Cardiorespiratory effects of continuous i.v. administration of the ACE inhibitor enalaprilat in the critically ill

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- 1 Cardiorespiratory effects of long-term, continuous i.v. administration of the ACE inhibitor enalaprilat were studied.
- 2 Forty-five consecutive critically patients suffering from trauma or postoperative complications were randomly separated into three groups (15 patients in each group) receiving either 0.25 mg h⁻¹ or 0.50 mg h⁻¹ enalaprilat, respectively, or saline solution as placebo (= control group). The infusion was continued for 5 days.
- 3 Haemodynamic and respiratory parameters were intensively monitored on admission to the intensive care unit (= 'baseline' values) and daily during the next 5 days.
- 4 Mean arterial blood pressure (MAP) decreased significantly only in the enalaprilat-treated patients, whereas heart rate (HR) remained unchanged in these patients.
- 5 Pulmonary capillary wedge pressure (PCWP) and pulmonary artery pressure (PAP) were decreased by enalaprilat (0.50 mg h⁻¹: PAP (mean ± s.d.) decreased from 28.0 ± 4.1 to 24.0 ± 3.0 mm Hg) and remained significantly lower than in the control group. In the untreated control group, cardiac index (CI), oxygen consumption (VO₂I) and oxygen delivery (DO₂I) significantly decreased, which was blunted by enalaprilat infusion. Oxygen extraction (O₂-extr) increased in both enalaprilat groups (0.25 mg h⁻¹: from 26.1 ± 5.5 to 30.4 ± 4.0%; 0.50 mg h⁻¹: 25.2 ± 5.6 to 30.9 ± 4.4%) and decreased in the control patients.
- 6 Right ventricular haemodynamics improved by enalaprilat infusion (0.50 mg h⁻¹: RVEF increased from 40.0 ± 3.5 to 45.5 ± 4.0%). Lactate plasma concentrations decreased in the group with 0.50 mg h⁻¹ enalaprilat (from 1.9 ± 1.0 to 1.3 ± 0.3 mg dl⁻¹) and increased in the control patients.
- 7 Continuous infusion of the ACE inhibitor enalaprilat exerted beneficial cardiorespiratory effects in the critically ill. The widespread common risk of altered perfusion with decreased CI, DO₂, VO₂, O₂-extr and increased lactate concentration was blunted by enalaprilat infusion.
- 8 Although 0.5 mg h⁻¹ enalaprilat was most effective, a dose of 0.25 mg h⁻¹ also showed beneficial haemodynamic effects in the critically ill.

Keywords angiotensin-converting enzyme inhibitors enalaprilat haemodynamics critically ill circulation microcirculation organ perfusion right ventricular function

Introduction

The renin-angiotensin-system (RAS) plays a pivotal role in the regulation of cardiovascular homeostasis [1]. The RAS is involved in short- as well as long-

term blood pressure control by influencing sodium reabsorption and by directly and indirectly influencing blood vessels. It is activated during 'stress response'

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associated with major surgery [2], and it mediates systemic hypertension. The RAS is also markedly involved in microcirculatory perfusion deficits: it has been shown, e.g., that the RAS plays an important role in mediating the disproportionate splanchnic hypoperfusion secondary to cardiogenic shock [3].

Angiotensin-converting enzyme (ACE) inhibitors are established drugs for the treatment of patients with hypertension and (chronic) heart failure [4]. In most reports, these substances were used orally. With enalaprilat an ACE inhibitor is available which can be used intravenously. Enalaprilat is the active diacid of the ACE inhibitor enalapril maleate [5].

The exact mechanisms of the vasodilating properties of ACE inhibitors are not fully elucidated [6]. The antihypertensive properties of these substances appear to be most likely derived from their ability to prevent conversion of angiotensin-I to angiotensin-II [7]. In addition to systemic circulating RAS, local (endothelial-related) RAS may also play an important role in regulating haemodynamic homeostasis [8]. Additional effects of ACE inhibitors such as interference with the degradation of bradykinin, accumulation of prostaglandin, and alteration of the release of noradrenaline influence their haemodynamic response and contribute to vasodilation [9, 10].

The beneficial haemodynamic effects of (oral) ACE inhibitors in patients with chronic congestive heart failure are well established [1, 4]. ACE inhibitors have also been shown to protect against ischaemia/reperfusion injury. The benefit of (acute) interruption of RAS during perioperative stress by single bolus administration of ACE inhibitors has recently been demonstrated [11]. Bolus injection, however, may be associated with marked reduction in blood pressure—thus continuous i.v. administration of enalaprilat appears to be of advantage. Long-term, continuous use of intravenous ACE inhibitors in the critically ill, however, has not been assessed. Thus it was the aim of the present study to investigate the cardiorespiratory effects of continuous administration of the ACE inhibitor enalaprilat in two different dosages in critically ill patients.

Methods

Patients and grouping

Forty-five consecutive patients from our surgical intensive care unit (ICU) were prospectively studied. According to the protocol of the Ethics Study Committee of the hospital, informed consent was obtained from the closest relatives of all patients. The study included patients with trauma (injury severity score (ISS) [12] >20) or patients requiring intensive care therapy due to complications secondary to major surgery (no vascular or cardiac surgery patients). Inclusion criterion was a mean arterial blood pressure (MAP) of >75 mm Hg. Exclusion criteria were renal failure (serum creatinine >2.5 mg dl⁻¹; urine output <20 ml h⁻¹), severe liver insufficiency, and haemo-

dynamic instability requiring catecholaminergic support at baseline. Prospectively, the patients were randomly separated into three groups:

group 1 ($n = 15$): 0.25 mg h⁻¹ enalaprilat were continuously administered,

group 2 ($n = 15$): 0.50 mg h⁻¹ enalaprilat were infused,

group 3 ($n = 15$): saline solution was given as placebo (= control group).

The infusion (of enalaprilat or placebo) was started after admission to the ICU (after baseline values were measured) and continued during the following 5 days. During the entire investigation period, lungs of all patients were mechanically ventilated and a mixture of fentanyl/midazolam was continuously infused. The FIO₂ was adjusted to keep PaO₂ between 100 and 150 mm Hg, PaCO₂ was maintained between 38 and 45 mm Hg throughout the entire investigation period, and PEEP levels ranged from 5 to 12 cm H₂O without showing differences between the groups.

To maintain filling pressures (central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP)) >12 mm Hg but <18 mm Hg, low-molecular weight hydroxyethyl starch solution (6% HES, mol wt: 200 000 Dalton, degree of substitution 0.5; Fresenius, Bad Homburg, Germany) and Ringer's solution were infused. Packed red blood cells (PRBC) were given when haemoglobin was less than 9 g dl⁻¹.

'Low-dose' dopamine was given in all patients (3 µg kg⁻¹ min⁻¹). When cardiac index (CI) was <2.5 l min⁻¹ m² in spite of sufficient volume therapy, adrenaline was administered. Noradrenaline was given when MAP was <60 mm Hg and systemic vascular resistance (SVR) was <700 dyn s cm⁻⁵. Antibiotics were adapted according to daily microbiological screening. The entire management of the patients (ventilation patterns, feeding, volume therapy) was carried out by physicians who were not involved in the study and blinded to the grouping. None of the patients were operated upon during the study period.

Measured parameters and data points

Heart rate (HR), mean arterial blood pressure (MAP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP) and cardiac output (CO, thermodilution technique) were monitored daily at 12.00 during a period of haemodynamic steady state of at least 30 min. Derived haemodynamic parameters were also calculated (systemic vascular resistance (SVR), cardiac index (CI)). Right ventricular ejection fraction (RVEF), right ventricular end systolic and end diastolic volumes (RVESV, RVEDV) were measured by thermodilution technique (TD). The catheter is equipped with a fast response thermistor (FRT; 50–100 ms) and two electrodes for intracardiac ECC recording. The typical downslope thermodilution washout curve follows an exponential decay, interrupted by the diastolic plateaus. The ratio between the temperature change of two successive diastolic plateaus represents the fraction of blood remaining in the right ventricle

(= residual fraction (RF)). Right ventricular ejection fraction is calculated from $EF = 1 - RF$. The thermistor of the catheter is able to measure beat-to-beat temperature variations of the downstream temperature changes after injection of 10 ml ice-cold dextrose. The microprocessor connected with the catheter determines the best fit to the exponential curve, using a special algorithm. As cardiac output and stroke volume (SV) are also calculated by the microprocessor ((Explorer, Baxter, Irvine, CA), $RVEDV$ can be derived from $SV/RVEF$ and $RVESV = RVEDV - SV$.

Blood gas analyses were carried out from arterial and mixed-venous blood samples. Oxygen consumption index (VO_2I), oxygen delivery index (DO_2I), and oxygen extraction ($O_2\text{-extr}$) were calculated from standard formulae using the same monitoring system (Explorer, Baxter, Irvine, CA). Plasma lactate concentrations were measured from arterial blood samples. All measurements were carried out on the day of admission (= 'baseline' values) and daily for the next 5 days at 12.00 h.

All patients were scored by physicians who were not involved in the study and blinded to the grouping of the patients. 'Sepsis' was defined using the guidelines of the members of ACCP/SCCM [13], acute respiratory distress syndrome (ARDS) was assessed according to Murray and colleagues [14].

Mean $\pm$ standard deviation (s.d.) was calculated for all data at every data point. One-way and two-

way analysis of variance (ANOVA) with repeated measures were used to determine the effects of group, time, and group-time interaction for each measured parameter. P values <0.05 were considered significant.

Results

Patients' demographics and intensive care treatment

Patients' characteristics and data from intensive care therapy did not differ between the groups (Table 1). The underlying disease, scoring at baseline, and survival rate during the study period were also without significant differences. The cumulative fluid balance was higher in both enalaprilat groups than in the control patients ($P < 0.05$) (Table 1). APACHE II decreases only in group 2 and showed the lowest value at the end of the study (Table 2). None of the patients suffered from severe side-effects (critical drop of MAP (<55 mm Hg), acute renal failure (serum creatinine never exceeded 2.0 mg dl^{-1}) or liver dysfunction during the study period.

Differences in haemodynamics between enalaprilat- and placebo-treated groups were mostly significant from the second day on. Thus 95% confidence interval for mean differences were calculated for the second day of treatment (Table 3).

Table 1 Patients' characteristics and data from intensive care management (mean $\pm$ s.d.)

	Enalaprilat		Control group
	0.25 mg h^{-1}	0.5 mg h^{-1}	
Age (years)	50 $\pm$ 13	52 $\pm$ 14	49 $\pm$ 14
range	34 to 65	24 to 65	25 to 64
Weight (kg)	82 $\pm$ 11.9	80.1 $\pm$ 13.1	77.3 $\pm$ 10.1
range	65 to 95	72 to 93	67 to 90
Gender (M/F)	8/7	9/6	6/9
<i>Patients' underlying disease on admission to ICU</i>			
P.o. complications	9	8	9
Trauma	6	7	6
ARDS	2	1	2
Survivors	13	13	12
Non-survivors	2	2	3
<i>Patients' scoring on admission</i>			
APACHE II score	18 $\pm$ 2	19 $\pm$ 3	19 $\pm$ 3
ISS	25 $\pm$ 3	24 $\pm$ 3	25 $\pm$ 3
<i>Catecholaminergic support</i>			
Adrenaline (number)	1	1	3
(range (μg min^{-1}))	4	5	5 to 8
Noradrenaline (number)	—	—	2
(range (μg min^{-1}))	—	—	5 to 8
Dopamine (number)	all	all	all
(range (μg min^{-1}))	200 to 270	200 to 300	200 to 290
<i>Cumulative fluid balance</i>			
At 5th day (ml)	+2050 $\pm$ 380	+2450 $\pm$ 250	+850 $\pm$ 180*

ICU: intensive care unit; ISS: injury severity score; ARDS: acute respiratory distress syndrome; p.o.: postoperative.

* $P < 0.05$ different from the enalaprilat groups.

Table 2 Number of patients at each data point, changes in APACHE II score and plasma lactate levels during the study period (mean $\pm$ s.d.)

Parameter	Group	Baseline	1st day	2nd day	3rd day	4th day	5th day
Number of patients	0.25 mg h ⁻¹ E	15	15	15	15	15	13
	0.50 mg h ⁻¹ E	15	15	15	15	14	13
	Control	15	15	15	14	12	12
APACHE II score	0.25 mg h ⁻¹ E	18 $\pm$ 2	17 $\pm$ 3	17 $\pm$ 2	17 $\pm$ 3	16 $\pm$ 3	15 $\pm$ 3
	0.50 mg h ⁻¹ E	19 $\pm$ 3	16 $\pm$ 3	15 $\pm$ 2	14 $\pm$ 3	13 $\pm$ 3*	13 $\pm$ 3*
	Control	19 $\pm$ 3	19 $\pm$ 3	21 $\pm$ 2	21 $\pm$ 3	20 $\pm$ 3	21 $\pm$ 3
Lactate (mg dl ⁻¹)	0.25 mg h ⁻¹ E	1.7 $\pm$ 0.9	1.5 $\pm$ 0.8	1.6 $\pm$ 0.6	1.6 $\pm$ 0.4	1.4 $\pm$ 0.5	1.5 $\pm$ 0.3
	0.50 mg h ⁻¹ E	1.9 $\pm$ 1.0	1.5 $\pm$ 0.6	1.3 $\pm$ 0.5	1.3 $\pm$ 0.3	1.2 $\pm$ 0.3	1.2 $\pm$ 0.6
	Control	1.7 $\pm$ 0.9	1.9 $\pm$ 0.8	2.7 $\pm$ 0.5*	2.9 $\pm$ 1.4*	2.4 $\pm$ 0.5*	2.3 $\pm$ 0.5*

E: enalaprilat.

* $P < 0.05$ different from the other groups.**Table 3** 95% confidence interval for mean differences $\pm$ s.d. (baseline—2nd day of treatment) in the three groups

	Difference: baseline – 2nd day	95% confidence interval
MAP (mm Hg)		
0.25 mg h ⁻¹ E	5.1 $\pm$ 8.2	0.9; 9.1
0.5 mg h ⁻¹ E	8.5 $\pm$ 6.6	5.1; 11.7
Control	-1.7 $\pm$ 10.8	4.3; -7.7
HR (beats min⁻¹)		
0.25 mg h ⁻¹ E	6.6 $\pm$ 9.3	1.9; 11.5
0.5 mg h ⁻¹ E	7.5 $\pm$ 11.6	2.3; 13.3
Control	-11.6 $\pm$ 10.9	-6.5; -16.7
PAP (mm Hg)		
0.25 mg h ⁻¹ E	4.3 $\pm$ 3.0	2.7; 5.9
0.5 mg h ⁻¹ E	5.1 $\pm$ 3.3	3.4; 6.9
Control	-2.1 $\pm$ 4.5	-0.4; -4.4
PCWP (mm Hg)		
0.25 mg h ⁻¹ E	3.1 $\pm$ 3.0	1.5; 4.6
0.5 mg h ⁻¹ E	5.6 $\pm$ 2.6	4.3; 6.9
Control	0.5 $\pm$ 3.7	-1.4; 2.2
CI (l min⁻¹ m²)		
0.25 mg h ⁻¹ E	-0.54 $\pm$ 0.81	-0.98; -0.24
0.5 mg h ⁻¹ E	-0.63 $\pm$ 0.70	-0.34; 0.23
Control	0.35 $\pm$ 0.79	-0.13; 0.18
RVEF (%)		
0.25 mg h ⁻¹ E	-2.1 $\pm$ 5.1	-5.1; 1.0
0.5 mg h ⁻¹ E	-6.4 $\pm$ 5.0	-3.7; -8.9
Control	7.8 $\pm$ 3.5	6.0; 9.5
Pao₂/Fio₂ (mm Hg)		
0.25 mg h ⁻¹ E	-20.1 $\pm$ 59.4	6.2; -32.0
0.50 mg h ⁻¹ E	-31.1 $\pm$ 37.0	-12.2; -51.1
Control	76.0 $\pm$ 44.2	53.2; 98.6
VO₂I (ml min⁻¹ m²)		
0.25 mg h ⁻¹ E	-13.5 $\pm$ 38.5	-33.2; 6.4
0.5 mg h ⁻¹ E	-12.1 $\pm$ 32.0	4.5; 41.8
Control	24.8 $\pm$ 19.1	14.5; 33.8
DO₂I (ml min⁻¹ m²)		
0.25 mg h ⁻¹ E	-2.3 $\pm$ 93.2	-49.3; 45.4
0.5 mg h ⁻¹ E	-37.5 $\pm$ 121.4	29.1; 103.8
Control	78.9 $\pm$ 117.3	17.5; 143.3

Systemic and pulmonary haemodynamic data

MAP dropped significantly in the patients who had received enalaprilat (0.25 mg h⁻¹: from 87.4 $\pm$ 6.2 to 82.4 $\pm$ 6.1 mm Hg; 0.50 mg h⁻¹: from 87.1.9 $\pm$ 5.2 to 77.0 $\pm$ 7.1 mm Hg), without, however, showing significant differences between these two groups (Figure 1). MAP remained lower in both enalaprilat groups than in the untreated control patients until the end of the investigation period ($P < 0.05$). HR was unchanged by enalaprilat infusion (Table 3), but increased in the non-treated patients (from 101 $\pm$ 11 to 99 $\pm$ 11 to 113 $\pm$ 9 beats min⁻¹ at day 2 ($P < 0.05$). In both enalaprilat groups, PAP decreased significantly (0.25 mg h⁻¹: from 27.0 $\pm$ 3.5 to 23.1 $\pm$ 2.5 mm Hg; 0.50 mg h⁻¹: from 28.0 $\pm$ 4.1 to 22.1 $\pm$ 3.0 mm Hg), whereas it increased in the control patients (Figure 1). PCWP was comparable at baseline in all groups. It decreased similarly in both enalaprilat groups ($P < 0.05$) and was significantly lower than in the control patients throughout the study period (Figure 1). At baseline, CI did not differ between the three groups. In the further course of the study, it decreased in the control group (from 3.30 $\pm$ 0.9 to 2.81 $\pm$ 0.7 l min⁻¹ m²) and slightly increased in both enalaprilat groups being significantly different to the CI in the control group (Figure 1). SVR decreased by the enalaprilat infusion (no difference between these groups) and significantly increased in the control patients.

Right ventricular haemodynamics

RVEF remained almost unchanged in the patients with low-dose enalaprilat and increased in patients who have received high-dose enalaprilat (from 40.0 $\pm$ 3.5 to 45.9 $\pm$ 4.0%; $P < 0.05$) (Figure 2). RVEF significantly decreased in the control patients (from 39.3 $\pm$ 3.8 to 29.5 $\pm$ 5.9%) and was different from the RVEF in both enalaprilat groups ($P < 0.05$) (Figure 2). Right ventricular loading (RVEDV, RVESV) increased in

Figure 1 Changes (mean $\pm$ s.d.) in mean arterial pressure (MAP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and cardiac index (CI). ■ 0.25 mg h⁻¹ enalaprilat, ○ 0.5 mg h⁻¹ enalaprilat, ▲ control. Data points: 0: 'baseline' value; 1: 1st day; 2: 2nd day; 3: 3rd day; 4: 4th day; 5: 5th day. * $P < 0.05$ different from the enalaprilat groups.

Figure 2 Changes (mean $\pm$ s.d.) in right ventricular ejection fraction (RVEF), right ventricular end diastolic volume (RVEDV), right ventricular end systolic volume (RVESV), and central venous pressure (CVP). ■ 0.25 mg h⁻¹ enalaprilat, ○ 0.5 mg h⁻¹ enalaprilat, ▲ control. Data points see Figure 1. * $P < 0.05$ different from the enalaprilat groups.

the control patients ($P < 0.01$) and remained unchanged in both enalaprilat groups (Figure 2). CVP showed similar data in all three groups within the entire study period (Figure 2).

Oxygenation and laboratory parameters

$\text{PaO}_2/\text{FIO}_2$ ratio remained stable in both enalaprilat groups, but it decreased significantly in the control patients (Figure 3). Both DO_2I and VO_2I increased in the enalaprilat groups, and were significantly lower in the control patients (Figure 3). O_2 -extraction increased in the patients who had received enalaprilat continuously (0.25 mg h^{-1} : from 26.1 ± 5.5 to $30.4 \pm 4.0\%$; 0.50 mg h^{-1} : 25.2 ± 5.6 to $30.9 \pm 4.4\%$) and it decreased in the non-treated control group (Figure 3). Lactate plasma levels decreased most pronouncedly in those patients in whom 0.50 mg h^{-1} enalaprilat was given (from 1.9 ± 1.0 to $1.2 \pm 0.3 \text{ mg dl}^{-1}$) ($P < 0.05$) and increased in the control patients (Table 2).

Discussion

The continuous i.v. administration of the ACE inhibitor enalaprilat in our intensive care patients showed overall beneficial cardiorespiratory effects. Enalaprilat resulted in vasodilation in arterial vessels and (to a lesser degree) also in the capacitance

system: MAP was significantly reduced and remained lower than baseline values throughout the study period, fluid balance was higher in both enalaprilat groups indicating increased venous pooling. As also shown by others using single bolus injection [15, 16], continuous i.v. enalaprilat was not associated with an increase in HR via reflex tachycardia.

Right ventricular haemodynamics were also beneficially influenced by continuous infusion of enalaprilat. Right ventricular function is known to be often impaired in the critically ill [17], which was confirmed by the changes of RVEF in our untreated control patients. Enalaprilat resulted in an improvement in right ventricular haemodynamics (increase in RVEF and a decrease in filling volumes (RVEDV, RVESV)), which was sustained throughout the entire study period. In patients with significantly impaired left ventricular function, 1.25 mg enalaprilat reduced ventricular filling volumes (RVEDV, RVESV) and increased RVEF significantly. These effects appear to be most likely due to beneficial actions of enalaprilat on left ventricular loading, which positively influences right ventricular function via ventricular interdependence [19]. In the present study, PAP was also reduced by enalaprilat, which may have contributed to the improved right ventricular function via reduction of right ventricular afterload.

Doses of enalaprilat given intravenously vary widely in the different studies ranging from 0.625 mg [20] to 40 mg [21]. In chronic congestive heart failure

Figure 3 Changes (mean $\pm$ s.d.) in $\text{PaO}_2/\text{FIO}_2$ ratio, oxygen delivery index (DO_2I), oxygen consumption index (VO_2I), and oxygen extraction ($\text{O}_2\text{-extr.}$). ■ 0.25 mg h^{-1} enalaprilat, ○ 0.5 mg h^{-1} enalaprilat, ▲ control. Data points see Figure 1. * $P < 0.05$ different from the enalaprilat groups.

(CHF), 0.625 mg enalaprilat appears to be enough to produce significant inhibition of angiotensin-converting enzyme and induce maximum haemodynamic response [16]. LeJemtel and colleagues [22] reported on the similarity of the peak haemodynamic response to 1.25 and 5.0 mg i.v. administered enalaprilat in patients suffering from CHF (NYHA III and IV). Systemic arterial blood pressure decreased by 16% and 14%, respectively, whereas CI increased by 16% and 25%. Also Kubo and colleagues [23] showed no further reduction in blood pressure and PCWP when the dose of enalaprilat was increased. In the present study, total daily dose added up to approximately 6 mg (group 1) and 12 mg (group 2) enalaprilat, respectively. MAP and PAP were slightly more reduced, RVEF and O_2 -extraction were more pronouncedly increased by 0.5 mg h⁻¹ than by 0.25 mg h⁻¹ enalaprilat. Plasma lactate level was more beneficially influenced when the higher dose of enalaprilat was given. However, most of the cardiorespiratory parameters of our patients already differed significantly between the low-dose enalaprilat group and the non-treated control patients. Thus in patients with lower MAP, 0.25 mg h⁻¹ enalaprilat can be used and most of the beneficial haemodynamic effects can be ensured nonetheless.

Blood pressure reducing properties of i.v. administration of enalaprilat [24, 25] were confirmed by the present data. Blood pressure remained lower than baseline values throughout the entire study period in both enalaprilat groups indicating no tachyphylaxis with continuous use of the substance. Owing to the sometimes marked decrease in blood pressure secondary to ACE inhibitor injection [26], it has been suggested that it should be administered by controlled infusion rather than by (intermittent) bolus injection.

There is good evidence that severe disturbances of microcirculation are involved in the development of multiple-organ failure (MOF) in the critically ill [27]. It seems that the vasoregulatory systems which are needed to control the distribution of cardiac output may be impaired in this situation [28]. Additionally, microcirculatory dysfunction is common in these patients. Vasopressin and angiotensin-II are known to mediate peripheral perfusion deficits [29]. Both substances cause splanchnic vasoconstriction although there is a marked increase in need for oxygen delivery in this situation [30]. The increase in gut mucosal permeability with the risk of bacterial translocation appears to be most likely secondary to a decrease in splanchnic blood flow. The influence of ACE inhibitors on organ perfusion has not yet been completely elucidated. ACE inhibitors have been shown to maintain or even improve blood flow to vital organs [31]. In an animal experiment, enalaprilat (1 mg kg⁻¹ i.v.) exerted protective effects against post-

ischaemic renal failure [32]. These positive effects may most likely result from the beneficial macro- and microcirculatory actions of the ACE inhibitors or by the inhibition of (local) angiotensin-II production. Additionally, some of these substances are reported to act as free oxygen radical scavengers [33].

Disturbance in the vascular control might play an important role in the genesis of extraction defects in tissues in the critically ill. Alterations in micro-regional perfusion may result in some capillary regions to be overperfused while others will be underperfused relative to O_2 needs [34]. Detrimental redistribution of local blood flow due to inappropriate vasoconstriction appears to be one of the most important sequels in the critically ill. In the present study, CI, VO_2 and DO_2 were maintained at higher levels by infusion of enalaprilat than in the untreated control group. Shoemaker and colleagues [35] demonstrated the importance of maintaining VO_2 and DO_2 at elevated levels to reduce the incidence of multiple-organ failure and overall mortality. Whether an increased VO_2 associated with an increased DO_2 represents a lesser extent of tissue hypoxia cannot be answered for certain at present. O_2 -extraction was increased by infusion of enalaprilat thus indicating an improved perfusion at the microcirculatory level.

The use of ACE inhibitors such as enalaprilat was reported to be associated with the risk of severe side-effects. Deleterious effects on renal function have been described [36]. In the present study, however, renal dysfunction could not be observed. According to Licker & colleagues [37], patients on chronic (oral) ACE inhibitors may need higher doses of alpha-receptor agonists than patients with an unimpaired RAS. Also this effect could not be confirmed by the present data: in both low-dose and high-dose regime enalaprilat there was no need for noradrenaline infusion to counteract the vasodilating properties of the substance.

It can be summarized that the renin-angiotensin system appears to play an important role in the pathophysiology of macro- and microcirculatory abnormalities in the critically ill. Critical illness normally results (more or less) in circulatory derangements with the risk of critical perfusion deficits. Continuous i.v. administration of the ACE inhibitor enalaprilat exerted sustained beneficial haemodynamic effects in our patients. Continuous infusion of 0.50 mg h⁻¹ enalaprilat resulted in overall more improvements of cardiorespiratory parameters associated with a more pronounced decrease in blood pressure, but the lower dose (0.25 mg h⁻¹) also showed beneficial haemodynamic effects. Our results encourage further investigations to assess the exact role of ACE inhibitors in this situation.

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