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

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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 μg · kg⁻¹ · 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 · min⁻¹ · 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). 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.

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, it influences the degree of myocardial dysfunction negatively, and it worsens pulmonary gas exchange.

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. 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. 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.

In a resuscitation model without myocardial infarction in pigs, vasopressin reduced cardiac index (CI) during the postresuscitation period. 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. 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. 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 deterior-
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 internal jugular vein was cannulated with a triluminal catheter (7 French; Mallinckrodt, Athlone, Ireland), to measure MAP and diastolic arterial pressure. The right ventricle was prepaped directly at its origin from the left coronary artery and closed by a clip during surgical exposure, the right femoral artery was cannulated with a triluminal catheter (7 French; Arrow International Inc.) for the administration of drugs and to measure the 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°C–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/dtmax) (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 milrinoone infusion with 0.4 μg · kg⁻¹ · 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 · s · cm⁻⁵ · kg), maximal rate of change of left ventricular pressure (dP/dtmax; mmHg/s), CI (l · min⁻¹ · 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-
disopivirian), 20

EPI

SD. No significant differences between groups.

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·kg⁻¹·h⁻¹ propofol (2% disopivirian), 20 µg·kg⁻¹·h⁻¹ fentanyl (Fentanyl-Jansen), and 0.2 mg·kg⁻¹·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.

### 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-
significantly 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).

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. 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. Because vasopressin is known to have severe adverse effects, such as a decrease in myocardial and renal medullary blood flow, a partner drug suitable for combination with vasopressin is missing. Lurie et al. 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. 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
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 arrhythmias17–35 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

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**Table 2. Time Course of Hemodynamic Variables**

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

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/dtmax = 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.
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 vasopresorific 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 milrinone32 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-
si, 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


Anesthesiology, V 106, No 1, Jan 2007

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