine–vasopressin groups. These findings are in contrast to those of Babar *et al.*,[34] who compared vasopressin and epinephrine treatment during CPR in an animal model. They observed a higher rate

of defibrillation success with only one shock in the vasopressin group. Besides and in contrast to our findings, they saw a significant improvement of CPP, which can be explained by the lack of myocardial infarction with consecutive myocardial deterioration.[34]

Similar to the findings of Mulligan *et al.*,[35] we showed that among vasopressin, epinephrine, and a combination of the two, there are no significant differences regarding MAP during and after CPR. Nevertheless, we found a higher systemic vascular resistance combined with a slightly reduced cardiac output in the vasopressin-treated group compared with the other study groups. This finding is in line with a study conducted by Lindner *et al.*[15] In contrast, animals treated with vasopressin–milrinone exhibited a significantly increased cardiac output with concurrent lower values of systemic resistance, but without deterioration of CPP and MAP. Consequently, we assume that within the scope of CPR, the vasodilatory effect of milrinone balances the vasopressive effect of vasopressin. This corresponds to the results by Niemann *et al.*[32]

Regarding the time course of MPAP, differences between the epinephrine- and vasopressin-treated animals were observed in this study. Whereas persistently increased MPAP values were found in the epinephrine and epinephrine–vasopressin groups after CPR, the vasopressin group showed a rapid normalization to baseline values. Animals receiving the additional milrinone treatment demonstrated values even lower than baseline at the end of the observation period. Lindner *et al.*[15] compared the treatment with epinephrine and vasopressin in similar CPR experiments and likewise saw a considerable increase of the MPAP values after successful CPR. Contrary to our findings, the MPAP values in their piglets did not decrease back to baseline values, possibly because of a higher vasopressin dosage (0.8 *vs.* 0.4 U/kg). Mayr *et al.*[36] also observed a persisting increase of MPAP in piglets during treatment with a combination of epinephrine and vasopressin, a finding that is in line with our data. In the case of single treatment with milrinone[32] during CPR, or as in our study with the combination of vasopressin and milrinone, more favorable MPAP values were obtained. This could be an explanation for the significantly increased CI we found, because lower MPAP values lead to a better right ventricular function and thus to an increased CI.

Because a better velocity increase of the pressure dP/dt_{max} was measured in the milrinone–vasopressin group, we assume that this drug combination could improve myocardial function after CPR. However, dP/dt_{max} is load dependent, and therefore, a decrease in afterload with a consecutive increase in CI can lead to an increased dP/dt_{max} without a real improvement of contractility.[37]

Because of the β-adrenergic effects of epinephrine, we expected a higher heart rate in animals resuscitated with epinephrine, but interestingly, we found no difference between the groups. With no difference in heart rate and an increased dP/dt_{max}, oxygen consumption in the milrinone–vasopressin group should be increased, an unwanted effect. But with milrinone reducing systemic vascular resistance index (table 2), we have a change in load conditions and therefore perhaps an increased dP/dt_{max} value, without increased oxygen consumption.

Combining vasopressin and milrinone, CI increased significantly after CPR compared with epinephrine, vasopressin, and epinephrine–vasopressin in our piglets. Regarding the optimization of organ perfusion after CPR, which, among other things, depends directly on the CI, this result is promising.

However, Faivre *et al.*,[29] who used levosimendan, a calcium sensitizer, in combination with either vasopressin or norepinephrine, showed that vasopressin in contrast to norepinephrine significantly decreased renal and aortic blood flow. This implies that the combination of epinephrine–milrinone or norepinephrine–milrinone compared with vasopressin–milrinone should also be of future interest, especially focusing on hemodynamics and vital organ blood flow.

Besides the positive findings, there are some limitations. The first limitation is the group size. Without any preliminary results on milrinone–vasopressin and therefore without any knowledge of the expected CI, no power analysis could be performed to find the optimal group size. Second, in our study, we performed open heart resuscitation, which is certainly not the standard procedure during cardiac arrest. However, this open chest model facilitates determination of many invasive pressures as well as producing an artificial myocardial infarction by clipping the circumflex coronary artery. A further limitation of our study is the difference in continuous drug administration in the milrinone–vasopressin group (continuous infusion of milrinone, also after ROSC) compared with the bolus therapy in the other three groups. However, we chose this protocol to investigate the effects of milrinone during the 20- to 30-min effect time of the vasopressin bolus. To find out whether the combination of milrinone and the short-acting epinephrine would also have a positive influence on hemodynamics during and after CPR, further studies comparing this combination with vasopressin–milrinone are necessary. Further limitations are the short observation period without 24-h outcome and the lack of the determination of vital organ blood flows. Although pigs are the most common animals for experimental settings on resuscitation, one should not forget that it could be a problem, because of species differences, to transfer results from animal studies to human patients.

In conclusion, the current study shows that a phosphodiesterase III inhibitor and vasopressin are a successful combination during CPR for ventricular fibrillation in piglets. Unfavorable effects of a therapy using vasopres-

sin, such as an extensive increase of myocardial afterload and reduction of CI, could be reversed by milrinone. Moreover, the drug combination of milrinone and vasopressin improved CI without influencing MAP and CPP negatively. Therefore, in the course of CPR, the combination of milrinone and vasopressin seems to be a promising concept when used in the compromised myocardium and justifies further investigations.

References

1. International Liaison Committee on Resuscitation Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 6: Advanced cardiovascular life support: Section 6: Pharmacology II: Agents to optimize cardiac output and blood pressure. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Circulation 2000; 102:I129–35
2. Nolan JP, Deakin CD, Soar J, Böttiger BW, Smith G: European Resuscitation Council Guidelines for Resuscitation 2005: Section 4: Adult advanced life support. Resuscitation 2005; 67:S39–86
3. Barton C, Callaham M: High-dose epinephrine improves the return of spontaneous circulation rates in human victims of cardiac arrest. Ann Emerg Med 1991; 20:722–5
4. Berg RA, Otto CW, Kern KB, Sanders AB, Hilwig RW, Hansen KK, Ewy GA: High-dose epinephrine results in greater early mortality after resuscitation from prolonged cardiac arrest in pigs: A prospective, randomized study. Crit Care Med 1994; 22:282–90
5. Hoekstra JW, Griffith R, Kelley R, Cody RJ, Lewis D, Scheatzle M, Brown CG: Effect of standard-dose *versus* high-dose epinephrine on myocardial high-energy phosphates during ventricular fibrillation and closed-chest CPR. Ann Emerg Med 1993; 22:1385–91
6. Hornchen U, Berg PW, Schüttler J: Potential risks of high-dose adrenaline for resuscitation following short-term heart arrest in animal experiments. Anasthesiol Intensivmed Notfallmed Schmerzther 1992; 27:274–8
7. Lindner KH, Ahnefeld FW, Prengel AW: Comparison of standard and high-dose adrenaline in the resuscitation of asystole and electromechanical dissociation. Acta Anaesthesiol Scand 1991; 35:253–6
8. Schmitz B, Fischer M, Bockhorst K, Hoehn-Berlage M, Hossmann KA: Resuscitation from cardiac arrest in cats: Influence of epinephrine dosage on brain recovery. Resuscitation 1995; 30:251–62
9. Ditchey RV, Lindenfeld J: Failure of epinephrine to improve the balance between myocardial oxygen supply and demand during closed-chest resuscitation in dogs. Circulation 1988; 78:382–9
10. Gazmuri RJ, Weil MH, Bisera J, Tang W, Fukui M, McKee D: Myocardial dysfunction after successful resuscitation from cardiac arrest. Crit Care Med 1996; 24:992–1000
11. Niemann JT, Haynes KS, Garner D, Rennie CJ III, Jagels G, Stormo O: Postcountershock pulseless rhythms: Response to CPR, artificial cardiac pacing, and adrenergic agonists. Ann Emerg Med 1986; 15:112–20
12. Tang W, Weil MH, Sun S, Noc M, Yang L, Gazmuri RJ: Epinephrine increases the severity of postresuscitation myocardial dysfunction. Circulation 1995; 92:3089–93
13. Tang W, Weil MH, Gazmuri RJ, Sun S, Duggal C, Bisera J: Pulmonary ventilation/perfusion defects induced by epinephrine during cardiopulmonary resuscitation. Circulation 1991; 84:2101–7
14. Lindner KH, Ahnefeld FW, Schuermann W, Bowdler IM: Epinephrine and norepinephrine in cardiopulmonary resuscitation: Effects on myocardial oxygen delivery and consumption. Chest 1990; 97:1458–62
15. Lindner KH, Brinkmann A, Pfenninger EG, Lurie KG, Goertz A, Lindner IM: Effect of vasopressin on hemodynamic variables, organ blood flow, and acid-base status in a pig model of cardiopulmonary resuscitation. Anesth Analg 1993; 77:427–35
16. Lindner KH, Dirks B, Strohmenger HU, Prengel AW, Lindner IM, Lurie KG: Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. Lancet 1997; 349:535–7
17. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH: A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med 2004; 350:105–13
18. Prengel AW, Lindner KH, Keller A, Lurie KG: Cardiovascular function during the postresuscitation phase after cardiac arrest in pigs: A comparison of epinephrine *versus* vasopressin. Crit Care Med 1996; 24:2014–9
19. Cuffe MS, Califf RM, Adams KF Jr., Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghiade M: Short-term intravenous milrinone for acute exacerbation of chronic heart failure: A randomized controlled trial. JAMA 2002; 287:1541–7
20. DiBianco R, Shabetai R, Kostuk W, Moran J, Schlant RC, Wright R: A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. N Engl J Med 1989; 320:677–83
21. Kikura M, Levy JH, Bailey JM, Shanewise JS, Michelsen LG, Sadel SM: A bolus dose of 1.5 mg/kg amrinone effectively improves low cardiac output state following separation from cardiopulmonary bypass in cardiac surgical patients. Acta Anaesthesiol Scand 1998; 42:825–33
22. Rathmell JP, Prielipp RC, Butterworth JF, Williams E, Villamaria F, Testa L, Viscomi C, Ittleman FP, Baisden CE, Royster RL: A multicenter, randomized, blind comparison of amrinone with milrinone after elective cardiac surgery. Anesth Analg 1998; 86:683–90
23. Evans DB: Overview of cardiovascular physiologic and pharmacologic aspects of selective phosphodiesterase peak III inhibitors. Am J Cardiol 1989; 63:9A–11A
24. Palmaers T, Albrecht S, Leuthold C, Heuser F, Schüttler J, Schmitz B: Myocardial function following cardiopulmonary resuscitation in pig model of myocardial infarction. Eur J Anaesthesiol 2004; 21 (suppl 32):184
25. Lindner KH, Prengel AW, Brinkmann A, Strohmenger HU, Lindner IM, Lurie KG: Vasopressin administration in refractory cardiac arrest. Ann Intern Med 1996; 124:1061–4
26. Lindner KH, Prengel AW, Pfenninger EG, Lindner IM, Strohmenger HU, Georgieff M, Lurie KG: Vasopressin improves vital organ blood flow during closed-chest cardiopulmonary resuscitation in pigs. Circulation 1995; 91:215–21
27. Voelckel WG, Lurie KG, McKnite S, Zielinski T, Lindstrom P, Peterson C, Wenzel V, Lindner KH, Benditt D: Effects of epinephrine and vasopressin in a piglet model of prolonged ventricular fibrillation and cardiopulmonary resuscitation. Crit Care Med 2002; 30:957–62
28. Voelckel WG, Wenzel V, Lindner KH: Is one drug enough? Arginine vasopressin in pediatric cardiopulmonary resuscitation. Resuscitation 2002; 52: 157–8
29. Faivre V, Kaskos H, Callebert J, Losser MR, Milliez P, Bonnin P, Payen D, Mebazaa A: Cardiac and renal effects of levosimendan, arginine vasopressin, and norepinephrine in lipopolysaccharide-treated rabbits. ANESTHESIOLOGY 2005; 103: 514–21
30. Ouattara A, Landi M, Le Manach Y, Lecomte P, Leguen M, Boccara G, Coriat P, Riou B: Comparative cardiac effects of terlipressin, vasopressin, and norepinephrine on an isolated perfused rabbit heart. ANESTHESIOLOGY 2005; 102: 85–92
31. Lurie KG, Voelckel WG, Iskos DN, McKnite SH, Zielinski TM, Sugiyama A, Wenzel V, Benditt D, Lindner KH: Combination drug therapy with vasopressin, adrenaline (epinephrine) and nitroglycerin improves vital organ blood flow in a porcine model of ventricular fibrillation. Resuscitation 2002; 54:187–94
32. Niemann JT, Garner D, Khaleeli E, Lewis RJ: Milrinone facilitates resuscitation from cardiac arrest and attenuates postresuscitation myocardial dysfunction. Circulation 2003; 108:3031–5
33. Wennerblom B, Holmberg S: Death outside hospital with special reference to heart disease. Eur Heart J 1984; 5:266–74
34. Babar SI, Berg RA, Hilwig RW, Kern KB, Ewy GA: Vasopressin *versus* epinephrine during cardiopulmonary resuscitation: A randomized swine outcome study. Resuscitation 1999; 41:185–92
35. Mulligan KA, McKnite SH, Lindner KH, Lindstrom PJ, Detloff B, Lurie KG: Synergistic effects of vasopressin plus epinephrine during cardiopulmonary resuscitation. Resuscitation 1997; 35:265–71
36. Mayr VD, Wenzel V, Voelckel WG, Krismer AC, Mueller T, Lurie KG, Lindner KH: Developing a vasopressor combination in a pig model of adult asphyxial cardiac arrest. Circulation 2001; 104:1651–6
37. Shapira N, Schaff HV, Piehler JM, White RD, Still JC, Pluth JR: Cardiovascular effects of protamine sulfate in man. J Thorac Cardiovasc Surg 1982; 84:505–14