Research

Effects of an angiotensin II antagonist on organ perfusion during the post-resuscitation phase in pigs

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Abstract

Background: The aim of this study was to compare pre-arrest and post-resuscitation organ perfusion values and to investigate whether, during the post-resuscitation phase, administration of the angiotensin II antagonist telmisartan (TELM) 10 min after restoration of spontaneous circulation (ROSC) could improve organ flow in comparison to placebo.
Results: Five minutes after ROSC in the TELM group, blood flow in the cortex and myocardium increased to 583% ($P < 0.05$) and 137% (not significant), respectively, whereas blood flow of the colon, stomach and pancreas decreased to 50% ($P < 0.05$), 28% ($P < 0.05$) and 19% ($P < 0.05$) of pre-arrest values, respectively. At 90 min after ROSC, pre-arrest perfusion values both in non-splanchnic and splanchnic organs were achieved. At no point in time were there significant differences between the two groups with respect to organ blood flow or speed of recovery of organ perfusion.
Conclusions: During the post-resuscitation phase, organ blood flow is characterized by the coincidence of increased cerebral and myocardial blood flow and decreased intestinal blood flow. Administration of TELM 10 min after ROSC did not improve the recovery of organ perfusion.

Keywords: angiotensin II antagonist, cardiopulmonary resuscitation, organ perfusion, post-resuscitation phase, telmisartan

Introduction

In an effort to improve the dismal outcome of cardiac arrest, a variety of vasopressor agents have been investigated in animal models and in humans [1–3]. In particular, in a porcine model of ventricular fibrillation, administration of vasopressin led to a significantly higher coronary perfusion pressure and myocardial blood flow than high dose epinephrine [3]. Vasopressin, however, is reported to be a potent splanchnic vasoconstrictor which leads to a disproportionate reduction in mesenteric blood flow [4,5]. In addition, activation of the renin-angiotensin system has been shown to be part of the neuroendocrine response to cardiac arrest [6,7] or severe systemic hypotension [4,8], and angiotensin II (ANG II) mediates highly selective and potent splanchnic vasoconstriction [4,8,9]. During hemorrhagic or cardiogenic shock, blockade of the renin-angiotensin axis has been shown to abolish selective splanchnic vasoconstriction [10–12]. However, blockade of the renin-angiotensin axis during the immediate post-resuscitation phase has not yet been evaluated. The purpose of this study was to compare splanchnic and non-splanchnic organ perfusion pre-arrest to post-resuscitation values after vasopressin administration in a porcine model of cardiopulmonary resuscitation (CPR) and to investigate whether, during the immediate post-resuscitation phase, administration of the ANG II antagonist telmisartan (TELM) could improve organ blood flow in comparison with saline.

Materials and methods

Animal preparation

This investigation was approved by the animal investigation committee of the state of Baden-Württemberg. Care and handling of the animals was in accordance with the United States National Institutes of Health Guidelines.

Sixteen domestic pigs of body weight between 25 and 29 kg were fasted for 10 h before surgery, but had free access to water. After premedication with azaperone (4 mg/kg im) and atropine (0.1 mg/kg) 30 min before induction of surgery, anesthesia was induced by injecting sodium pentobarbital (15 mg/kg) into an ear vein, followed by continuous infusion of pentothal at a dosage of 0.5 mg/kg per min. Analgesia was achieved with a bolus dose of buprenorphine (0.02 mg/kg). The animals were intubated endotracheally and ventilation was performed using a Servo ventilator (Servo, Siemens, Erlangen, Germany) with 65% nitrous oxide in oxygen at 20 breaths/min with the tidal volume set to maintain normocapnia.

A standard II electrocardiogram was recorded using three subcutaneous electrodes. Three 7-Fr catheters were inserted via femoral cutdowns in the descending aorta for monitoring of blood pressure or withdrawal of blood samples. A 7-Fr catheter was placed under digital control via the right external jugular vein into the hepatic vein.

The correct position of this catheter was confirmed both by hepatic venous oxygen saturation control and by autopsy at the end of the experiment. Two separate 5-Fr catheters in the right atrium and in the inferior vena cava were used for drug administration. A 7-Fr pigtail catheter was advanced under pressure control via a femoral cutdown into the left ventricle in order to inject radiolabeled microspheres for the measurement of organ perfusion. A 7.5-Fr pulmonary artery catheter (Edwards Critical-Care Division, Irvine, CA, USA) was placed via the left external jugular vein into the pulmonary artery. Body temperature (blood temperature) was recorded from the thermistor of the pulmonary artery catheter and maintained between 37.5°C and 38.5°C using a heating pad. During the preparation and post-resuscitation phase, the animals received 6 ml/kg per h Ringer's solution and a total of 500 ml 3% gelatine solution to replace blood loss due to surgical preparation. In addition, during the preparation phase, right atrial and pulmonary arterial pressures were used to guide volume replacement in order to maintain comparable left ventricular and right ventricular filling pressures before induction of cardiac arrest.

Experimental protocol

Before the induction of cardiocirculatory arrest, hemodynamic parameters, and arterial, mixed venous and hepatic venous blood gases, as well as vital organ perfusion were measured. Ventricular fibrillation was induced with a 50 Hz alternating current administered to the thorax via two subcutaneous needle electrodes. Ventilation was stopped at this point. After 4 min of cardiac arrest, closed-chest CPR was performed at a rate of 80/min. The compression force was applied to the animal's midsternum, whereas relaxation (decompression) was allowed to occur passively. The depth of compression was approximately 25% of the anterior-posterior thorax diameter and the duration of compression was approximately 50% of the total cycle time. On initiation of cardiac massage, ventilation was resumed with 100% oxygen, a respiratory rate of 20 breaths/min and at a tidal volume that had been determined as resulting in normocapnia before arrest.

In a previous animal study, vasopressin was shown to be superior to epinephrine with respect to the percentage of successful resuscitations [3]. After 3 min of CPR, therefore, all animals received 0.4 U/kg vasopressin (Pitressin, Parke-Davis GmbH, Freiburg, Germany) given via a central venous catheter over a period of 5 s. Ninety seconds after vasopressor administration, we attempted to restore spontaneous circulation with direct current shocks using a LIFEPAK 6 defibrillator (Physiocontrol Corporation, Redmont, Washington, USA). Three countershocks were initially administered at an energy setting of 3 J/kg. In the case of persisting ventricular fibrillation, the same drug was administered at the same dose as initially given and CPR was resumed for a further 90 s with three subsequently delivered countershocks at an energy setting of 5 J/kg. The same protocol (without defibrillation) was used if asystole or pulseless electrical activity developed. Restoration of spontaneous circulation (ROSC) was defined as coordinated electrical activity and a systolic blood pressure $>$ 90 mmHg for at least 5 min. At the beginning of the post-resuscitation phase, anesthesia was resumed with a continuous infusion of 0.2 mg/kg per min pentobarbital and a further 0.01 mg/kg bolus of buprenorphine.

Ten minutes after ROSC, the animals were randomly allocated to receive either a 1 mg/kg bolus of the ANG II antagonist TELM (Karl Thomae GmbH, Biberach, Germany) diluted in 10 ml physiologic saline, followed by a continuous infusion of TELM at a dosage of 30 mg/kg per h (TELM group), or placebo (control group). Telmisartan is a selective antagonist of the ANG II receptor subtype 1 and has no agonistic properties [13,14]. Telmisartan interacts neither with ANG II receptor subtype 2 nor with other receptor systems. In previous experiments, the dosage chosen has been found to perform insurmountable antagonism of cardiovascular effects induced by ANG II [13].

Measurements

Heart rate was recorded from the signal of a standard electrocardiograph. Pressures were continuously recorded from the aorta, right atrium and pulmonary artery using a multi-channel recorder (ADAS, Thomae GmbH, Germany). These pressures were evaluated pre-arrest and at 5, 30, 90 and 240 min after ROSC (ie pre-arrest, 5 min before, and 20, 80 and 230 min after drug administration). Using a cardiac output computer (Baxter Edwards Critical Care, Irvine, CA, USA), cardiac output was evaluated in triplicate

by the thermodilution technique pre-arrest, and at 5, 30, 90 and 240 min after ROSC.

Arterial, mixed venous and hepatic venous blood gases, and hemoglobin content were measured with a blood gas analyzer (Radiometer, ABL 330, Copenhagen, Denmark).

Using radiolabeled microspheres [15], organ blood flow was measured pre-arrest and at 5, 30, 90 and 240 min after ROSC. Microspheres (New England Nuclear, Dreieich, Germany; mean diameter 15 ± 1.5 mm) were labeled with ^{141}cerium, ^{95}niobium, ^{103}ruthenium, ^{46}scandium and ^{85}strontium. Each microsphere vial was placed into a water bath and subjected to ultrasonic vibration for 1 min before injection. Approximately 5×10^5 microspheres were diluted in 10 ml saline and then immediately injected into the left ventricle. Using an automatic withdrawal pump (Braun, Melsungen, Germany), blood was continuously withdrawn from the catheter lying in the descending aorta at a rate of 6 ml/min (known `organ' blood flow) for 2 min. At the end of the experiment, aliquots of left ventricular free wall, cerebrum, liver, spleen, stomach, pancreas, jejunum, colon, kidney and adrenal gland were removed. The radioactivity of the blood collected (count of the reference `organ' with known flow) was measured with a gamma scintillation spectrometer (LB 5300, Berthold, Wildbad, Germany) as was the radioactivity in the homogenized tissue samples (count of the organs with unknown flow). The flow of any organ (unknown organ flow) could be calculated using the following relationship:

Unknown organ flow/count in the organ with unknown flow = known `organ' flow/count in the `organ' with known flow.

Hepatic blood flow was evaluated by infusing indocyanine green (ICG; Cardio Green, Hynson, Westcott and Dunning, Baltimore, MD, USA) into a peripheral vein [16,17]. This method is based on the Fick principle which means that under constant flow conditions, the blood volume moving through an organ (eg the liver) can be calculated by determining the amount of indicator extracted over that time and the concentration difference of the indicator entering (arterial) and leaving (hepatic venous) that organ. In the case of ICG which is exclusively removed by the liver, the intravenous infusion rate equals the rate of hepatic removal. The ICG was infused continuously for at least 90 min before sampling to achieve steady state conditions of ICG concentration. Pre-arrest and at 30, 90 and 240 min after ROSC, three blood samples at 3-min intervals were taken simultaneously from the artery and hepatic vein for ICG measurement. Immediately after centrifugation, the plasma was frozen at -76°C until the time of analysis. Using spectrophotometric detection, the absorbance of the samples was read at 800 nm and the concentration of ICG was calculated using standard curves constructed from control samples.

Statistical analysis

Data are given as mean ± SEM. The Friedmann test followed by the Wilcoxon matched pairs test was used to compare pre-arrest values with those 5 min and 240 min after ROSC within one group. The Mann-Whitney U test (two-tailed) with Bonferroni correction for multiple comparison was used to determine differences between the TELM group and the control group. $P < 0.05$ was considered statistically significant.

Results

There were no significant differences in the total number of defibrillations per animal or the total dose of vasopressin between the TELM and control group.

Cardiac index, mean arterial pressure, and cerebral and myocardial blood flow pre-arrest and during the post-resuscitation phase are shown in Table 1. In both groups, cardiac index and mean arterial pressure were significantly lower, and cerebral blood flow was significantly higher 5 min after ROSC, in comparison to pre-arrest values. At 240 min after ROSC, cerebral blood flow was significantly higher when compared to pre-arrest values in both groups. In contrast, at the same point in time, cardiac index was significantly lower in comparison to pre-arrest values only in the control group. At no point in time was there any significant difference between the two groups.

Splanchnic organ blood flows pre-arrest and during the post-resuscitation phase before and after drug administration are shown in Table 2. Five minutes after ROSC, organ blood flow of the adrenal gland was significantly higher than pre-arrest in both groups. At the same point in time, organ blood flow of the liver, spleen, stomach, pancreas, jejunum and colon, was significantly lower than pre-arrest. In both groups, splanchnic organ blood flow normalized to pre-arrest values at 90 min after ROSC, and at 240 min after ROSC, organ blood flow of the liver, pancreas, jejunum, colon, kidney and adrenal gland (only in the TELM group) significantly exceeded pre-arrest values. At no point in time were there relevant differences between the groups with respect to organ perfusion.

Hepatic plasma flow and hepatic blood flow pre-arrest and during the post-resuscitation phase are shown in Table 3. In both groups, hepatic plasma flow and hepatic blood flow achieved pre-arrest values at 90 min after ROSC, and at 240 min after ROSC both parameters were significantly higher in comparison to pre-arrest values. At no point of observation was there a relevant difference between groups with respect to hepatic plasma or blood flow.

Table 1

Hemodynamic variables, and myocardial and cerebral blood flow (mean ± SEM) pre-arrest, and during the post-resuscitation phase before and after drug administration

Variable	Group	Pre-arrest	Post-resuscitation phase				Friedmann
			5 min	30 min	90 min	240 min	
MAP	TELM	114 ± 4	91 ± 7*	84 ± 3	91 ± 3	90 ± 2*	$P < 0.01$
(mmHg)	Control	122 ± 11	93 ± 12*	91 ± 4	93 ± 4	92 ± 4*	$P < 0.05$
CI	TELM	115 ± 6	66 ± 7*	77 ± 7	98 ± 7	108 ± 5	$P < 0.001$
(ml/min/kg)	Control	129 ± 9	72 ± 7*	77 ± 4	114 ± 14	102 ± 5*	$P < 0.001$
LVMBF	TELM	1.9 ± 0.2	2.6 ± 0.4	1.3 ± 0.1	2.1 ± 0.4	2.3 ± 0.5	$P < 0.05$
(ml/min/g)	Control	2.1 ± 0.3	2.3 ± 0.3	1.4 ± 0.1	2.4 ± 0.3	2.6 ± 0.5	ns
Cortex	TELM	0.36 ± 0.02	2.10 ± 0.36*	0.29 ± 0.02	0.32 ± 0.03	0.57 ± 0.14*	$P < 0.0001$
(ml/min/g)	Control	0.38 ± 0.03	2.27 ± 0.31*	0.36 ± 0.02	0.44 ± 0.07	0.57 ± 0.05*	$P < 0.001$

CI = cardiac index; LVMBF = left ventricular myocardial blood flow; MAP = mean arterial pressure; ns = not significant; TELM = angiotensin II antagonist telmisartan. *$P < 0.05$ *vs* pre-arrest values by Wilcoxon matched pairs test.

Table 2

Splanchnic organ blood flow (mean ± SEM) pre-arrest and during the post-resuscitation phase before and after drug administration

	Group	Pre-arrest	Post-resuscitation phase				Friedmann
			5 min	30 min	90 min	240 min	
Liver	TELM	0.79 ± 0.14	0.63 ± 0.13*	0.78 ± 0.14	0.75 ± 0.15	1.10 ± 0.10*	$P < 0.05$
(ml/min/g)	Control	0.68 ± 0.2	0.46 ± 0.09*	0.58 ± 0.09	0.81 ± 0.09	0.93 ± 0.20*	$P < 0.01$
Spleen	TELM	3.45 ± 0.59	0.53 ± 0.15*	3.45 ± 0.76	3.99 ± 0.67	3.49 ± 0.39	$P < 0.01$
(ml/min/g)	Control	3.60 ± 0.26	0.77 ± 0.37*	4.44 ± 0.59	4.89 ± 0.41	3.82 ± 0.40	$P < 0.001$
Stomach	TELM	0.29 ± 0.06	0.08 ± 0.01*	0.17 ± 0.02	0.23 ± 0.03	0.30 ± 0.04	$P < 0.001$
(ml/min/g)	Control	0.23 ± 0.03	0.06 ± 0.01*	0.16 ± 0.02	0.20 ± 0.02	0.28 ± 0.04	$P < 0.0001$
Pancreas	TELM	0.26 ± 0.01	0.05 ± 0.01*	0.18 ± 0.01	0.37 ± 0.04	0.55 ± 0.05*	$P < 0.00001$
(ml/min/g)	Control	0.25 ± 0.04	0.05 ± 0.01*	0.15 ± 0.02	0.31 ± 0.05	0.48 ± 0.05*	$P < 0.00001$
Jejunum	TELM	0.37 ± 0.03	0.20 ± 0.02*	0.36 ± 0.03	0.41 ± 0.04	0.55 ± 0.05*	$P < 0.0001$
(ml/min/g)	Control	0.44 ± 0.02	0.23 ± 0.02*	0.41 ± 0.04	0.42 ± 0.02	0.52 ± 0.04*	$P < 0.001$
Colon	TELM	0.40 ± 0.03	0.20 ± 0.02*	0.48 ± 0.04	0.51 ± 0.03	0.57 ± 0.03*	$P < 0.00001$
(ml/min/g)	Control	0.49 ± 0.07	0.25 ± 0.04*	0.61 ± 0.08	0.61 ± 0.07	0.57 ± 0.09*	$P < 0.0001$
Kidney	TELM	3.40 ± 0.10	2.36 ± 0.41	2.67 ± 0.21	3.85 ± 0.30	4.62 ± 0.22*	$P < 0.0001$
(ml/min/g)	Control	3.40 ± 0.21	2.50 ± 0.41	2.82 ± 0.11	3.80 ± 0.22	4.63 ± 0.16*	$P < 0.001$
Adrenal gland	TELM	1.69 ± 0.20	6.36 ± 1.56*	3.11 ± 0.81	2.01 ± 0.21	2.43 ± 0.35*	$P < 0.05$
(ml/min/g)	Control	1.70 ± 0.09	5.09 ± 0.97*	2.14 ± 0.16	2.51 ± 0.24	2.19 ± 0.22	$P < 0.05$

TELM = angiotensin II antagonist telmisartan; *$P < 0.05$ *vs* pre-arrest values by Wilcoxon matched pairs test.

Arterial and hepatic venous blood gases pre-arrest and during the post-resuscitation phase are shown in Tables 4 and 5. At no point of observation was there any significant difference between the groups with respect to arterial or hepatic venous blood gases. By analogy, we found no relevant differences between the two groups with respect to hemoglobin concentrations or mixed venous blood gases (data not presented).

Discussion

This study was designed to compare pre-arrest and post-resuscitation splanchnic and non-splanchnic organ blood flow after vasopressin administration in a pig model of CPR, and to investigate whether, during the post-resuscitation phase, administration of an ANG II antagonist could improve splanchnic and non-splanchnic perfusion in comparison to saline. Results from our study demonstrate that 5 min after ROSC regional organ blood flow of the brain, heart and adrenal gland was increased, whereas cardiac index and splanchnic organ blood flow were decreased. During the post-resuscitation phase, administration of an ANG II antagonist did not change cardiac index and mean arterial pressure when compared to saline. In addition, no

Table 3

Hepatic plasma flow and hepatic blood flow (mean ± SEM) pre-arrest and during the post-resuscitation phase

	Group	Pre-arrest	Post-resuscitation phase			Friedmann
			30 min	90 min	240 min	
Hepatic plasma flow	TELM	0.46 ± 0.04	0.48 ± 0.05	0.51 ± 0.06	0.64 ± 0.10*	$P < 0.01$
(l/min)	Control	0.43 ± 0.06	0.45 ± 0.05	0.52 ± 0.06	0.61 ± 0.12*	$P < 0.01$
Hepatic blood flow	TELM	0.64 ± 0.06	0.66 ± 0.06	0.68 ± 0.07	0.83 ± 0.13*	$P < 0.05$
(l/min)	Control	0.60 ± 0.08	0.62 ± 0.07	0.72 ± 0.09	0.81 ± 0.16*	$P < 0.05$

*$P < 0.05$ *vs* pre-arrest values by Wilcoxon matched pairs test.

Table 4

Arterial blood gases (mean ± SEM) pre-arrest and during the post-resuscitation phase

	Group	Pre-arrest	Post-resuscitation phase				Friedmann
			5 min	30 min	90 min	240 min	
pH	TELM	7.47 ± 0.01	7.33 ± 0.02*	7.34 ± 0.02	7.45 ± 0.01	7.50 ± 0.01*	$P < 0.0001$
	Control	7.47 ± 0.01	7.34 ± 0.02*	7.39 ± 0.02	7.44 ± 0.01	7.49 ± 0.01	$P < 0.001$
PaO_2	TELM	433 ± 10	424 ± 20	423 ± 24	444 ± 16	425 ± 14	ns
(mmHg)	Control	434 ± 8	426 ± 15	433 ± 18	442 ± 18	439 ± 13	ns
$PaCO_2$	TELM	37.8 ± 0.3	39.4 ± 2.4	42.7 ± 1.6	37.9 ± 0.4	38.8 ± 0.4	$P < 0.05$
(mmHg)	Control	39.2 ± 0.9	42.6 ± 2.3	41.8 ± 1.1	39.1 ± 1.2	38.0 ± 0.6	$P < 0.05$
BE	TELM	4.0 ± 0.5	-4.6 ± 1.0*	-2.0 ± 1.1	2.4 ± 0.8	6.2 ± 0.4*	$P < 0.00001$
	Control	4.4 ± 0.3	-2.5 ± 0.4*	-0.2 ± 0.8	2.6 ± 1.3	5.4 ± 0.9	$P < 0.001$

ns = not significant. PaO_2 = arterial partial pressure of oxygen; $PaCO_2$ = arterial partial pressure of carbon dioxide. *$P < 0.05$ *vs* pre-arrest values by Wilcoxon matched pairs test.

Table 5

Hepatic venous blood gases (mean ± SEM) pre-arrest and during the post-resuscitation phase

	Group	Pre-arrest	Post-resuscitation phase				Friedmann
			5 min	30 min	90 min	240 min	
pH hep ven	TELM	7.42 ± 0.01	7.21 ± 0.02*	7.29 ± 0.02	7.40 ± 0.01	7.44 ± 0.01	$P < 0.0001$
	Control	7.42 ± 0.01	7.24 ± 0.01*	7.31 ± 0.01	7.39 ± 0.01	7.43 ± 0.01	$P < 0.001$
$PHVO_2$	TELM	37.9 ± 1.6	29.4 ± 3.2	36.3 ± 1.8	34.4 ± 3.8	33.4 ± 1.7	ns
(mmHg)	Control	34.7 ± 2.8	28.2 ± 3.3	31.7 ± 2.3	31.2 ± 2.0	29.1 ± 2.9	ns
$PHVCO_2$	TELM	45.1 ± 1.1	57.7 ± 1.7*	52.1 ± 2.4	45.7 ± 1.1	45.9 ± 0.8	$P < 0.0001$
(mmHg)	Control	46.3 ± 1.5	58.9 ± 1.6*	54.0 ± 1.6	47.2 ± 0.8	45.8 ± 0.9	$P < 0.001$
BE	TELM	4.5 ± 0.5	-5.3 ± 1.0*	-1.8 ± 1.1	2.9 ± 1.3	6.1 ± 0.6	$P < 0.0001$
	Control	4.9 ± 0.4	-3.1 ± 0.4*	+0.1 ± 0.9	4.0 ± 1.4	5.7 ± 1.0	$P < 0.001$

pH hep ven = hepatic venous pH; $PHVO_2$ = hepatic venous partial pressure of oxygen; $PHVCO_2$ = hepatic venous partial pressure of carbon dioxide; BE = base excess; TELM = angiotensin II antagonist telmisartan; ns = not significant. *$P < 0.05$ *vs* pre-arrest values by Wilcoxon matched pairs test.

significant differences in splanchnic or non-splanchnic organ perfusion between the two groups were found.

In response to cardiac arrest, cardiocirculatory shock or heart failure, vasopressor hormones are endogenously released to maintain vital organ perfusion by increasing peripheral vascular resistance [7,18,19]. The splanchnic hemodynamic response to circulatory shock is characterized by a disproportionate, selective vasoconstriction resulting in a more pronounced decrease in intestinal perfusion, particularly if the shock is severe and/or prolonged [20,21]. Catecholamines, in addition to precapillary splanchnic vasoconstriction, predominantly increase systemic venous return by alpha-stimulation of post-capil-

lary venous beds [22], and vasopressin is reported to selectively constrict intestinal and splenic resistance vessels [23,24]. Angiotensin II is considered the most potent intestinal vasoconstrictor, and the splanchnic hemodynamic response to circulatory shock is mediated predominantly by the renin-angiotensin axis [25]. In dogs subjected to cardiogenic shock, the degree of splanchnic vasospasm correlated with serum ANG II concentrations, and either surgical or pharmacological ablation of the renin-angiotensin system completely prevented this disproportionate splanchnic vasoconstriction [20,21].

Results from our study demonstrate that, during the immediate post-resuscitation phase in pigs, the perfusion conditions in vital organs such as the brain or heart, as well as splanchnic organs, are much more disproportionate. In particular, we found that 5 min after ROSC, in both the TELM group and control group (TELM/control), regional organ blood flow of the cortex, adrenal gland and left ventricular myocardium increased to 583/597%, 376/300%, and 137/110% of pre-arrest values, respectively, whereas cardiac index and regional organ blood flow of the liver, kidney, jejunum, colon, stomach, pancreas and spleen decreased to 57/56%, 80/68%, 69/74%, 54/52%, 50/51%, 28/26%, 19/20% and 15/21% of pre-arrest values, respectively. However, 90 min after ROSC, pre-arrest perfusion values both in non-splanchnic and splanchnic organs were achieved in both groups. At 240 min after ROSC, perfusion of both splanchnic and non-splanchnic organs exceeded pre-arrest values. This could be attributed to a biphasic effect of vasopressin causing a strong initial vasoconstriction, with a consecutive vasodilatation [26,27]. In particular, no significant differences between the TELM and the control group were found with respect to the degree or speed of recovery of organ perfusion, indicating no additional benefit of ANG II antagonism with respect to organ perfusion. In addition, total peripheral resistance and hence systemic blood pressure are reported to be significantly affected by changes in splanchnic vascular resistance [9]. In our study, no significant differences in mean arterial pressure between the two groups were found and, therefore, clinically relevant changes in splanchnic vascular resistance after TELM administration are unlikely. On the other hand, in all of the studies in which beneficial effects of blockade of the renin-angiotensin system on splanchnic perfusion were found, the degree of hemorrhagic and/or cardiogenic shock was more severe, its duration was more pronounced, and blockade of the renin-angiotensin axis was performed before induction of circulatory depression [20,28]. We therefore conclude that, during the immediate post-resuscitation phase in pigs, splanchnic vasoconstriction must be mainly attributed to vasopressors other than ANG II, and that activation of the renin-angiotensin axis is not the predominant mechanism responsible for splanchnic hypoperfusion in this particular situation. Although we did not measure plasma hormone levels in this study, these results agree to some extent with what we have found in humans. In comparison with the normal ranges of values, plasma concentrations of catecholamines and vasopressin during CPR were much higher than those of renin [7,18].

Ultimately, we used vasopressin during CPR because this drug has been shown to be superior to epinephrine with respect to cerebral/myocardial perfusion in this setting and the percentage of successful resuscitations [3]. However, both in normotensive and in hemorrhagic cats, the renin-angiotensin and vasopressin systems have been reported to be redundant mechanisms with respect to intestinal vasoconstriction, as in the absence of one control system the other maintains intestinal resistance [29]. In addition, vasopressin administration in normotensive animals has been found to inhibit renin release via direct action on juxtaglomerular cells [30,31]. To what degree similar mechanisms can be found during CPR conditions before and after vasopressin administration is, however, open to question. As we were not able to measure plasma levels of renin, angiotensin and vasopressin, interactions between these three hormones in this particular situation cannot be excluded.

Independent of whether severe splanchnic hypoperfusion is induced by cardiac tamponade, partial mechanical occlusion or vasoconstrictor infusion, a major factor protecting the intestinal tissue from ischemic damage is its ability to increase oxygen extraction [32–34]. In addition, intestinal oxygen extraction depends on the effects of vasoconstrictive drugs on intestinal vasculature. Alpha-receptor stimulation depresses O_2 extraction by closing precapillary sphincters and thus limiting cellular oxygen supply [35]. Vasopressin, epinephrine in high doses or epinephrine after propranolol had similar effects to norepinephrine, whereas epinephrine in low doses increased oxygen extraction of the small bowel, presumably by dilatating hypoperfused capillaries [34]. At no point during our study did we observe clinically relevant differences in global or regional intestinal blood flow between the groups. It is therefore not surprising that, with respect to hepatic venous PO_2, we also found no significant differences between the groups.

The relevance of this study is limited as an experimental model with healthy animals were used. Pre-existing atherosclerosis, long lasting hypoxia and the need for higher vasopressor doses after prolonged arrest times may cause a more profound cardiovascular dysfunction after CPR and a more pronounced impairment of splanchnic and non-splanchnic organ perfusion during and after CPR. In addition, the time delay from ventricular fibrillation to restoration of spontaneous circulation may be an important period for the activation of the renin-angiotensin system, and, therefore, administration of an ANG II antagonist pre-arrest

or during CPR seems to be reasonable. However, impairment of vasoconstriction due to blockade of the renin-angiotensin system could affect resuscitation success by deteriorating coronary perfusion pressure during CPR.

We therefore conclude that during the immediate post-resuscitation phase in pigs, regional organ perfusion is disproportionate and characterized by the coincidence of increased cerebral or myocardial blood flow and decreased intestinal blood flow. Normalization of regional organ blood flow occurred within 90 min after ROSC; and after administration of an ANG II antagonist, no significant differences in splanchnic and non-splanchnic organ perfusion in comparison to saline were found.

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