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An Inhibitor of Angiotensin Converting Enzyme (Enalapril) Augments Endotoxin-Induced Hypotension in the Pig

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ABSTRACT

Septic shock causes an extensive inflammatory reaction including increased capillary leakage and a decrease in systemic blood pressure. Human septic shock can be replicated in the endotoxaemic pig. Angiotensin converting enzyme (ACE) is involved in the degradation of bradykinin, an inflammatory mediator, and in the regulation of blood pressure. Inhibition of ACE is a common approach to reduce hypertension as well as left ventricular insufficiency. Fifteen anaesthetised pigs received a continuous 3 h endotoxin infusion. The animals were randomly given an inhibitor of ACE (enalapril) [at a dose (0.5 mg x kg^{-1}) that did not *per se* reduce mean arterial blood pressure (MAP); (n=7)], or the corresponding volume of saline (n=8). Another seven pigs were randomised for treatment with enalapril (0.5 mg x kg^{-1}) + saline (n = 3). Four pigs were randomised to serve as untreated controls (saline + saline). Basic physiologic variables were registered. Endotoxaemia progressively reduced MAP. This decrease was significantly augmented by enalapril. Hypovolemia caused by increased permeability or salt/water excretion did not seem to explain this effect as neither blood haemoglobin nor plasma sodium differed between the two groups of endotoxaemic pigs. Inhibitors of ACE are known to potentiate the cardio - depressant effect of bradykinin. This may explain the reduction in MAP by enalapril during porcine endotoxaemia.

INTRODUCTION

During the last decade new approaches in the treatment of hypertension and left ventricular insufficiency have led to a wide spread use of inhibitors of angiotensin converting enzyme (ACE). With a progressively increasing number of patients being treated with ACE inhibitors (ACE-I) it is important to increase the knowledge of the effects of such drugs in patients with various diseases. ACE, which catalyses the conversion of angiotensin I to angiotensin II (AT II) and inactivates bradykinin by hydrolysis, is mainly located in the pulmonary endothelium (23). The renin-angiotensin system counteracts water and salt excretion during hypovolemia and bradykinin is a natriuretic. ACE is via the kallikrein-kinin and fibrinolytic systems directly linked to the inflammatory process (8, 9) and also to manifestations of systemic inflammatory challenge (*e.g.* increase in angiotensin II due to vasodilatation). ACE-I potentiates kinin induced microvascular permeability intradermally (8, 9), in the rat paw (6), and in the lungs (28). Other peptides, *e.g.* the neuronal tachykinin substance P, that augment capillary outflow are released during inflammation and cause a prolonged period of leakage in the presence of an ACE inhibitor (9). AT II modulates acute pulmonary hypoxic vasoconstriction in man (13). AT II may also cause oedema by induction of vascular permeability factor mRNA expression by human vascular smooth muscle cells independent of changes in haemodynamics (27).

Gram-negative bacteria have a wall surfaced with endotoxin, a lipopolysaccharide, which is released during bacterial lysis. Endotoxaemia mediates the characteristics of septic shock (24), which is an obvious example of an extensive systemic inflammatory reaction. Reductions in cardiac performance, oxygenation levels and the devlopment of metabolic acidosis as well as activations of the coagulation, fibrinolytic, and cytokine cascades are seen in septic shock. The effects of ACE-I in this condition is not very well characterised.

Septic shock leading to the early phase of the adult respiratory distress syndrome can be replicated in the endotoxaemic pig being a suitable model for studies of therapeutic strategies and pathogenic events (19). We designed a prospective and randomised study to evaluate the effects

of an ACE-I (enalapril), in a dose that potentiates bradykinin (20) but does not reduce mean arterial pressure (MAP) *per se*. The more specific aims of this study were to evaluate: 1. Whether enalapril further reduces the blood pressure in the endotoxaemic pig. 2. The possible effect of enalapril on pulmonary wet weight and oxygenation. 3. Whether increased microvascular permeability, a characteristic of both septic shock and porcine endotoxaemia, contributes to hypovolemia.

MATERIALS AND METHODS

Animals

Apparently healthy pigs of both sexes, aged 12-14 weeks and weighing between 23 and 30 kg (mean 25.5 kg) were used in this experiment which was approved by the Animal Ethics Committee of the University of Uppsala, Sweden (C 279/96).

Anaesthesia and surgical procedures

The essential procedures are previously described in detail (11, 12). Briefly, each pig was given an intramuscular injection of 6 mg x kg^{-1} of Zoletil 100® (Tilétamine, Zolazépam; Reading France) mixed with 2.2 mg x kg^{-1} of Rompun Vet® (Xylazin, tiazin; Bayer Germany) and 0.04 mg x kg^{-1} of atropine in order to induce anaesthesia. A continuous intravenous infusion of

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Abbreviations used: ACE = angiotensin converting enzyme; ACE-I = angiotensin converting enzyme inhibitor; ATII = angiotensin II; BSA = body surface area; CaO_2 = oxygen content in arterial blood; CI = cardiac index; CO = cardiac output; CvO_2 = oxygen content in mixed venous blood; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; O_2ext = oxygen extraction; $PaCO_2$ = arterial CO_2 partial pressure; PaO_2 = arterial oxygen tension; PCWP = pulmonary capillary wedge pressure; PEEP = positive end expiratory pressure; PVRI = pulmonary vascular resistance index; SVRI = systemic vascular resistance index.

Pentobarbital natrium®, 8 mg x kg^{-1} x h^{-1} (Apoteksbolaget Sweden) was given in order to maintain anaesthesia. Twenty mg of morphine (Pharmacia Sweden) were injected intravenously, and a tracheotomy was rapidly performed. Thirty per cent oxygen were given in N_2O during the insertion of catheters (see *Monitoring*). Otherwise 30% oxygen were administered in N_2. A urinary catheter was inserted through a small vesicostomy. The body temperature was maintained by a heating pad (KanMed Sweden). The animals were given intermittent positive pressure ventilation with a Servo 900C ventilator (Siemens-Elema Sweden). The ventilatory minute volume was set to obtain an initial $PaCO_2$ between 5.0 and 5.5 kPa and thereafter kept constant during the experiment. The respiratory rate was 25 x min^{-1} and the inspiratory/expiratory time was 1:3. After induction of anaesthesia and surgical preparation, each animal was placed in the prone position and a positive end expiratory pressure (PEEP) of 5 cm H_2O was used throughout the experiment in order to minimise atelectasis (16). A balanced electrolyte solution with 2.5% glucose (Rehydrex™, Pharmacia-Upjohn Sweden) was infused at 30 mL x kg^{-1} x h^{-1} during the first hour, and thereafter at 10 mL x kg^{-1} x h^{-1}.

Monitoring

MAP (mm Hg) was continuously recorded via a catheter inserted, via a cervical artery, into the proximal part of aorta. It was also used for blood sampling. The amount of blood sampled for analysis was less than 5% of the total blood volume of each pig. Arterial blood gases were analysed on an ABL5 ™ blood gas analyser (Radiometer, Denmark). A central venous catheter and a 7 F Swan-Ganz catheter equipped with a thermistor were both introduced, via the right external jugular vein, into the superior caval vein and into the pulmonary artery, respectively. CVP (mm Hg) and PCWP (mm Hg) were determined. MPAP and heart rate were also monitored continuously.

Calculations

CO (litre x min^{-1}) was calculated by the thermodilution technique, where 10 mL of chilled saline was used as an indicator. The mean of at least three determinations was adopted. Body surface area (m^2) was calculated using the Dubois' equation: BSA = Body $weight^{0.425}$ x $length^{0.725}$ x 0.007184) on a Siemens Sirecust (Medical Electronics Inc., Danvers, MA). Haemodynamic parameters were calculated using the following equations: CI = CO/BSA, SVRI = (MAP-CVP)/CI x 60 and PVRI = (MPAP-PCWP)/CI x 60, CaO_2 = (Hb x SaO_2 /100) x 0.062+ PaO_2 x 0.01, (Hb x SvO_2/100) x 0.062 + PvO_2 x 0.01 and (CaO_2-CvO_2)/CaO_2 (5).

Experimental procedures

Seven pigs were randomised to receive either 0.5 mg x kg-1 of enalapril (Renitec™ purchased from Merck Sharp and Dohme, NJ) i.v. or the corresponding volume of saline (n=8) i.v. over 10 min. Thereafter, all these animals received a continuous infusion of endotoxin (Escherichia coli: 0111: B4; Sigma Chemical, St Louis, MO) at a dose of 10 μg x kg^{-1} x h^{-1} over 3 h. Another three pigs were randomised to receive 0.5 mg x kg^{-1} of enalapril i.v. followed by saline and 4 randomised pigs, serving as untreated controls, were only given saline. Physiologic measurements were performed and blood samples were drawn thereafter every hour for 3 h. The inclusion criteria were: $PaO_2 \geq$ 10 kPa (75 mm Hg) and a MPAP < 2.7 kPa (20 mm Hg) one hour after completion of the surgical procedure. The animals also had to survive at least an hour of endotoxaemia. Those who survived the experimental period were, still under anaesthesia, sacrificed by an intravenous overdose of potassium chloride. The right lung was extirpated and weighed for wet weight measurement.

Laboratory investigations

Sodium and potassium concentrations in plasma were determined with the KONE microlyte analyser (KONE Instruments, Espo, Finland). The initial blood samples were taken immediately before the onset of the injection of enalapril and thereafter every hour. The blood samples were

treated with heparin in accordance with the guidelines given in the instructions for the microlyte analyser. The blood samples were centrifuged at 3,000 x g for 1 minute at 20° C and the plasma was collected immediately and kept at 4° C until analysis. The accuracy of analysis was checked by using prefabricated solutions with known ion concentrations.

Statistics

Differences between the groups of pigs during the endotoxaemic period were calculated by an analysis of variance (ANOVA) test. We used the statistical package of Excel 7.0™ running under Windows™ 95. The results are expressed as mean ± SD. $P < 0.05$ was considered significant.

RESULTS

The animals had comparable physiologic baseline variables. All animals responded to the *E. coli* endotoxin infusion with a pronounced increase in MPAP which occurred after about half an hour. There was also a subsequent progressive systemic circulatory derangement during the endotoxaemic challenge. One saline+endotoxin pig and 2 enalapril+endotoxin pigs died after 2h.

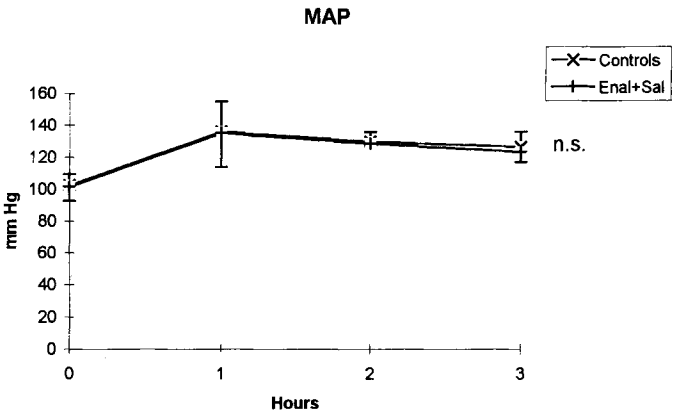

Fig. 1. Mean arterial blood pressure (MAP) in saline + saline infused controls (n=4) *vs* Enalapril 0.5 mg x kg^{-1} + saline (n=3) infused pigs. "0 h" = Start of endotoxin infusion. Mean ± SD.

Neither the anaesthetic procedure nor pretreatment of the pigs with 0.5 mg x kg-1 of enalapril caused any significant alteration in MAP (Fig 1). Endotoxaemia reduced MAP and this reduction was significantly ($P < 0.05$) potentiated in pigs pretreated with enalapril (Fig. 2).

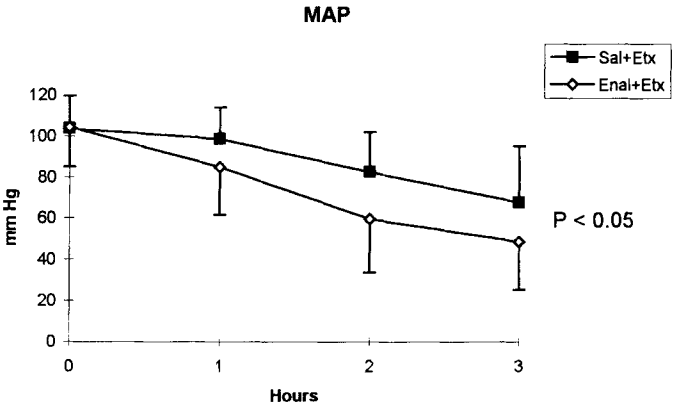

Fig. 2. Mean arterial blood pressure (MAP; mm Hg) in saline injected + endotoxin infused (10 μg x kg^{-1} x h^{-1}) pigs (n=8) *vs* enalapril injected (0.5 mg x kg^{-1}) + endotoxin infused (10 μg x kg^{-1} x h^{-1}) pigs (n=7). "0 h" = Start of endotoxin infusion. Mean ± SD.

There was no significant difference in either PVRI, SVRI, O_2ext, MPAP, CI or SaO_2 in endotoxaemic pigs injected with enalapril and saline, respectively. There were moderate, but non-significant, increases in haemoglobin in all endotoxaemic pigs (Table 1). Haemoglobin remained essentially unchanged during the experimental period in the three pigs given enalapril + saline and the four untreated controls (data not shown). There was no difference between these two groups.

There were no significant differences in lung weight between the two groups of endotoxaemic pigs nor in the lung weights of the two groups of non-endotoxaemic animals (results not shown).

The plasma concentrations of sodium and potassium, respectively, were essentially similar in the four groups of pigs (Table 2).

Table 1. Pulmonary vascular resistance index (PVRI; 10^6 x N x s x m^{-5}), systemic vascular resistance index (SVRI; 10^6 x N x s x m^{-5}), oxygen extraction (O_2ext; %), mean pulmonary arterial pressure (MPAP; mm Hg), cardiac index (CI; L x m^{-2}), arterial oxygen saturation (SaO_2; %) and hemoglobin (Hb; g x L^{-1}) in endotoxaemic pigs (10µg x kg^{-1} x h^{-1}) pretreated with 0.5 mg x kg^{-1} of enalapril (Enal + Etx) and saline (Sal + Etx), respectively. "0 h" = Start of endotoxin infusion. Mean ± SD.

	0 h	1 h	2 h	3 h
		PVRI		
Enal+Etx	5±2	11±3	15±4	20±13
			n.s.	
Sal+Etx	5±2	10±2	13±2	15±3
		SVRI		
Enal+Etx	34±11	32±4	27±12	29±7
			n.s.	
Sal+Etx	28±11	31±11	29±15	32±16
		0_2ext		
Enal+Etx	39±7	55±9	67±16	77±14
			n.s.	
Sal+Etx	32±5	38±3	50±6	73±16
		MPAP		
Enal+Etx	21±3	33±3	37±6	31±6
			n.s.	
Sal+Etx	22±5	34±3	36±3	34±6
		C.I.		
Enal+Etx	3.2±0.9	2.6±0.8	2.2±0.8	1.8±0.8
			n.s.	
Sal+Etx	3.9±1.1	3.4±1.1	3.3±1.4	2.3±0.9
		SaO_2		
Enal+Etx	99±1	89±8	91±6	92±8
			n.s.	
Sal+Etx	99±1	96±3	95±4	96±1
		Hb		
Enal+Etx	78 ± 5	90 ± 8	92 ± 6	93 ± 4
			n.s.	
Sal+Etx	82 ± 5	94 ± 6	97 ± 4	103 ± 7

Table 2. Plasma sodium (mmol x L^{-1}) and potassium (mmol x L^{-1}) concentrations in pigs infused with endotoxin (Etx; 10μg x kg^{-1} x h^{-1}) or saline (Sal) and pre treated with 0.5 mg x kg^{-1} of enalapril (Enal) and saline, respectively. "0 h" = Start of endotoxin infusion. Mean ± SD.

	0 h	1 h	2 h	3 h
		Sodium		
Enal+Sal	131 ± 1	128 ± 2	128 ± 2	126 ± 1
Sal+Sal	134 ± 2	132 ± 1	131 ± 2	129 ± 1
Sal+Etx	131 ± 4	129 ± 2	129 ± 5	126 ± 2
Enal+Etx	132 ± 2	130 ± 3	129 ± 3	128 ± 2
		Potassium		
Enal+Sal	3.60 ± 0.08	3.77 ± 0.08	3.76 ± 0.09	3.97 ± 0.37
Sal+Sal	3.40 ± 0.17	3.48 ± 0.07	3.61 ± 0.04	3.81 ± 0.41
Sal+Etx	3.55 ± 0.18	3.54 ± 0.22	3.61 ± 0.27	4.18 ± 0.63
Enal+Etx	3.49 ± 0.26	3.45 ± 0.27	3.92 ± 0.39	4.26 ± 0.77

DISCUSSION

Hypotension and a subsequently deteriorating perfusion pressure contributing to multiple organ failure is seen in humans during septic shock and in porcine endotoxaemia replicating the human condition (19). In this study, we have shown that the drop in blood pressure is aggravated by an ACE inhibitor. This did not seem to be explained by vascular dilatation, as SVRI, indicating vascular tonus, was not significantly lower during endotoxaemia in the enalapril injected endotoxaemic pigs as compared to the endotoxaemic pigs injected with saline. However, SVRI was not measured but calculated. Mann and co-workers have shown that inhibition of ACE does not affect the cardio-pulmonary response of endotoxaemic sheep (17). However, species differences do exist. For instance, sheep have, in contrast to both pig and man, collateral ventilation (15). Although several reports have suggested a positive inotropic effect of bradykinin (2, 1), treatment with an ACE-I reducing the elimination of bradykinin shows a cardio-depressant effect in the endotoxaemic pig. We could not show any augmentation of cardiac performance by

enalapril in endotoxaemic pigs. In contrast, positive inotropic effects of bradykinin, and 2 analogs resistant to ACE, on isolated guinea pig atrial preparations were potentiated by enalapril (18).

Release of kinins is a part of the inflammatory response in septic patients which induces vascular permeability that may be augmented by inhibition of ACE (6,8,9,22,28). In this study, the lung wet weight was similar in the enalapril + endotoxin group of pigs as compared to saline injected endotoxaemic animals. This suggests that other factors than enalapril-mediated ones, are important in the development of pulmonary oedema in porcine endotoxaemia. Interestingly, it was recently found that bradykinin did not increase oedema in free perfused rabbit lungs even in the presence of an inhibitor of ACE (4). However, bradykinin did increase pulmonary vascular resistance. In the present study, neither PVRI nor MPAP differed between the two groups of endotoxaemic pigs, indicating that the increases in pulmonary wet weights were caused by increased permeability and not hydrostatic load. The pulmonary vascular endothelium is rich in ACE (7,23). This may be an important mechanism in several species, counteracting the effect of inflammatory mediators produced by the endothelial cells or brought there from elsewhere in the body (3). Unopposed increase in capillary permeability would cause an extensive threat to the host by impairing gas exchange. In this study, we found no reduction in SaO_2 in endotoxaemic pigs treated with ACE-I. It may have been prevented by the use of PEEP which improves the distribution of ventilation and perfusion in the lungs.

Haemoglobin concentration increased more in the endotoxaemic pigs receiving only a saline injection. Haemoconcentration reflects the increased capillary permeability in this model (11) in which no hemolysis has been found (10). Aside from bradykinin, ACE is related to permeability also via AT II which can induce the expression of vascular permeability factor mRNA independent of changes in haemodynamics. This is an AT II receptor subtype 1-mediated event (27). Since this effect of AT II reaches its maximum after 3 h, it may help to explain some of the findings in this study. Infusion of Staphylococcus aureus increases the activity of ACE in serum (25). As AT II increases the systemic arterial and, consequently, perfusion pressure, it may be a

defensive mechanism designed to counteract the deteriorating haemodynamics seen in endotoxaemia. The plasma levels of sodium and potassium, respectively, were not significantly affected by enalapril in our study groups. Short-term treatment with enalapril during mechanical ventilation with PEEP in man does not affect sodium and water excretion (26).

In brief, enalapril in a dose that does not affect MAP *per se* reduces MAP during porcine endotoxaemia. ACE is the major AT II forming enzyme in the heart *in vivo* (14). AT II facilitates sympathetic transmitter release in the heart. ACE-I reduce such release in the absence of hypernatraemia (21). No sodium retention occurred in our model. Thus, ACE-I given at a dose causing a moderate reduction in blood pressure in the normal human may, during septic shock, aggravate the fall in MAP.

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