Placebo-Controlled, Randomized, Double-Blind Study of Intravenous Enalaprilat Efficacy and Safety in Acute Cardiogenic Pulmonary Edema

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Background Converting enzyme inhibitors meet most of the criteria required to be used in acute pulmonary edema. However, they could also induce deleterious effects on renal function and electrolytes. The purpose of this study was to evaluate the efficacy and safety of a single intravenous 2-hour infusion of enalaprilat (1 mg) after an acute pulmonary edema.

Methods and Results This was a placebo-controlled, randomized, double-blind study performed in 20 congestive heart failure patients (New York Heart Association class III or IV). Systemic and regional hemodynamic parameters, biological parameters, and blood gases were measured before and repeatedly after the onset of infusion. Compared with placebo, enalaprilat decreased pulmonary capillary wedge pressure (−37% versus −10%, P=.001), diastolic and mean systemic blood pressures (−21% versus 0%, P=.009, and −18% versus −1%, P=.026, respectively), diastolic and mean pulmonary blood pressures (−21% versus −8%, P=.040; −18% versus −9%, P=.046), and brachial and renal resistances (−44% versus −14%, P=.017, and −22% versus −2%, P=.014, respectively); increased brachial and renal blood flows (+77% versus +8%, P=.036, and +12% versus 0%, P=.043, respectively), arterial oxygen tension (+2% versus −16%, P=.041), and arterial oxygen saturation (+1% versus −2%, P=.045); and tended to decrease rate-pressure product (−19% versus −7%, P=.076), increase brachial artery diameter (+13% versus 0%, P=.081), and improve intrapulmonary shunt (−18% versus +16%, P=.080). Enalaprilat did not affect cardiac output or carotid or hepatosplanchnic hemodynamics.

Conclusions Early administration of enalaprilat is effective and well tolerated in acute pulmonary edema. (***Circulation.* 1996;94:1316-1324.**)

Key Words • heart failure • drugs • hemodynamics • pharmacology • regional blood flow

The use of ACE inhibitors has grown, and they are now established therapy in hypertension[1] and congestive heart failure.[2] There is strong evidence that ACE inhibitors reduce mortality in end-stage heart failure[3] as well as in less seriously ill patients.[4,5] There is similarly strong evidence that ACE inhibitors improve survival of patients with left ventricular dysfunction after acute myocardial infarction.[6]

Acute cardiogenic pulmonary edema is the most frequent reason for admission of congestive heart failure patients to the intensive care unit. Because patients are hemodynamically unstable and have a high renin state during such episodes,[7] the clinician usually stops ACE inhibitors temporarily to avoid deleterious effects on renal function and electrolytes. However, ACE inhibitors have immediate alleviating effects on both increased preload and afterload without unfavorable effects on myocardial oxygenation,[8] and they improve myocardial energy balance.[9] Several reports indicate that oral or intravenous ACE inhibitors may relieve pulmonary congestion and maintain both cardiac function and arterial oxygenation in the postinfarct period.[10,11] Recently, similar findings have been shown[12] in critically ill patients with acute intractable heart failure after myocardial infarction. Thus, if ACE inhibitors meet most of the criteria for a drug devoted to the treatment of cardiogenic pulmonary edema in theory, their efficacy and safety in this acute context remain to be evaluated in practice. Therefore, we decided to investigate the effects of early administration of intravenous enalaprilat on systemic hemodynamics, regional hemodynamics (of the brachial, carotid, renal, and hepatosplanchnic territories), the major hormones that regulate the cardiovascular system, plasma and urinary electrolytes, and arterial and venous oxygenation parameters during an acute cardiogenic pulmonary edema unrelated to acute myocardial infarction. We chose the intravenous form of enalapril to ensure a complete disposition of the drug and thus to optimize treatment.

Methods

This was a placebo-controlled, randomized, double-blind study performed on two groups of congestive heart failure patients who received a single intravenous 2-hour infusion of either enalaprilat (1 mg) or placebo.

The study protocol was approved by our hospital ethics committee. Informed written consent was obtained from all patients.

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Selected Abbreviations and Acronyms

ANF = atrial natriuretic factor
BBF = brachial blood flow
BP = blood pressure
bpm = beats per minute
BVR = brachial vascular resistance
CBF = carotid blood flow
CI = cardiac index
CO = cardiac output
CVR = carotid vascular resistance
DBP = diastolic systemic blood pressure
Do_2 = oxygen transport
Eo_2 = oxygen extraction ratio
HBF = hepatosplanchnic blood flow
HR = heart rate
MBP = mean systemic blood pressure
PCWP = pulmonary capillary wedge pressure
Qs/Qt = venous admixture
RAP = right atrial pressure
RBF = renal blood flow
SBP = systolic systemic blood pressure
SVI = stroke volume index

Selection of Patients

The aim of the recruitment process was to enroll congestive heart failure patients with acute cardiogenic pulmonary edema. To ensure uniform management of these patients, selection was based on a two-stage procedure.

First, patients above the legal age of consent were preincluded if they fulfilled all of the following criteria: (1) mild to severe congestive heart failure (NYHA class III or IV), (2) acute cardiogenic pulmonary edema (respiratory rate >30 breaths per minute, bilateral lung rales, bilateral alveolointerstitial syndrome on chest roentgenogram, arterial oxygen tension <80 mm Hg at room air, and PCWP >25 mm Hg), (3) SBP >80 mm Hg, and (4) plasma creatinine <180 μmol/L. Patients were excluded if they met one of the following criteria: (1) need for mechanical ventilation, (2) evidence of recent (<3 months) myocardial infarction or unstable angina pectoris, (3) evidence of severe stenotic valve disease, (4) evidence of active infection or hematological or hepatic disorders, (5) known history of cancer or AIDS, (6) treatment with ACE inhibitors during the 2 weeks preceding the pulmonary edema episode, or (7) previous digoxin treatment.

All patients who were determined to be eligible for preinclusion then received a standardized intravenous treatment that included a single furosemide dose, isosorbide dinitrate, and if needed, dobutamine, with oxygen supplementation through a face mask at F_{IO_2}=0.40. All other treatments except amiodarone were stopped. This first period lasted at least 6 hours, did not exceed 12 hours, and was ended by the search for inclusion criteria.

We then reviewed eligible patients for the following inclusion criteria: (1) substantial improvement as a result of the initial treatment (respiratory rate <25 breaths per minute, substantial regression of lung rales, arterial oxygen tension >80 mm Hg at F_{IO_2}=0.40, and PCWP <25 mm Hg), (2) SBP always >80 mm Hg, and (3) provision of informed, written consent.

Treatments

Two indistinguishable formulations, containing either enalaprilat or placebo, were supplied for the study by Merck Sharp & Dohme-Chibret Laboratories (Paris, France). Placebo formulations were presented as vials of 2.5 mL sodium chloride 0.9%. Enalaprilat formulations were presented as identical vials of 2.5 mL sodium chloride 0.9% that contained 2.5 mg enalaprilat (1 mg/mL). The treatment (enalaprilat 1 mg or placebo) was administered intravenously (infusion of 100 mL of sodium chloride 0.9%) in the antecubital fossa of the left arm. The infusion was performed over a 2-hour period with an electric pump.

Investigated Parameters

Systemic and Pulmonary Hemodynamics

SBP and DBP were measured by use of a brachial sphygmomanometer. HR was determined from RR intervals from lead II of the ECG. Systolic and diastolic pulmonary blood pressures, RAP, and PCWP were measured by use of a flow-directed thermodilution pulmonary artery catheter (Baxter Healthcare Corp, Edwards Division) introduced via the right internal jugular vein and connected to a monitor (Hewlett Packard 78353B fitted to a 78342A multichannel recorder). We determined CO by thermodilution technique using a CO computer (Baxter COM-2TM, Edwards Division).

The following parameters were calculated by use of standard formulas: MBP and pulmonary blood pressures, rate-pressure product, CI, SVI, and systemic and pulmonary vascular resistance indexes.

These parameters were recorded or calculated at baseline and 2, 4, and 8 hours after onset of infusion. For each measured parameter, the final value was the mean of five consecutive measurements.

Regional Hemodynamics

Brachial and carotid artery diameters, BBF, and CBF were measured by use of two-dimensional pulsed Doppler (Echovar Doppler pulsé 8 MHz, Alvar Electronics) as previously described and validated in hypertensive patients[13] and as widely used in healthy volunteers[14,15] and congestive heart failure patients.[16,17] BVR and CVR and the corresponding regional distribution ratios (%) were calculated as BVR=MBP×60/BBF, CVR=MBP×60/CBF, BBF/CO, and CBF/CO.

Plasma renal flow was determined from the para-aminohippuric acid clearance,[18] and RBF was calculated as RBF=Plasma Renal Flow(1−hematocrit). Plasma hepatosplanchnic flow was determined from indocyanine green clearance,[19] and HBF was calculated as HBF=Plasma Hepatosplanchnic Flow(1−hematocrit). Renal and hepatosplanchnic vascular resistances and the corresponding regional distribution ratios (%) were calculated as Renal Vascular Resistance=(MBP−RAP)×60/RBF, Hepatosplanchnic Vascular Resistance=(MBP−RAP)×60/HBF, RBF/CO, and HBF/CO.

These parameters were recorded or calculated at baseline and 4 hours after the onset of infusion.

Hormonal Parameters

Plasma ACE activity was measured by use of a spectrophotometric method.[20] Plasma renin activity, aldosterone, antidiuretic hormone, and, after extraction, ANF were determined by use of radioimmunoassays.[21-24] Finally, plasma norepinephrine and epinephrine were measured by high-performance liquid chromatography.[25]

These parameters were recorded at baseline and 4 and 8 hours after the onset of infusion.

Blood Gas Parameters

Arterial and mixed venous oxygen tensions (Pa_{O_2} and $P\bar{v}_{O_2}$) and saturations (Sa_{O_2} and $S\bar{v}_{O_2}$) were measured by use of standard techniques. The following derived oxygenation variables were calculated by use of standard formulas: arterial and mixed venous oxygen content (Ca_{O_2} and $C\bar{v}_{O_2}$), arteriovenous oxygen difference (mL/L), Do_2, $\dot{V}o_2$, Eo_2, and Qs/Qt.

These parameters were recorded or calculated at baseline and 2, 4, and 8 hours after the onset of infusion.

Safety Evaluation

SBP, DBP, and HR were monitored every 10 minutes during the first 2 hours of treatment infusion and then hourly until the end of the study. Serum concentrations of sodium, potassium, nitrogen, and creatinine were determined at baseline and 4 and 8 hours later. Urine volume and concentrations of sodium, potassium, nitrogen, and creatinine were determined during the corresponding time in-

tervals from 4 hours before the onset of infusion to 8 hours afterward. Urine output and clearances during the corresponding time intervals were calculated by use of standard formulas.

Study Protocol

The study comprised three consecutive periods. The first period, the duration of which was between 6 and 12 hours, allowed us to establish the diagnosis of cardiogenic pulmonary edema, carry out a standardized treatment, and assess each patient's response to that treatment. This first period, which began with the search for preinclusion criteria, ended with the search for inclusion criteria. The second period, the duration of which was 6 hours, was a wash-out period that consisted of withdrawal of the standardized treatment, except oxygen (FIO_2=0.40). This second period ended with measurement of the baseline values of the investigated parameters and with randomization of patients. The third period, the duration of which was 8 hours, allowed us to perform the intravenous infusion (enalaprilat or placebo) for 2 hours and to assess repeatedly for 6 hours its safety and its efficacy on the investigated parameters. This period ended for all patients with the administration of a 2.5-mg oral dose of enalapril. In the succeeding days, the doses of enalapril and of diuretics and nitrates were adapted so that patients were discharged from the hospital with an appropriate long-term treatment.

Sample-Size Calculation

The primary end points for efficacy were PCWP and RBF. According to previous studies,[16,17,26] we assumed standard deviations of 6 mm Hg for PCWP and 200 mL/min for RBF. Under these conditions, with the type I error (α) set at .05, we calculated that 20 patients would be necessary to detect a 12 mm Hg decrease in PCWP and a 450 mL/min increase in RBF with a 95% power (ie, a type II error (β)=.05).

Statistical Analysis

Statistical analysis was performed with BMDP statistical software.[27] Homogeneity of pretreatment means between groups was tested by use of Student's t test (BMDP 3D). Comparison of treatment effects between groups was performed by ANCOVA (BMDP 1V for parameters that were evaluated once; BMDP 2V for parameters evaluated more than once), with the pretreatment value used as the covariate. For parameters that were only evaluated once (ie, at 4 hours), treatment effect was analyzed only when the parallelism test was not significant. For parameters evaluated more than once (ie, at 2, 4, and 8 hours or at 4 and 8 hours), treatment effect was analyzed only when the time-treatment interaction was not significant. For each analysis, values of $P \leq .05$ were considered statistically significant.

In "Results," reported percentages of variation for a given parameter were computed for each treatment between the values observed at peak effect and at baseline.

TABLE 1. Clinical Characteristics of the Study Population

	Placebo	Enalaprilat	Combination
Age, y	77±9	77±7	77±8
Weight, kg	65±18	69±12	67±15
Height, cm	167±8	163±11	165±10
Sex, M/F	5/4	6/5	11/9
NYHA class, III/IV	4/5	4/7	8/12
Etiology, IHD/DCM	7/2	9/2	16/4
LVEF, %	18±4	19±3	19±3
LVEDD, mm	63±6	61±5	62±5
CTI, %	62±4	65±3	63±3
Nitroglycerin, mg	9.9±9.7	9.6±9.6	9.8±9.4
Furosemide, mg	27±14	36±22	32±19
Dobutamine, yes/no	1/8	1/10	2/20

IHD indicates ischemic heart disease; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; and CTI, cardiothoracic index.

TABLE 2. Main Parameters Recorded at Entry (Admission in the Intensive Care Unit) and at Inclusion (End of Standardized Treatment Period)

	Placebo	Enalaprilat	Combination
RR, breaths/min			
Entry	34±3	36±3	35±3
Inclusion	19±2	19±3	19±3
SBP, mm Hg			
Entry	128±25	135±15	132±20
Inclusion	132±23	139±25	135±24
HR, bpm			
Entry	92±19	99±26	96±23
Inclusion	81±7	81±12	81±10
PCWP, mm Hg			
Entry	37±4	36±4	36±4
Inclusion	20±4	19±4	19±4
Pao_2, mm Hg			
Entry	64±9	58±13	61±12
Inclusion	89±3	87±7	88±5

RR indicates respiratory rate.

Results

Description of the Study Population

Twenty patients were included in the study between September 1992 and May 1993. Eleven patients received enalaprilat and 9 received placebo. The imbalanced distribution between the two groups is owing to the fact that the randomization was prepared according to groups of 6. This ensured a balanced distribution between the two groups up to the 18th patient, but the 19th and 20th patients were both allocated to the same treatment (enalaprilat).

Table 1 shows the clinical characteristics of the patients, including age, weight, height, sex, NYHA functional class, causes of their congestive heart failure, their isotopic or angiographic left ventricular ejection fraction, left ventricular end-diastolic dimension, cardiothoracic index, and treatments received during the first period. The patients were suffering from advanced congestive heart failure (40% NYHA class III and 60% NYHA class IV), and their cardiomyopathies were predominantly (80%) of ischemic origin.

Table 2 shows the clinical and biological quantitative parameters recorded at entry (to determine preinclusion) and at the end of the standardized treatment period (to determine inclusion). At the time of inclusion, all patients had shown a substantial response to the standardized treatment, with decreases of respiratory rate (−46%), HR (−16%), and PCWP (−47%) and an increase in Pao_2 (+44%).

At baseline, after the 6-hour wash-out period, both preload and afterload had deteriorated substantially in all patients. The evolution was similar in the two groups. As a matter of fact, the investigated parameters were comparable between the two groups for all parameters except ANF. Data recorded at baseline and the corresponding statistical analyses are presented in Tables 3 through 9 together with the effects observed during the investigational period.

Treatment Evaluation

Systemic Hemodynamic Effects

Compared with placebo, enalaprilat significantly decreased DBP (−21% versus 0% at 8 hours) and MBP (−18% versus −1% at 8 hours). No significant difference was observed between the two groups for SBP, HR, CI, SVI, or systemic vascular resistance index. Finally, enalaprilat tended to decrease rate-pressure product (−19%

TABLE 3. Kinetics of Effects on Systemic Hemodynamic Parameters

	Time of Measurement*				Probability Values		
	T0	T2	T4	T8	Baseline	Treatment	Interaction
SBP, mm Hg							
Enalaprilat	133±19	121±23	116±27	111±25	.4134	.1766	.1128
Placebo	125±21	114±20	118±16	121±12			
DBP, mm Hg							
Enalaprilat	71±13	64±14	60±14	56±11	.9324	.0092‡	.0288†
Placebo	70±20	67±18	67±18	70±17			
MBP, mm Hg							
Enalaprilat	91±13	83±14	79±17	75±15	.6981	.0255†	.0372†
Placebo	88±20	83±18	84±16	87±15			
HR, bpm							
Enalaprilat	82±16	78±12	78±10	80±8	.8482	.1980	.2306
Placebo	81±28	85±30	79±18	79±21			
RPP, mm Hg/bpm							
Enalaprilat	10 960±2661	9440±2507	9065±2198	8823±1926	.6865	.0760	.8230
Placebo	10 300±4467	9759±4252	9309±2673	9586±2890			
CI, $L \cdot min^{-1} \cdot m^{-2}$							
Enalaprilat	2.4±0.5	2.4±0.8	2.3±0.6	2.2±0.7	.9626	.7862	.8497
Placebo	2.4±0.7	2.5±0.8	2.3±0.5	2.4±0.8			
SVI, mL/m^2							
Enalaprilat	30±7	31±9	29±7	28±9	.4820	.9422	.5023
Placebo	33±15	32±14	31±11	32±15			
SVRI, $dyne \cdot s^{-1} \cdot cm^{-5} \cdot m^{-2}$							
Enalaprilat	911±217	875±313	874±249	870±343	.6945	.6309	.7784
Placebo	950±214	911±349	975±357	977±289			

RPP indicates rate-pressure product; SVRI, systemic vascular resistance index.
*Measurements taken at baseline (T0) and 2 (T2), 4 (T4), and 8 (T8) hours after infusion of drug or placebo.
†$P<.05$; ‡$P<.01$.

versus −7% at 8 hours), but this effect failed to reach the level of statistical significance ($P=.076$). (See Table 3.)

Pulmonary Hemodynamic Effects

Compared with placebo, enalaprilat significantly decreased diastolic pulmonary BP (−21% versus −8% at 4 hours), mean pulmonary BP (−18% versus −9% at 4 hours), and PCWP (−37% versus −10% at 4 hours). No significant difference was observed between the two groups for systolic pulmonary BP, RAP, or pulmonary vascular resistance index. Nevertheless, it should be observed that enalaprilat tended to decrease RAP (−42% versus −11% at 4 hours). (See Table 4.)

Regional Hemodynamic Effects

Compared with placebo, enalaprilat tended to increase brachial artery diameter (+13% versus 0%), but this effect failed to reach the level of statistical significance

TABLE 4. Kinetics of Effects on Pulmonary Hemodynamic Parameters

	Time of Measurement*				Probability Values		
	T0	T2	T4	T8	Baseline	Treatment	Interaction
SPBP, mm Hg							
Enalaprilat	56±15	47±16	47±19	51±19	.3915	.1058	.3884
Placebo	50±14	50±11	45±11	50±12			
DPBP, mm Hg							
Enalaprilat	28±7	25±7	22±8	24±9	.2994	.0395†	.9880
Placebo	25±5	25±5	23±5	25±6			
MPBP, mm Hg							
Enalaprilat	38±10	32±9	31±12	33±12	.3251	.0464†	.8231
Placebo	34±7	34±7	31±7	34±8			
RAP, mm Hg							
Enalaprilat	12±5	10±6	7±5	8±5	.3176	.1411	.5626
Placebo	9±4	9±5	8±5	9±4			
PCWP, mm Hg							
Enalaprilat	27±6	22±9	17±7	20±9	.0559	.0013‡	.2477
Placebo	21±6	21±7	19±6	22±7			
PVRI, $dyne \cdot s^{-1} \cdot cm^{-5} \cdot m^{-2}$							
Enalaprilat	122±57	131±73	170±91	179±64	.3971	.4125	.1611
Placebo	143±54	157±61	154±70	141±54			

SPBP indicates systolic pulmonary BP; DPBP, diastolic pulmonary BP; MPBP, mean pulmonary BP; and PVRI, pulmonary vascular resistance index.
*Measurements taken at baseline (T0) and 2 (T2), 4 (T4), and 8 (T8) hours after infusion of drug or placebo.
†$P<.05$; ‡$P<.01$.

TABLE 5. Effects on Brachial and Carotid Hemodynamic Parameters

	Time of Measurement*		Probability Values		
	T0	T4	Baseline	Treatment	Equality of Slopes
BAD, cm					
Enalaprilat	0.38±0.05	0.43±0.04	.2724	.081	.005
Placebo	0.41±0.05	0.41±0.06			
BBF, mL/min					
Enalaprilat	39±24	69±39	.9368	.036†	.774
Placebo	40±14	43±14			
BVR, mm Hg·s^{-1}·mL^{-1}					
Enalaprilat	162±54	90±50	.5284	.017†	.582
Placebo	145±54	124±43			
BBF/CO, %					
Enalaprilat	0.9±0.5	1.7±1.1	.6774	.122	.428
Placebo	1.0±0.4	1.2±0.4			
CAD, cm					
Enalaprilat	0.45±0.05	0.47±0.05	.0811	.720	.615
Placebo	0.50±0.05	0.51±0.04			
CBF, mL/min					
Enalaprilat	140±45	161±64	.1729	.842	.816
Placebo	183±81	191±74			
CVR, mm Hg·s^{-1}·mL^{-1}					
Enalaprilat	45±25	32±12	.2042	.466	.104
Placebo	32±9	29±10			
CBF/CO, %					
Enalaprilat	3.3±1.1	4.0±1.5	.1002	.578	.408
Placebo	4.8±2.4	5.8±3.1			

BAD indicates brachial artery diameter; CAD, carotid artery diameter.
*Measurements taken at baseline (T0) and 4 hours after infusion of drug or placebo (T4).
†$P<.05$.

($P=.081$). Moreover, enalaprilat significantly increased BBF (+77% versus +8%) and decreased BVR (−44% versus −14%). Finally, no significant difference was observed between the two groups for the BBF/CO distribution ratio. In contrast, compared with placebo, enalaprilat did not modify carotid artery diameter and slightly (and nonsignificantly) increased CBF and the CBF/CO distribution ratio and decreased CVR. (See Table 5.)

Compared with placebo, enalaprilat significantly increased RBF (+12% versus 0%) and decreased renal vascular resistance (−22% versus −2%) and did not modify the RBF/CO distribution ratio. In contrast, compared with placebo, enalaprilat did not modify HBF, hepatosplanchnic vascular resistance, or the HBF/CO distribution ratio. (See Table 6.)

Hormonal Effects

Compared with placebo, enalaprilat significantly decreased plasma ACE activity (−81% versus −30% at 4 hours) and tended to increase plasma renin activity and decrease aldosterone plasma levels between 4 and 8 hours, but these effects remained nonsignificant. Moreover, enalaprilat did not modify antidiuretic hormone, ANF, norepinephrine, or epinephrine plasma levels. (See Table 7.)

Blood Gases and Oxygenation-Derived Variables

Compared with placebo, enalaprilat significantly improved Pa_{O_2} (+2% versus −16% at 8 hours) and Sa_{O_2} (+1% versus −2% at 8 hours) and tended to improve Qs/Qt (−18% versus +16% at 8 hours), but this latter effect failed to reach the level of statistical significance ($P=.080$). In contrast, compared with placebo, enalaprilat did not modify $P\bar{v}_{O_2}$ or $S\bar{v}_{O_2}$, arteriovenous oxygen difference, D_{O_2}, $\dot{V}_{O_2}$, or E_{O_2}. (See Table 8.)

Biochemical Variables

Compared with placebo, enalaprilat significantly decreased serum sodium (−4% versus −1% at 8 hours) but did not modify serum potassium, nitrogen, or creatinine concentrations. Similarly, no significant difference was observed between the two groups for urine output or sodium, potassium, nitrogen, or creatinine clearances. (See Table 9.)

Treatment Safety

During the study period, no patient suffered from excessive hypotension or reported any adverse effect. At the end of the study period, in addition to oral enalapril, diuretics, and nitrates, 4 of the 9 patients randomized to placebo and 2 of the 11 assigned to enalaprilat also required inotropic drugs (ie, dobutamine). Two patients in the placebo group and 1 in the enalaprilat group died of intractable heart failure.

Discussion

To evaluate the efficacy and safety of a single intravenous infusion of 1 mg enalaprilat in acute cardiogenic pulmonary edema, we selected patients with severe congestive heart failure during an exacerbation of their illness unrelated to acute myocardial infarction. However, for ethical purposes, the study was performed 12 to 18 hours after the acute episode, ie, when the condition of these patients was less severe but they were still in pulmonary edema. The dose and infusion rate of enalaprilat were those used in the CONSENSUS II study.[28]

Regarding central hemodynamics, enalaprilat reduced both preload and afterload from 2 to at least 8 hours after the start of infusion. We observed a strong decrease in PCWP and reductions in DBP and MBP that reflected

TABLE 6. Effects on Renal and Hepatosplanchnic Hemodynamic Parameters

	Time of Measurement*		Probability Values		
	T0	T4	Baseline	Treatment	Equality of Slopes
RBF, mL/min					
Enalaprilat	617±322	690±337	.7547	.043†	.559
Placebo	570±219	577±210			
RVR, mm Hg·s^{-1}·mL^{-1}					
Enalaprilat	9.7±5.5	7.6±4.5	.7584	.014†	.866
Placebo	9.0±2.7	8.8±2.3			
RBF/CO, %					
Enalaprilat	14±7	16±7	.7776	.736	.614
Placebo	15±6	17±6			
HBF, mL/min					
Enalaprilat	631±252	599±257	.8841	.961	.352
Placebo	646±174	616±210			
HVR, mm Hg·s^{-1}·mL^{-1}					
Enalaprilat	11.1±11.8	10.0±10.2	.4514	.146	.545
Placebo	7.9±2.8	8.5±3.3			
HBF/CO, %					
Enalaprilat	16±7	14±6	.6158	.253	.250
Placebo	17±4	18±6			

RVR indicates renal vascular resistance; HVR, hepatosplanchnic vascular resistance.
*Measurements taken at baseline (T0) and 4 hours after infusion of drug or placebo (T4).
†$P<.05$.

both venous and arteriolar vasodilation in the context of no change in CI. Enalaprilat induced similar effects in the right circulation as evidenced by the tendency for RAP to decrease and by reductions in diastolic pulmonary BP and mean pulmonary BP. These similar effects on MBP and RAP on the one hand and on mean pulmonary BP and PCWP on the other also explain, in the context of no change in CI, why calculated systemic and pulmonary vascular resistance indexes were not significantly modified. The fact that CI was not modified is the result of unchanged HR and SVI. Whereas the lack of effect on HR was expected with an ACE inhibitor,[29,30] the lack of effect on SVI was more surprising in the context of afterload reduction. In fact, the possible rise of SVI may have been counteracted by the inhibition of angiotensin II formation.[31] Finally, enalaprilat tended to decrease rate-pressure product, which indicates a probable reduction in myocardial oxygen requirements. These effects on central hemodynamics are in line with those reported in chronic stable congestive heart failure[16,32] and, more recently, in open trials in postinfarct heart failure.[11,12]

TABLE 7. Kinetics of Effects on Plasma Hormonal Parameters

	Time of Measurement*			Probability Values		
	T0	T4	T8	Baseline	Treatment	Interaction
PCEA, mmol·mL^{-1}·min^{-1}						
Enalaprilat	13.1±5.6	2.5±1.9	3.1±2.0	.3591	.0014‡	.5979
Placebo	16.2±9.2	11.4±7.8	11.1±6.5			
PRA, ng·L^{-1}·min^{-1}						
Enalaprilat	68±61	455±581	445±430	.0551	.1833	.8961
Placebo	23±24	23±22	27±22			
Aldosterone, ng/100 mL						
Enalaprilat	25±23	14±11	15±11	.5791	.1180	.8155
Placebo	19±16	16±12	19±17			
ADH, pg/mL						
Enalaprilat	2.1±2.2	1.3±0.9	1.7±2.0	.7664	.6332	.9441
Placebo	2.4±1.4	1.6±0.9	2.0±1.6			
ANF, pg/mL						
Enalaprilat	76±25	67±24	70±27	.0114†	.5126	.8130
Placebo	149±82	149±94	156±94			
Norepinephrine, pg/mL						
Enalaprilat	665±471	687±819	1127±2388	.9074	.9879	.8110
Placebo	696±716	660±1095	1286±2798			
Epinephrine, pg/mL						
Enalaprilat	72±47	66±33	73±46	.8303	.4170	.9941
Placebo	67±65	53±27	59±32			

PCEA indicates plasma angiotensin I–converting enzyme activity; PRA, plasma renin activity; and ADH, antidiuretic hormone.
*Measurements taken at baseline (T0) and 4 (T4) and 8 (T8) hours after infusion of drug or placebo.
†$P<.05$; ‡$P<.01$.

TABLE 8. Kinetics of Effects on Blood Gases

	Time of Measurement*				Probability Values		
	T0	T2	T4	T8	Baseline	Treatment	Interaction
Pa_{O_2}, mm Hg							
Enalaprilat	83±34	83±25	85±28	85±30	.6636	.0411†	.5824
Placebo	77±21	69±10	71±15	65±9			
Sa_{O_2}, %							
Enalaprilat	94±4	95±3	95±4	95±2	.8793	.0449†	.2128
Placebo	94±3	94±3	94±2	92±4			
$P\bar{v}_{O_2}$, mm Hg							
Enalaprilat	31±4	31±3	31±4	30±4	.8862	.0873	.0565
Placebo	32±8	28±3	29±3	32±6			
$S\bar{v}_{O_2}$, %							
Enalaprilat	59±7	59±7	58±8	58±8	.8565	.3481	.1171
Placebo	58±12	55±6	55±7	59±6			
DAV, mL/L							
Enalaprilat	57±15	59±15	60±13	61±17	.6618	.8891	.0309†
Placebo	61±24	66±19	66±20	57±18			
Do_2, $mL \cdot min^{-1} \cdot m^{-2}$							
Enalaprilat	357±61	362±96	340±78	333±86	.5635	.7591	.9063
Placebo	385±147	398±160	363±126	372±159			
$\dot{V}o_2$, $mL \cdot min^{-1} \cdot m^{-2}$							
Enalaprilat	136±40	139±45	132±32	132±40	.9411	.3338	.3995
Placebo	138±47	163±65	147±44	131±53			
Eo_2, %							
Enalaprilat	38±8	38±8	39±7	40±8	.8605	.8032	.0440
Placebo	39±14	41±7	42±8	36±6			
Qs/Qt, %							
Enalaprilat	17±10	15±8	14±8	14±7	.7875	.0804	.1353
Placebo	19±10	17±7	16±6	22±8			

DAV indicates arteriovenous oxygen difference.
*Measurements taken at baseline (T0) and 2 (T2), 4 (T4), and 8 (T8) hours after infusion of drug or placebo.
†$P<.05$.

Regarding regional hemodynamics, enalaprilat induced favorable effects in the brachial and renal vascular beds and had no deleterious effects in the cerebral and hepatosplanchnic territories.

Concerning renal hemodynamics, it must be stressed that RBF, which is the chief determinant of renal function in patients with severe congestive heart failure,[33] is generally increased with ACE inhibitors.[16,26,32,34-36] However, in theory, in situations of hyperreninemia and of massive and quick diuresis, as usually observed in acute heart failure, administration of ACE inhibitors is regarded as potentially deleterious for renal function. In fact, in this acute context, the enalaprilat-induced effects on RBF and renal vascular resistance were comparable qualitatively to those observed in chronic stable congestive heart failure.[16,26,32,34,35] Moreover, because neither creatinine or nitrogen clearances were modified, we can assume that enalaprilat did not alter glomerular filtration.

Concerning brachial hemodynamics, enalaprilat induced both arteriolar and large-artery vasodilation as evidenced by the decrease in BVR and the increase in brachial artery diameter, respectively. As a result, BBF increased. In the context of a decrease in MBP and as previously reported in stable chronic congestive heart failure patients,[16] hypertensives,[37] and healthy volunteers,[38] vasodilation of the brachial artery is an active phenomenon that reflects an increase in arterial compliance. Moreover, because impaired brachial artery function may increase impedance to left ventricular performance,[39] the enalaprilat-induced large-artery vasodilation may contribute to decreased left ventricular end-systolic stress. Finally, although BBF/CO did not increase significantly, the fact that enalaprilat significantly increased BBF without changing CO suggests that it probably induced some redistribution of CO toward the musculocutaneous territory.

Concerning carotid hemodynamics, our study shows that in our patients and compared with healthy volunteers[38,40] and/or hypertensives,[37,41] carotid artery diameter and CBF were markedly decreased and CVR was increased at baseline. These observations are similar to those reported in the brachial territory in stable chronic congestive heart failure.[16,17,39] In contrast with the effects previously reported with ACE inhibitors in healthy volunteers[38,40] and hypertensives,[37] enalaprilat did not significantly modify carotid artery hemodynamics. However, CBF and CVR were increased by 15% and decreased by 29%, respectively. In fact, hemodynamics of the common carotid artery represent those of two different vascular beds, the facial musculocutaneous one, which depends on the external carotid artery, and the intracerebral one, which is a tributary of the internal carotid artery. In healthy volunteers, it has been shown that ACE inhibitors affect only the external carotid territory and do not modify the internal one, which is autoregulated.[42] In our study, because enalaprilat strongly increased musculocutaneous blood flow (as shown, for instance, in the brachial vascular bed), the fact that CBF was only slightly increased probably can be accounted for by an unchanged intracerebral blood flow.

Finally, it appears from our data that enalaprilat had no significant effect on hepatosplanchnic hemodynamics, thus confirming previously reported data with ACE inhibitors in chronic stable congestive heart failure.[16,26,32,34]

TABLE 9. Kinetics of Effects on Plasma Electrolytes and Urine Output and Clearances

	Time of Measurement*			Probability Values		
	T0	T4	T8	Baseline	Treatment	Interaction
Sodium, mmol/L						
Enalaprilat	136±9	132±7	131±7	.1881	.0186†	.2685
Placebo	140±3	138±3	139±3			
Potassium, mmol/L						
Enalaprilat	4.1±0.6	4.0±0.5	4.1±0.5	.4293	.5980	.0805
Placebo	3.9±0.5	4.0±0.5	3.8±0.4			
Nitrogen, mmol/L						
Enalaprilat	8.0±3.5	7.6±3.5	7.5±3.0	.5608	.5529	.5850
Placebo	7.2±2.3	6.6±2.6	6.4±2.2			
Creatinine, μmol/L						
Enalaprilat	116±34	103±18	112±29	.8247	.1050	.3661
Placebo	111±51	96±36	97±29			
Urine output, mL/min						
Enalaprilat	2.9±1.9	1.4±0.7	1.0±0.6	.3670	.7469	.1001
Placebo	4.2±4.0	1.4±1.2	1.5±1.2			
Sodium clearance, mL/min						
Enalaprilat	1.3±1.7	0.4±0.3	0.2±0.2	.5511	.3156	.2344
Placebo	1.8±2.1	0.5±0.5	0.5±0.4			
Potassium clearance, mL/min						
Enalaprilat	20±14	11±8	7±6	.2096	.4389	.4308
Placebo	33±28	14±12	12±11			
Nitrogen clearance, mL/min						
Enalaprilat	65±49	40±36	23±24	.5673	.8589	.1715
Placebo	81±77	37±37	37±35			
Creatinine clearance, mL/min						
Enalaprilat	172±142	110±100	63±61	.9989	.9831	.3861
Placebo	172±135	94±100	81±77			

*Measurements taken at baseline (T0) and 4 (T4) and 8 (T8) hours after infusion of drug or placebo for electrolytes; for urine output and clearances, T0 represents the period from 4 hours before infusion to onset of infusion, T4 represents the period from onset of infusion to 4 hours after onset of infusion, and T8 represents the period from 4 to 8 hours after onset of infusion.

†$P<.05$.

Regarding hormonal effects, as expected, enalaprilat induced a strong inhibition of plasma ACE activity 4 hours after onset of the infusion, and this effect lasted for at least 8 hours. The simultaneous tendencies of plasma renin activity to increase and of aldosterone to decrease are in line with the lowering of angiotensin II concentrations. In contrast, enalaprilat did not significantly affect antidiuretic hormone, ANF, norepinephrine, or epinephrine. These results, which are similar to those recently reported in acute intractable heart failure after myocardial infarction,[12] contrast with most of those previously reported in chronic stable congestive heart failure, in which decreases in norepinephrine[16,26,32,43] and in ANF[43] plasma levels were observed. Concerning ANF, the lack of a large reduction in atrial stretch, well reflected by the nonsignificant decrease in RAP, may account for this discrepancy.

Regarding tissue oxygenation, our study indicates that as a result of the lack of variation in CO, oxygen delivery remained unchanged. The balance between D_{O_2} and $\dot{V}_{O_2}$ was well maintained, as shown by the lack of variation of $S\bar{v}_{O_2}$ and E_{O_2}. The decrease in PCWP induced by enalaprilat was probably associated with a reduction in edema fluid filtration and consequently with an improvement of Pa_{O_2} and Sa_{O_2}. Moreover, enalaprilat slightly improved Qs/Qt. This result is of great clinical importance because other vasodilators, such as sodium nitroprusside or nitrates, which inhibit hypoxic pulmonary vasoconstriction and thus increase Qs/Qt, usually cause hypoxemia.[44]

Finally, as previously reported in critically ill patients,[11,12,45] enalaprilat was well tolerated. SBP and diuresis were maintained throughout the study period. The observed decrease in serum sodium was moderate and never required any specific treatment. Moreover, serum potassium was never altered.

In conclusion, in cardiogenic pulmonary edema, an early intravenous administration of a 1-mg dose of enalaprilat alleviates both preload and afterload, improves musculocutaneous and renal hemodynamics and arterial oxygenation, and tends to reduce Qs/Qt while maintaining cardiac function, cerebral and hepatosplanchnic hemodynamics, and creatinine and electrolyte clearances. These results suggest that there is a clinical advantage to the use of intravenous enalaprilat in the early course of acute cardiogenic pulmonary edema in congestive heart failure.

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