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Isolated circulatory response to intravenous administration of the ACE inhibitor enalaprilat

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1 The isolated vascular effects of intravenous administration of the angiotensin converting enzyme (ACE) inhibitor enalaprilat were investigated.

2 Thirty male patients undergoing cardiopulmonary bypass (CPB) were studied. According to a randomized sequence, 0.04 mg kg^{-1} enalaprilat (low-dose, $n = 10$), 0.08 mg kg^{-1} (high-dose, $n = 10$) enalaprilat or saline solution as placebo (control group, $n = 10$) was given as an i.v. bolus during CPB.

3 Changes in mean arterial pressure (MAP) and venous reservoir (RV) of the extracorporeal circulation were studied as indices of arterial resistance and venous capacitance.

4 Mean arterial blood pressure (MAP) and peripheral vascular resistance (SVR) were significantly more reduced in the high-dose enalaprilat group (MAP: −36 mm Hg after 9 min; SVR: −836 dyn s cm^{-5}) than in the low-dose group (MAP: −13 mm Hg after 10 min).

5 Volume of the reservoir (RV) decreased in both enalaprilat treated groups indicating additional (dose-dependent) venous pooling effects of the substance (low-dose: −300 ml; high-dose: −520 ml; control group: −100 ml).

6 Skin capillary blood flow measured by laser Doppler flowmetry (LDF) increased after injection of 0.04 mg kg^{-1} enalaprilat, whereas it decreased significantly when MAP fell markedly in patients treated with high-dose enalaprilat.

7 I.v. enalaprilat had dose-dependent vasodilating properties in the arterial and venous vessel system indicating reduction in pre- and afterload.

8 Microcirculation in both enalaprilat treated groups improved as long as reduction in blood pressure was not limited.

Keywords angiotensin converting enzyme inhibitor enalaprilat circulatory effects cardiopulmonary bypass laser Doppler flowmetry microcirculation

Introduction

Angiotensin converting enzyme (ACE) inhibitors are established drugs for the treatment of patients with hypertension and heart failure [1]. The antihypertensive actions of ACE-inhibitors are mainly caused by their blocking properties on the conversion of angiotensin I to angiotensin II [2]. In addition, ACE inhibitors appear to have effects which are independent of the renin-angiotensin system (RAS) and which may also contribute to the reduction in blood pressure: ACE inhibitors also influence the release of and the response to noradrenaline, prevent the cleavage of the (endogenous) vasodilator bradykinin, and facilitate synthesis of prostaglandins [3, 4].

There are only a few studies reporting on the effects of intravenous preparations of ACE inhibitors in the critically ill. Enalaprilat is one of these ACE-inhibiting compounds which can be given intravenously. It is the active diacid of the ACE inhibitor enalapril maleate [5]. I.v. enalaprilat was used successfully to control blood pressure in the post-bypass period of cardiac surgery patients [6] or during intubation [3].

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When vasoactive drugs are given, their haemodynamic response is influenced by their effects on the arterioles, on the capacity system, and by their (direct or indirect) myocardial effects. Thus in the clinical setting, it is difficult to assess a drug's isolated circulatory properties. After intravenous administration of enalaprilat, global haemodynamic changes (e.g. changes in filling pressures, heart rate and cardiac output) are more obvious than its isolated circulatory effects. Moreover, alterations in microperfusion have not been reported after i.v. enalaprilat. Thus the aim of the present study was to investigate the isolated circulatory effects and changes in microcirculatory cutaneous blood flow of two different doses of enalaprilat given intravenously.

Methods

Patients

Thirty male patients undergoing elective cardiac surgery with cardiopulmonary bypass (CPB) were studied. Each patient gave informed consent according to the guidelines of the Ethic Study Board of the hospital. No patient with renal insufficiency (creatinine >1.5 mg dl^{-1}), preoperative hypertension (systolic blood pressure >160 mm Hg), and medication with ACE inhibitors or calcium channel blockers was included. All patients took nitroglycerine in their history. Cyclooxygenase inhibitors were stopped 7 days before the operation and the kallikrein inhibitor aprotinin was not used in the study. Inclusion criterion was a mean arterial blood pressure (MAP) of >80 mm Hg during steady state of CPB.

Induction and maintenance of anaesthesia were comparable for all patients and consisted of weight-related doses of fentanyl, pancuronium bromide, and midazolam. No volatile anaesthetics were used. Before start of CPB, 0.3 mg fentanyl and 10 mg midazolam were given to the patients to exclude insufficient anaesthesia. During steady state of CPB (approximately 20 min after start of CPB) either

0.04 mg kg^{-1} enalaprilat ('low-dose', $n = 10$),
0.08 mg kg^{-1} enalaprilat ('high-dose' $n = 10$) or
saline solution as placebo (control group; $n = 10$)

was randomly given as an i.v. bolus to the extracorporeal circuit.

Cardiopulmonary bypass (CPB)

CPB was carried out by a non-pulsatile pump and membrane oxygenators (Sorin 41, Sorin, Torino, Italy). The circuit was primed with 1000 ml Ringer's solution, 1000 ml dextrose (5%), and 250 ml human albumin (5%). A non-pulsatile flow of 2.4 l min^{-1} m^2 was maintained during the entire bypass period. Almost normothermia (nasopharyngeal temperature 34.0 ± 0.2° C, rectal temperature 33.4 ± 0.3° C) was used. $PaCO_2$ was kept between 35 and 40 mm Hg and PaO_2 between 150 and 250 mm Hg by varying fresh gas flow to the membrane oxygenator. For myocardial preservation ice-cold Bretschneider's cardioplegic solution was infused. A two-stage cannula was used for venous drainage and 'partial' CPB was used throughout the study. Within 15 min after beginning CPB, the perfusate was concentrated by a haemoconcentrator (Haemofilter HF-80, Fresenius, Bad Homburg, FRG) in order to achieve a haemoglobin between 8 and 9 g dl^{-1}. All CPB procedures were carried out by the same perfusionist.

Measured parameters and data points

Mean arterial blood pressure (MAP), central venous pressure (CVP), and changes in reservoir volume (RV) were monitored continuously. Systemic vascular resistance (SVR) was calculated using a standard formula. Haemoglobin, osmolarity, plasma viscosity and colloid osmotic pressure (COP) were additionally measured from arterial blood samples.

Capillary skin blood perfusion was measured by laser Doppler flowmetry using a double-channel laser Doppler flow monitor (MBF-3D, Moor Instruments, Devon, Great Britain). This method uses the frequency shift of laser light induced by reflection on moving cells to measure red cell flux. The laser light is transmitted by efferent optical fibres, the back-scattered light is conveyed to the monitor for signal processing by afferent fibres.

Laser Doppler flow (LDF) is expressed in arbitrary flow units. The laser Doppler measures blood flow in approximately 2 mm^3 of tissue; response time of the system is approximately 0.2 s. The coefficient of variation was reported to be 4–11% (forehead flow) and 8–19% (forearm) respectively [7]. Coefficient of variation in the present study was similar (forehead: 6–16%; forearm: 5–13%). Further technical specification and evaluation of the laser Doppler flowmetry have been described in more detail elsewhere [8, 9]. One optical fibre probe was mounted on the patient's forehead (LDF-forehead), another one on the inner part of the right forearm (LDF-forearm) using double-sided adhesive tapes. Temperature probes were placed next to the laser Doppler probes to measure skin temperatures simultaneously with rectal, nasopharyngeal and blood temperatures.

Haemodynamic and microcirculatory changes were documented before injection of enalaprilat (= '0') and then every minute for 15 min by physicians who were blinded to the grouping of the patients. During this period no anaesthetics or volume was added to the circuit, perfusion flow and blood temperature were kept strictly constant.

Statistics

All parameters are expressed as mean ± standard deviation (s.d.). One- and two-way analyses of variance (including multivariate analyses of variance followed by Scheffé test) were carried out for statistical interpretation. Since laser Doppler monitor gives flow in arbitrary units, percentage changes from LDF values obtained before administration of enalaprilat were

calculated and tested by H-test (Kruskall-Wallis). P values <0.05 were considered to be statistically significant.

Results

The three groups were comparable with regard to biometric data and CPB procedure (Table 1). All temperatures (rectal, nasopharyngeal, forehead and forearm) were without differences between the groups (Table 1). Fluid balance during CPB was significantly higher in the enalaprilat treated groups than in the control patients (Table 1). Haemoglobin, osmolarity, pH, plasma viscosity, and COP were similar in all patients and did not differ during the entire investigation period.

MAP was significantly reduced in both enalaprilat groups. In the patients who had received 0.08 mg kg^{-1} enalaprilat, MAP decrease was more pronounced (maximum −36 mm Hg after 9 min) than in patients with 0.04 mg kg^{-1} enalaprilat (maximum −13 mm Hg after 10 min). By contrast, MAP slightly increased in the control group (maximum +8 mm Hg) (Figure 1).

SVR was reduced by a maximum of −836 dyn s cm^{-5} in the high-dose enalaprilat group (Figure 1), whereas this reduction was significantly lower in the patients who had received low-dose enalaprilat (maximum −375 dyn s cm^{-5}). In the control group, SVR increased slightly (maximum +110 dyn s cm^{-5}).

Volume of the oxygenator (Figure 2) decreased in all groups, even in the control group (maximum −100 ml in the 10th min). This decrease was more pronounced in the high-dose enalaprilat patients (maximum −520 ml at 15 min) than in the low-dose enalaprilat group (maximum −300 ml at 15 min).

Capillary skin blood flow measured at the forehead (Figure 3) increased significantly from baseline values in the low-dose enalaprilat group (maximum +32% in the 7th min after injection). In the high-dose enalaprilat group, LDF also increased in the first 5 min after injection. Thereafter, there was a marked decrease in capillary skin perfusion (maximum −30% in 9th min) which paralleled the decrease in perfusion pressure. In the control group, a continuous decrease in LDF was noticeable until the end of the investigation period (−34%). LDF values measured at the forearm were also different among the groups (Figure 3): it increased in group 1 (0.04 mg kg^{-1}) (maximum +18%), whereas it decreased in group 2 (maximum −29% in the 9th min) and in the control (maximum −31%). Additionally measured skin temperatures did not show any differences among the three groups.

None of the patients suffered from organ failure perioperatively. All patients could be weaned without any problems from the CPB and none of the patients needed positive inotropics or vasoconstrictors in the immediate post-bypass period.

Discussion

Cardiopulmonary bypass (CPB) represents a very useful experimental model to study the effects of drugs on the peripheral vasculature [10]. Since myocardial effects and influence of the lungs are excluded during CPB, it is a unique opportunity to assess the isolated vascular actions of drugs. In this situation, changes in resistance and capacitance vessels are reflected by changes in MAP and filling volume of the extracorporeal circuit [11]. Many investigations, however, using this technique carried out CPB in hypothermia (approximately 28° C or even less). It is not precisely known in how far the drug's effect is influenced by these temperatures. In the present

Table 1 Biometric data and data from cardiopulmonary bypass (CPB) (mean ± s.d.)

	Enalaprilat (mg kg^{-1})		
	0.04	*0.08*	*Control*
Age (years)	62.1 ± 6.5	63.3 ± 6.2	63.8 ± 5.1
Weight (kg)	78.6 ± 6.6	76.1 ± 8.8	79.2 ± 10.1
LVEF (%)	71.9 ± 9.1	68.5 ± 6.5	72.2 ± 2.9
LVEDP (mm Hg)	15.2 ± 4.3	15.8 ± 4.5	14.0 ± 2.0
CPB (min)	86.6 ± 14.3	87.7 ± 20.1	92.8 ± 18.8
Ischaemia (min)	51.8 ± 14.0	54.4 ± 10.9	56.8 ± 16.8
Temperature (°C)			
rectal	34.1 ± 0.2	34.0 ± 0.3	34.1 ± 0.6
nasopharyngeal	33.6 ± 0.3	33.4 ± 0.5	33.7 ± 0.6
Fluid balance during CPB (ml)	+710 ± 250	+990 ± 380	+350 ± 700*

Ischaemia: period of aortic cross-clamping.
LVEF: left ventricular ejection fraction; LVEDP: left ventricular end diastolic pressure.
*$P < 0.05$ different to the other groups.

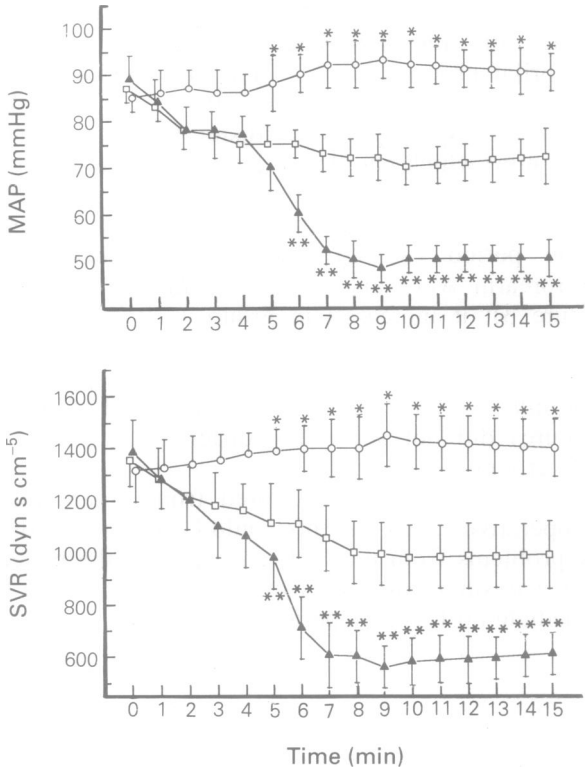

Figure 1 Changes of mean arterial (perfusion) pressure (MAP) and peripheral vascular resistance (SVR) (mean ± s.d.). ○ control, □ enalaprilat 0.04 mg, ▲ enalaprilat 0.08 mg. *$P < 0.05$ different to both enalaprilat groups, ** $P < 0.05$ different to the low-dose group.

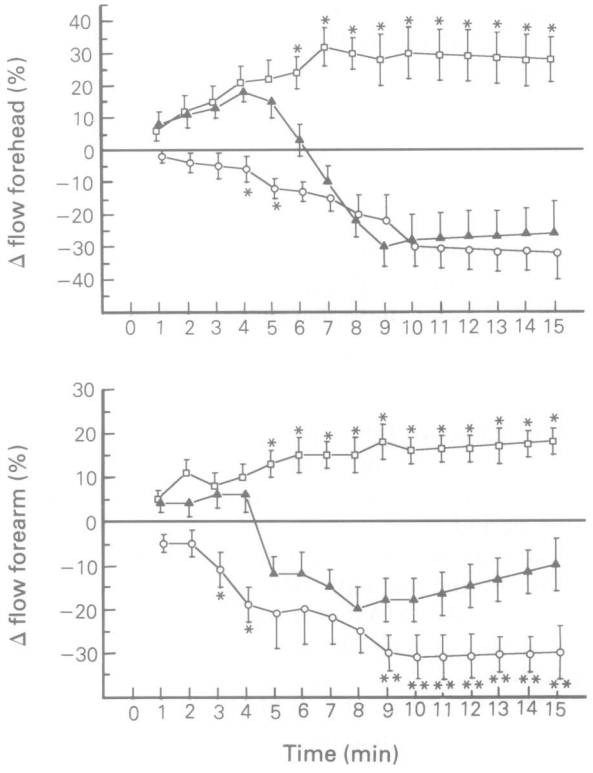

Figure 3 Changes in the skin capillary blood flow (%) measured at the forehead and at the forearm (mean ± s.d.). ○ control, □ enalaprilat 0.04 mg, ▲ enalaprilat 0.08 mg. *$P < 0.05$ different to the other two groups, **$P < 0.05$ different to the low-dose group.

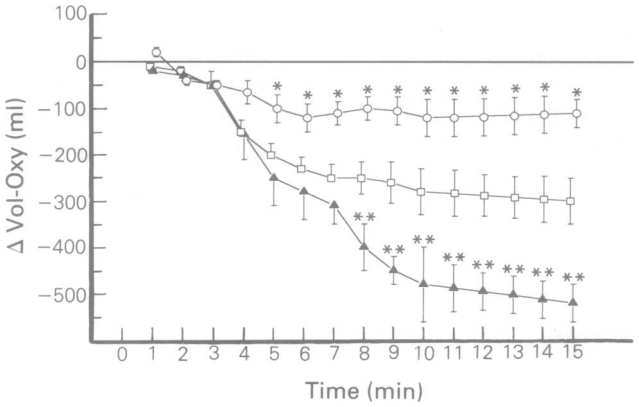

Figure 2 Changes in volume of the extracorporeal circuit (Vol-Oxy) (mean ± s.d.). ○ control, □ enalaprilat 0.04 mg, ▲ enalaprilat 0.08 mg. *$P < 0.05$ different to both enalaprilat groups, **$P < 0.05$ different to the low-dose group.

study, almost normothermia was used, and thus monitoring of the vascular effects of enalaprilat appears to be more valid. The study period was limited to 15 min during steady state of CPB, because thereafter several imponderables (rewarming, volume administration, additional anaesthetics) make interpretation of circulatory changes difficult or even impossible.

Laser Doppler flowmetry was found to be very useful for continuous non-invasive monitoring of microcirculatory blood flow [8]. Real-time recordings of microcirculatory skin blood flow can be made continuously and non-invasively by this technique. One major advantage of laser Doppler flowmetry is the negligible influence of the transducer on the microvascular bed under study. The accuracy of laser Doppler flow measurements in comparison with electromagnetic flow probes [12], (photo-) plethysmography [13], capillaroscopy [14], and xenon washout technique [15] was reported.

The renin-angiotensin system plays an important role in cardiovascular homeostasis. A marked activation of the renin-angiotensin system has been demonstrated in patients undergoing cardiopulmonary bypass [16, 17]. During CPB, sympathetic activity is often elevated most likely due to excitatory afferents from underperfused tissues and/or increased activity of baroreceptors. The increased sympathetic activity results in renal hypotension by which the renin-angiotensin system is activated and which in turn enhances sympathetic activity. These consequences of CPB may in part explain the increase in blood pressure during bypass although all patients have received high doses of fentanyl and benzodiazepines for anaesthesia.

The major finding of the present study was that enalaprilat has vasodilating properties on both, the arterial and venous side of circulation: perfusion pressure which is dependent on the arteriolar vessel tone, and volume of the reservoir which represents

venous pooling, were significantly reduced after i.v. administration of enalaprilat. Moreover, fluid balance after CPB was most positive in the patients who have received high-dose enalaprilat, also indicating most pronounced vasodilation in the capacitance vessels in these patients.

One question which is widely discussed is the ideal dosage of enalaprilat. Kubo *et al.* [18] could not demonstrate differences in haemodynamic response to increasing doses of enalaprilat ranging from 1.25 to 10.0 mg. LeJementel *et al.* [19] documented that the peak haemodynamic response to 1.25 mg and 5 mg enalaprilat given intravenously in patients suffering from congestive heart failure (NYHA III and IV) was similar. Systemic arterial blood pressure fell by 16% and 14%, respectively, whereas cardiac index increased by 16% and 25%. When using enalaprilat intravenously (0.625 to 1.25 mg) in hypertensive, awake patients, Neutel *et al.* [20] demonstrated only a decrease in blood pressure of approximately 10 to 12%. In most of the studies enalaprilat was not given on a mg kg^{-1} basis. In the present study, decrease in blood pressure (and SVR) was significantly more pronounced in the patients having received 0.08 mg kg^{-1} than after 0.04 mg kg^{-1} enalaprilat. We have chosen a rather high dosage (i.e. 0.08 mg kg^{-1} in a 80 kg man is approximately 6.5 mg) particularly compared with the doses used by Chatterjee *et al.* [21] who stated that 0.625 mg enalaprilat appears to be enough to produce significant inhibition of ACE and induce maximal haemodynamic response. In the present study, enalaprilat was added to the extracorporeal circuit. Volume of distrubution of enalaprilat (V) is approximately 23 l (0.3l kg^{-1}). Thus the additional priming of the extracorporeal circuit (2.250 l) study does not appear to markedly influence pharmacokinetics of enalaprilat.

In the present study, reduction in blood pressure was observed within 10 min. This is in accordance with Rutledge *et al.* [22] who found a decrease in blood pressure within 5 to 10 min after i.v. enalaprilat. Also Dickstein *et al.* [23] reported on a rapid hypotensive response when using enalaprilat intravenously (–20 mm Hg within 20 min [–23%]).

The influence of ACE inhibitors on organ perfusion is not yet completely elucidated. In (awake) patients suffering from congestive heart failure, ACE inhibitors are reported to maintain or improve blood flow to vital organs [24]. We only monitored changes in cutaneous microcirculation by laser Doppler flowmetry. It cannot be definitely concluded from changes in skin capillary blood flow to vital organ blood flow and the present results must be interpreted carefully. In the critically ill, however, it has been suggested that monitoring of skin microcirculatory blood flow by laser Doppler technique may provide useful information related to total body perfusion [25, 26].

The results from the present study demonstrated that although blood pressure decreased, skin microcirculatory blood flow increased significantly (in the low-dose and partly in the high-dose enalaprilat group). This gives evidence that we are too much pressure orientated instead of looking at blood flow: in the control patients, although MAP slightly increased, LDF was overall reduced, indicating the often altered relationship between pressure and flow in this situation. When blood pressure dropped markedly, however, also skin capillary blood flow decreased significantly (high-dose enalaprilat group). Thus when i.v. enalaprilat is used to control blood pressure, high doses should be used carefully and close haemodynamic monitoring is recommended.

It can be concluded that i.v. administration of the ACE-inhibitor enalaprilat resulted in dose-dependent vascular dilatation in the arterial and venous vessels assuming a decrease in pre-and afterload. Skin microcirculation was improved as long as blood pressure was not reduced markedly. Drugs with both venous and arteriolar dilating properties in parenteral preparation are rare. The vascular effects of i.v. enalaprilat in combination with its possible improvement in (micro-) perfusion appear to be of benefit particularly in the critically ill patient suffering from heart failure.

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