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Effects of the AT1-selective angiotensin II antagonist, telmisartan, on hemodynamics and ventricular function after cardiopulmonary resuscitation in pigs[1]

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Abstract

The purpose of this study was to investigate the effects of the angiotensin II (ANG II) antagonist, telmisartan, on hemodynamics, myocardial function and myocardial blood flow during the postresuscitation phase in a porcine model of CPR and to compare these to saline. After 4 min of ventricular fibrillation and 5 min of closed-chest CPR, defibrillation was performed in 16 domestic pigs to restore spontaneous circulation (ROSC). Ten minutes after ROSC, animals were allocated to receive either the ANG II antagonist, telmisartan, at a dose of 1 mg/kg ($n = 8$) or saline ($n = 8$). Hemodynamics, myocardial function and myocardial blood flow were measured prearrest and at 5, 30, 90 and 240 min after ROSC. Using a Swan-Ganz catheter with a fast responding-thermistor and a micromanometer tipped catheter, right ventricular end-diastolic and end-systolic volume, right ventricular ejection fraction, left ventricular contractility were 67 ± 6 ml (mean $\pm$ S.E.M.), 42 ± 4 ml, $38 \pm 2\%$, 2036 ± 77 mmHg/s in the telmisartan group and 82 ± 2 ml ($P < 0.05$), 59 ± 3 ml ($P < 0.01$), $28 \pm 2\%$ ($P < 0.01$), 1596 ± 82 mmHg/s ($P < 0.01$) in the control group, at 240 min after ROSC. No significant differences in mean aortic and pulmonary artery pressure, cardiac index or myocardial blood flow between the two groups were found. We conclude that the ANG II antagonist telmisartan administered during the postresuscitation phase in pigs increases myocardial contractility without changing cardiac index, systemic vascular resistance, pulmonary vascular resistance, or myocardial perfusion. © 1997 Elsevier Science Ireland Ltd.

Keywords: Angiotensin II antagonist; Cardiopulmonary resuscitation; Domestic pigs; Myocardial contractility; Postresuscitation phase; Telmisartan

1. Introduction

The endogenous release of vasopressor hormones such as catecholamines, angiotensin II (ANG II), endothelin and vasopressin in response to cardiac arrest and CPR is not usually sufficient for restoration of spontaneous circulation (ROSC), so that high dose administration of exogenous vasopressors is required in order to raise myocardial perfusion to sufficiently high levels for ROSC [1,2]. However, whereas peripheral vasoconstriction contributes to resuscitation success during CPR, neurohormonal activation and myocardial stunning after ROSC may impair myocardial function and reduce cardiac index during the immediate postresuscitation phase [3–6]. Angiotensin converting enzyme (ACE) inhibitors have become a well accepted treatment of congestive heart failure [7] and in patients with

Abbreviations: ACE, angiotensin converting enzyme; ANG II, angiotensin II; CPR, cardiopulmonary resuscitation; ROSC, restoration of spontaneous circulation.

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acute myocardial infarction, early treatment with an ACE inhibitor has been shown to improve short-term and long-term outcome [8]. ACE inhibitors have been found to improve myocardial performance in the reperfusion phase following myocardial ischemia [9] and ANG II blockade has also been shown to improve recovery of stunned myocardium [10]. In acute myocardial dysfunction following cardiac arrest and CPR, however, blockade of the renin-angiotensin system as a whole has not as yet been evaluated. Therefore, the purpose of this study was to assess myocardial function and hemodynamic effects of the ANG II antagonist selective for the AT_1 receptor subtype, telmisartan [11,12], during the immediate postresuscitation phase in a porcine model of CPR and to compare these to saline. In particular, the following three questions have been addressed in this study: (i) does telmisartan reverse the pressure response to cardiac arrest in the post-resuscitation period? (ii) Does telmisartan modify cardiac contractility in this situation? (iii) Are there any adverse effects on coronary perfusion?

2. Methods

2.1. Animal preparation

This investigation was approved by the animal protection agency of the state of Baden-Württemberg, Germany. Care and handling of the animals were in accordance with United States National Institutes of Health Guidelines. All animals were fasted for 10 h before surgery, but had free access to water. The animals were premedicated using an intramuscular injection of azaperon (Stresnil, 40 mg/ml solution, 4 mg/kg, Janssen, Neuss, Germany) 30 min before induction of anesthesia. Anasthesia was induced in pigs (male and female, weighing between 25 and 29 kg, aged 10–12 weeks) by injecting sodium pentobarbital (Nembutal, 60 mg/ml solution, 15 mg/kg, Sanofi, Hannover, Germany) into an ear vein, and anesthesia was maintained by continuous infusion of pentothal 0.5 mg/kg per h. Analgesia was achieved with a bolus dose of buprenorphine (Temgesic, 0.3 mg/ml, 0.02 mg/kg, Boehringer Mannheim GmbH, Mannheim, Germany). The animals were then fixed in the dorsal recumbent position, intubated endotracheally during spontaneous respiration, and ventilated using a Servo ventilator (Siemens, Erlangen, Germany) with 65% nitrous oxide in oxygen at 20 breaths/min, with a tidal volume to maintain normocapnia (Pa_{CO_2} 35–40 mmHg).

For monitoring cardiac rhythm, a standard II electrocardiogram was recorded using three subcutaneous electrodes. Reference blood samples for measurement of myocardial blood flow were taken from a 7-Fr catheter, which was advanced by femoral cutdown into the descending aorta. Two 7-Fr catheters were inserted via femoral cutdowns in the descending aorta for monitoring of blood pressure and withdrawal of blood samples. Two separate 5-Fr catheters in the right atrium and the inferior caval vein were used for drug administration. A 7-Fr pigtail catheter (Cordis Medizinische Apparate, Haan, Germany) was advanced under pressure control via femoral cutdown into the left ventricle in order to inject radiolabelled microspheres for the measurement of vital organ blood flow. A 7.5-Fr pulmonary artery and right ventricular ejection fraction catheter (model 93A-434-7.5FG, Edwards Critical-Care Division, Irvine, CA) was placed via left external jugular vein into pulmonary artery. A micromanometer tipped catheter (Micro-Tip PC-350, Millar, Houston, TX) was placed into the left ventricle via cutdown of the left carotid artery for measurement of intraventricular pressure. Body temperature (blood temperature) was recorded from pulmonary artery catheter and was maintained between 37.5 and 38.5°C using a heating pad. All catheters were pressure flushed during the preparation and postresuscitation phase using saline containing 5 U/ml sodium heparin at a rate of 3 ml/h (Intraflow II, Abbott laboratories, North Chicago, Ill). In addition during the preparation and postresuscitation phase, animals received 6 ml/kg/h of Ringer's solution and a total of 500 ml of a 3% gelatine solution to replace blood loss due to surgical preparation. Normally, infusions were performed at the rates stated, but when necessary, the infusion rates were corrected for filling pressures to avoid under- or overloading in individual cases. After completion of surgery and 10 min before induction of cardiac arrest, oxygen was increased to 100% and phenobarbital administration was stopped. At the same time, 300 U/kg sodium heparin was administered intravenously to prevent intracardiac clot formation. At the end of the experiment, all animals were autopsied to check correct position of the catheters and to look for damage to the rib cage and internal organs.

2.2. Experimental protocol

Before induction of cardiocirculatory arrest, hemodynamic parameters, arterial and venous blood gases, and vital organ perfusion were measured simultaneously. A 50 Hz, 60 V alternating current was applied via two subcutaneous needle electrodes to induce ventricular fibrillation. Cardiac arrest was confirmed by noting the typical electrocardiographic rhythm of ventricular fibrillation and a sudden decrease in aortic pressure wave-form to zero. Ventilation was stopped at this point. After 4 min of cardiac arrest, manual closed-chest CPR was performed at a rate of 80/min. The compression force was applied to the midsternum whereas relaxation (decompression) was allowed to oc-

cur passively. The depth of compression was approximately 25% of the anterior-posterior thorax diameter. When cardiac massage was begun, ventilation was resumed with 100% oxygen at a respiratory rate of 20 breaths/min and at that tidal volume which had been determined as resulting in normocapnia before arrest. Cardiac massage was always performed by the same person.

In a previous animal study, vasopressin has been shown to be superior to epinephrine with respect to the percentage of successful resuscitations [13]. Regarding the relative hemodynamic effects of vasopressin (0.4 U/kg) or epinephrine (0.045 mg/kg) administered during CPR, the pressor response during the early postresuscitation phase (i.e. up to 30 min after ROSC) was more pronounced after vasopressin than after epinephrine, resulting in a significantly higher systemic vascular resistance and a significantly lower cardiac index in the vasopressin group. During the remaining period of observation which lasted for 240 min after ROSC, no significant differences in systemic vascular resistance or cardiac index were found between the two groups [14]. Therefore after 3 min of CPR, all animals received 0.4 U/kg vasopressin (Pitressin, Parke-Davis, Freiburg, Germany) diluted in 10 ml of physiological saline given via central venous catheter over a period of 5 s. Ninety seconds after vasopressor administration, we attempted to restore spontaneous circulation with a DC countershock (LIFEPAK 6 defibrillator, Physiocontrol, Redmond, Washington). Three DC countershocks were initially administered at an energy setting of 3 J/kg. If ventricular fibrillation or ventricular tachycardia persisted, the same drug was administered at a dose of 0.4 U/kg, and closed-chest CPR was reinitiated for an additional 90 s. Three further DC countershocks (5 J/kg) were then delivered in rapid sequence. The same protocol (without defibrillation) was used if asystole or pulseless electrical activity developed. When, after successful defibrillation further defibrillation was necessary because of recurrence of ventricular fibrillation, the energy level of this repeated shock was the same as the initially successful shock. Sustained ventricular dysrhythmias were treated by injecting lidocaine (Xylocain, 20 mg/ml, Astra Chemicals GmbH, Wedel, Germany) at a dose of 1.5 mg/kg. Restoration of spontaneous circulation (ROSC) was defined as coordinated electrical activity and a systolic blood pressure >90 mm Hg for at least 5 min, during which no further resuscitation measures were necessary. The period of the postresuscitation phase was measured from that point in time onwards.

Ten minutes after ROSC, animals were assigned to receive either a 1 mg/kg bolus of telmisartan (Dr Karl Thomae, Biberach an der Riß, Germany) diluted in 10 ml of physiologic saline followed by a continuous infusion of telmisartan at a dosage of 30 μg/kg/h or placebo (10 ml bolus of saline followed by a continuous infusion of saline). Telmisartan is a competitive, selective inhibitor of the ANG II receptor subtype 1 and has no agonistic properties [7,8]. In preliminary experiments, the dosage chosen has been found to perform insuperable antagonism of ANG II induced cardiovascular effects. The time-delay between onset of ventricular fibrillation and restoration of spontaneous circulation may be more important to the activation of the renin–angiotensin system and therefore in this experimental setting, the drug may have been administered after the peak of any ANG II on coronary circulation. However during CPR, adequate coronary perfusion pressure due to increased vascular resistance is crucial for ROSC and therefore at that point in time, administration of an ANG II antagonist may be detrimental for resuscitation success. The animals were allocated to drug treatment by random numbers and all investigators were blinded.

At the beginning of the postresuscitation phase, anasthesia was resumed by continuous infusion of pentobarbital at a dose of 0.2 mg/kg per min and a further bolus dose of buprenorphine (0.01 mg/kg). No other drugs were given during the postresuscitation period.

2.3. Measurements

Heart rate was recorded from the signal of standard ECG. Pressures were continuously measured from the aorta, right atrium and pulmonary artery using a multichannel recorder (Hewlett Packard 7758, Böblingen, Germany) with calibrated pressure transducers (model 1290A, Hewlett Packard, Boeblingen, Germany) and zero established to atmospheric pressure at the level of the right atrium. Using an ejection fraction cardiac output computer (REF/1, Baxter Edwards Critical Care, Irvine, CA), cardiac output, right ventricular ejection fraction, right ventricular end-systolic and end-diastolic volume were determined in triplicate by the thermodilution technique (5 ml of iced saline injected into the right atrium) prearrest and at 5, 30, 90 and 240 min after ROSC (i.e. at 5 min before and at 20, 80 and 230 min after drug administration).

Left ventricular intracavity pressures were continuously measured with a micromanometer tipped catheter which was coupled to a monitor-recorder unit provided with a contractility module and a non-commercially available software package (ADAS system, Dr Karl Thomae, Biberach, Germany). Left ventricular systolic and end-diastolic pressure, the rate of left ventricular pressure development (dP/dt), the negative deflection of this curve as a measure for left ventricular relaxation ($-dP/dt$) were recorded simultaneously. Left ventricular end-diastolic pressure, dP/dt and $-dP/dt$ were evaluated prearrest and 5, 30, 90, and 240 min after ROSC. At the end of the experiment, heart rate, mean

arterial and pulmonary arterial pressure, left ventricular contractility and cardiac index were evaluated at 2, 5 and 10 min after ANG II administration. Cardiac index, pulmonary and systemic vascular resistance were calculated using standard formulas.

Arterial and mixed venous blood gases, haemoglobin content and oxygen saturation were measured with a blood gas analyzer (Radiometer, ABL 330, Copenhagen, Denmark) and corrected for temperature.

Vital organ perfusion was measured using radiolabelled microspheres according to the technique as previously described [15]. Organ blood flow was measured in this study at 15 min before induction of ventricular fibrillation and at 5, 30, 90 and 240 min after ROSC. Microspheres (New England Nuclear, Dreieich, Germany) with a mean diameter of 15 ± 1.5 μm and specific activity of 10 mCi/g were used. The microspheres were labelled with ^{141}Cereum, ^{95}Niobium, ^{103}Ruthenium, ^{46}Scandium and ^{85}Strontium. Before injection, the microsphere vial was placed in an ultrasonically vibrated water bath for 1 min. Approximately 5×10^5 microspheres diluted in 10 ml of saline were then immediately injected into the left ventricle. With the use of an automatic withdrawal pump (Braun, Melsungen, Germany), blood was continuously withdrawn over a period of 2 min from the catheter lying in the descending aorta at a rate of 6 ml/min over a period of 2 min. At the end of the experiment, the entire heart was removed. The left ventricular wall was sectioned into three layers. Aliquots of right ventricular, left ventricular and septal tissue were weighted, homogenized and then placed into vials. The radioactivity of the blood collected, which served as a reference organ, was measured with a gamma scintillation spectrometer (LB 5300, Berthold, Wildbad, Germany) as was the radioactivity in the homogenized tissues.

2.4. Statistical analysis

Values are expressed as mean $\pm$ S.E.M. Statistical analysis was carried out using the STATISTIKA™ software package, Release 4.5 (STATSoft, Tulsa, OK). Because data did not satisfy the assumption of approximate equality of variance of sample distribution, Mann-Whitney U test (two-tailed) was performed to determine differences between the telmisartan and the control groups. For multiple comparisons within one group, the Bonferroni method was applied. Statistical significance was considered to be at the $P < 0.05$ level.

3. Results

In 16 of the 17 animals included in this investigation the whole protocol could be performed as planned. In one animal, spontaneous circulation could not be restored because a complete atrioventricular block which occurred after the sixth defibrillation attempt. This animal was excluded from the study. In all animals of both groups, a single dose of 0.4 U/kg vasopressin was sufficient for restoration of spontaneous circulation, and in all animals, the first countershock was performed after 8.5 min of cardiac arrest. Repeated countershocks, because of recurrence of ventricular fibrillation, were necessary in six animals of the telmisartan group and in six animals of the placebo group. It was necessary to give 3.5 ± 0.7 shocks/animal (mean $\pm$ S.E.M.) in the telmisartan group and 2.1 ± 0.3 shocks/animal in the placebo group ($P = 0.2075$), respectively. The total lidocaine doses in the telmisartan group and the placebo group were 50 ± 9 and 50 ± 7 mg, respectively ($P = 0.8748$).

Hemodynamic variables prearrest and during the postresuscitation phase are shown in Table 1. At 240 min after ROSC, left ventricular contractility and right ventricular ejection fraction were significantly higher, right ventricular end-diastolic and end-systolic volume were significantly lower in the telmisartan group in comparison to the control group. In all the other hemodynamic variables shown in Table 1, no clinically important differences were found between the two groups.

At no point in time, either prearrest or during the postresuscitation phase, was there a clinically important difference found between the two groups with respect to haemoglobin or arterial or mixed venous blood gases.

At no point, either prearrest or during the postresuscitation phase, was there significant differences found between the two groups with respect to left ventricular or right myocardial blood flow or to the endocardial/epicardial ratio of myocardial perfusion (Table 2).

4. Discussion

Results of this study demonstrate that during the postresuscitation phase in pigs, administration of the ANG II antagonist telmisartan results in an improvement of both left and right ventricular function without changing myocardial perfusion, cardiac output, pulmonary or peripheral vascular resistance in comparison to saline.

Activation of the renin-angiotensin-system can be regarded as part of the neuroendocrine response to hypotension in order to maintain normal organ perfusion. Major factors stimulating the release of renin are renal hypoperfusion and renal β-receptor stimulation via baroreceptor activation and increased sympathetic adrenergic discharge [16]. ANG II enhances sympathetic reflex activity [17] and promotes the secretion of aldosterone and vasopressin [18]. Because of the

Table 1
Hemodynamic variables (mean ± S.E.M.) prearrest and during the postresuscitation phase before and after drug administration

Variable	Group	Prearrest	Postresuscitation phase			
			DA			
			5 min	30 min	90 min	240 min
Heart rate (beats/min)	Telm	109 ± 5	155 ± 13	130 ± 13	128 ± 15	110 ± 11
	Control	107 ± 5	157 ± 10	121 ± 7	147 ± 19	115 ± 13
MAP (mmHg)	Telm	114 ± 4	91 ± 7	84 ± 3	91 ± 3	90 ± 2
	Control	122 ± 11	93 ± 12	91 ± 4	93 ± 4	92 ± 4
MPAP (mmHg)	Telm	17 ± 1	19 ± 1	17 ± 1	16 ± 1	15 ± 1
	Control	16 ± 1	19 ± 1	17 ± 1	16 ± 1	15 ± 1
RAP (mmHg)	Telm	4 ± 1	6 ± 1	4 ± 1	3 ± 1	2 ± 1
	Control	3 ± 1	7 ± 1	5 ± 1	2 ± 1	2 ± 1
PCWP (mmHg)	Telm	6 ± 1	12 ± 1	9 ± 1	5 ± 1	3 ± 1
	Control	6 ± 1	13 ± 1	8 ± 1	6 ± 1	5 ± 1
CO (l/min)	Telm	3.1 ± 0.2	1.8 ± 0.3	2.1 ± 0.2	2.7 ± 0.2	2.9 ± 0.1
	Control	3.5 ± 0.2	2.0 ± 0.3	2.1 ± 0.1	3.1 ± 0.1	2.8 ± 0.1
SVR (dyn/s per cm^5)	Telm	2886 ± 152	4064 ± 291	3203 ± 215	2760 ± 236	2435 ± 145
	Control	2803 ± 264	3690 ± 393	3354 ± 166	2562 ± 317	2660 ± 147
PVR (dyn/s per cm^5)	Telm	277 ± 38	303 ± 62	323 ± 33	334 ± 34	314 ± 26
	Control	231 ± 19	258 ± 43	319 ± 28	302 ± 22	296 ± 16
dP/dt_{max} (mmHg/s)	Telm	2029 ± 93	1863 ± 391	1507 ± 141	1996 ± 173	2036 ± 77
	Control	2054 ± 80	1861 ± 316	1344 ± 127	1709 ± 192	1596 ± 82[b]
$-dP/dt_{max}$ (mmHg/s)	Telm	2905 ± 109	1838 ± 466	1803 ± 115	2364 ± 207	2890 ± 114
	Control	2976 ± 141	1930 ± 373	1868 ± 227	2414 ± 252	2669 ± 182
LVEDP (mmHg)	Telm	12 ± 0	9 ± 1	9 ± 0	9 ± 1	10 ± 0
	Control	12 ± 0	11 ± 1	10 ± 0	10 ± 1	10 ± 0
RVEF (%)	Telm	35 ± 4	24 ± 5	23 ± 3	30 ± 3	38 ± 2
	Control	37 ± 3	24 ± 4	23 ± 2	31 ± 2	28 ± 2[b]
RVEDV (ml)	Telm	72 ± 3	57 ± 6	69 ± 4	73 ± 6	67 ± 6
	Control	67 ± 6	61 ± 5	71 ± 5	72 ± 3	82 ± 2[a]
RVESV (ml)	Telm	47 ± 4	46 ± 7	54 ± 5	52 ± 6	42 ± 4
	Control	49 ± 5	47 ± 5	55 ± 5	51 ± 4	59 ± 3[b]

DA, drug administration; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; RAP, right atrial pressure; PCWP, pulmonary capillary wedge-pressure; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; dP/dt_{max}, maximal rate of left ventricular pressure development; $-dP/dt$, negative deflection of dP/dt_{max}; LVEDP, left ventricular end-diastolic pressure; RVEF, right ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; Telm, angiotensin II antagonist Telmisartan.

[a] $P<0.05$ vs. Telmisartan group.

[b] $P<0.01$ vs. Telmisartan group by two-tailed Mann-Whitney U test.

tremendous neuroendocrine activation during cardiac arrest, vasopressor levels including those of the renin-angiotensin-system are still elevated during the immediate postresuscitation phase [19–21]. Impaired myocardial function as part of the postresuscitation syndrome has been described earlier [5,6]. By increasing cardiac afterload, high ANG II levels may contribute to the aggravation of heart failure [22]. In patients with congestive heart failure, it has been shown that the degree of neuroendocrine activation is an important prognostic factor for long-term survival. Furthermore, the beneficial effect of ACE-inhibitors in reducing mortality was confined to the patients with the most extensive hormonal activation including ANG II and norepinephrine [23,24].

In several studies, ACE inhibition has been investigated during the very early stage of acute myocardial infarction, but the beneficial effects are controversial [8,25,26]. During acute myocardial dysfunction in the immediate postresuscitation phase, however, blockade of the renin-angiotensin-system has not been investigated. The results from our study show that administration of an ANG II antagonist results in an improvement of both left and right ventricular function without changing cardiac output or vascular resistance. These findings suggest that in this model of postresuscitation heart failure, ANG II antagonism improves global cardiac performance via effects on myocardial function rather than by afterload reduction. Since pulmonary artery pressure is comparable in the two treatment groups, the decrease in right ventricular end-diastolic and end-systolic volumes in the telmisartan may be secondary to increased myocardial contractility rather than to an influence on ventricular load.

Table 2
Myocardial blood flow (mean ± S.E.M.) prearrest and during the post resuscitation phase before and after drug administration

Variable	Group	Prearrest	Postresuscitation phase			
			DA			
			5 min	30 min	90 min	240 min
LVMBF (ml/min per g)	Telm	1.9 ± 0.2	2.6 ± 0.4	1.3 ± 0.1	2.1 ± 0.4	2.3 ± 0.5
	Control	2.1 ± 0.3	2.3 ± 0.3	1.4 ± 0.1	2.4 ± 0.3	2.6 ± 0.5
	P	0.5628	0.8972	0.9078	0.4622	0.2480
Endo-Epi ratio	Telm	1.3 ± 0.03	0.9 ± 0.06	1.4 ± 0.08	1.3 ± 0.08	1.3 ± 0.03
	Control	1.3 ± 0.03	0.8 ± 0.04	1.4 ± 0.03	1.3 ± 0.08	1.2 ± 0.05
Septum (ml/min per g)	Telm	1.9 ± 0.2	2.3 ± 0.4	1.3 ± 0.2	2.0 ± 0.3	2.3 ± 0.4
	Control	2.0 ± 0.2	2.0 ± 0.4	1.6 ± 0.1	2.6 ± 0.3	2.7 ± 0.5
	P	0.6985	0.6985	0.2774	0.2471	0.2471
RVMBF (ml/min per g)	Telm	1.5 ± 0.3	3.4 ± 0.8	1.1 ± 0.2	1.7 ± 0.5	1.5 ± 0.3
	Control	1.3 ± 0.1	3.1 ± 1.0	1.2 ± 0.2	1.9 ± 0.3	1.6 ± 0.1
	P	0.7750	0.6985	0.4822	0.3124	0.3545

DA, drug administration; LVMBF, left ventricular myocardial blood flow; Endo-Epi ratio, ratio endocardial blood flow—epicardial blood flow of the left ventricle; RVMBF, right ventricular myocardial blood flow. Telm, angiotensin II antagonist Telmisartan.

In addition to the endocrine ANG II formation in the vascular endothelium, which is presumed to provide short-term cardiovascular homeostasis, paracrine tissue renin–angiotensin-system seems to play an important role in the local control of vascular resistance and has tissue specific functions, particularly in the heart [27]. Besides its positive chronotropic and inotropic effects [28–30], ANG II is thought to cause coronary vasoconstriction [31] and necrosis of cardiac tissue [32]. These effects of ANG II have been shown to be mediated via the ANG II receptor subtype 1, whereas the function of the subtype 2 binding site is not yet known [33]. Cardiac ACE activity or ANG II formation have been reported to correlate with the degree of myocardial dysfunction [34,35] and to increase after myocardial infarction [36]. Blockade of the renin-angiotensin-system by ACE inhibitors has been shown to increase coronary blood flow and to improve global myocardial performance in the reperfusion phase following myocardial ischemia [9]. However, the beneficial effects of ACE inhibition have in part been attributed to the increased formation of nitric oxide and prostacyclin via decreased bradykinin metabolism [37–39], and a part of the conversion angiotensin I to ANG II may occur independently of ACE via a chymase [40,41]. ANG II blockade has also been shown to be effective in improving recovery of stunned myocardium [10]. The results of our study support these observations and show that during the immediate postresuscitation in pigs, early blockade of the renin–angiotensin-system by ANG II antagonism results in a significant improvement in myocardial function without causing hypotension and thus threatening myocardial perfusion. In particular, in the face of the isolated changes in myocardial contractility without affecting myocardial blood flow, heart rate or blood pressure, an effect of ANG II antagonism at the cellular level needs to be taken into consideration. Further studies will be needed, however, to determine whether the initiation of renin-angiotensin-blockade at this early state of myocardial dysfunction can prevent the development of congestive heart failure and improve long-term survival.

This study has some limitations which should be commented on. Firstly, this animal model has not been conclusively demonstrated to be predictive of clinical studies. It is an experimental model with healthy animals, and short arrest and cardiopulmonary resuscitation times was used. Preexisting coronary atherosclerosis, myocardial infarction or impaired myocardial function, long lasting myocardial hypoxia and the need for higher vasopressor doses after prolonged arrest times may cause a more pronounced cardiovascular dysfunction after cardiopulmonary resuscitation. In addition, investigation of perfusion and function of other organ systems such as gut, liver and kidney are necessary in order to evaluate the effects of ANG II antagonism during the postresuscitation phase more completely. Secondly, it is open to question, why the differences in right ventricular volume and left ventricular contractile function differ between groups only at the 240 min time point. One possible reason could be that myocardial function (i.e. dp/dt) of the telmisartan group improves with time, but that the *P*-value does not reach statistical significance until the 240 min point of observation. On the other hand, it cannot be excluded that despite the strictly standardized study protocol, some unspecific factors such as cumulative effects of the anesthetics or differences in loading conditions may have adversely affected the control group and the telmisartan group. Thirdly, myocardial perfusion vari-

ables show a trend towards reduced myocardial blood flow at most time points following telmisartan, but the between-group *P*-values for these variables to indicate the between-group differences are not statistically different. Nevertheless, it cannot be excluded that with only eight animals in each group, this study may not have the statistical power to uncover a difference. This would be a very important factor when translated to the clinical setting of cardiac arrest in the context of acute myocardial ischemia or infarction.

We conclude that during the postresuscitation phase in pigs, administration of the ANG II antagonist telmisartan improves myocardial contractility without significantly changing myocardial perfusion, cardiac output or vascular resistance.

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