Rapid Improvement of Acute Pulmonary Edema with Sublingual Captopril
Richard J. Hamilton, MD, Wallace A. Carter, MD, E. John Gallagher, MD

ABSTRACT

Objective: To test the hypothesis that sublingual captopril produces a more rapid improvement of acute pulmonary edema (APE) than does placebo, when added to a standard regimen of O₂, nitrates, morphine, and furosemide.

Methods: Prospective, randomized, double-blind, placebo-controlled clinical trial in an urban teaching hospital ED. Adults brought to the ED with APE were given captopril or placebo sublingually. Every 5 minutes a clinical APE distress score (APEX) was obtained.

Results: Over the first 40 minutes of treatment, the mean APEXs were significantly better for the patients given captopril \[p < 0.001, F = 14.5, \text{one-way (repeated-measures) analysis of variance (ANOVA)}\]. At 30 minutes, the patients given captopril had a mean APEX improvement of 43% (i.e., to 57% of initial distress); the group given the current standard regimen plus placebo improved only 25% (i.e., to 75% of initial distress; \[p = 0.03, \text{multiway ANOVA}\]). In addition, there was less respiratory failure necessitating mechanical ventilation in the captopril patients (9%) vs the placebo patients (20%), which did not achieve significance (\[p = 0.10, \text{Fisher’s exact test}\]).

Conclusion: In APE, the addition of sublingual captopril to the standard regimen of O₂, nitrates, morphine, and furosemide produces more rapid clinical improvement than does the standard regimen alone.

Key words: pulmonary edema; congestive heart failure; captopril; angiotensin-converting enzyme inhibitor.


The therapy for acute pulmonary edema (APE) has remained unchanged for years. Preload reduction with nitrates and morphine, improvement of oxygenation, and diuresis constitute the current standard regimen. Recently, angiotensin-converting enzyme (ACE) inhibitors have assumed a prominent role in the therapy for chronic congestive heart failure (CHF) and recovery from myocardial infarction with reduced left ventricular (LV) function.1–3 These ACE inhibitors have reduced mortality and improved exercise tolerance in CHF patients.

Captopril, in its normal tablet form, is readily absorbed via the sublingual route, with increases in renin and decreases in blood pressure (BP) evident within 30 minutes of administration.4 Previous studies have demonstrated that sublingual captopril produces a beneficial effect on the hemodynamics of chronic CHF.5–7 While these studies provide useful information about captopril, they have a limited applicability to the treatment for APE in the ED. Previously reported patients were either stabilized or experiencing only a mild exacerbation of...
CHF. They had not entered into the cycle of increasing sympathetic tone, sodium and water retention, and pulmonary edema typical of APE. Furthermore, while using captopril as a single agent will improve CHF hemodynamics, it may not provide additional benefit when added to aggressive treatment with nitrates, morphine, and diuretics. In this study, we addressed the hypothesis that the addition of sublingual captopril to a standard regimen would result in a more rapid clinical improvement of APE than would use of the standard regimen alone.

I METHODS

Study Design

This study was a prospective, randomized, double-blind, placebo-controlled trial. The primary outcome measurement was a composite variable for measuring the clinical manifestations of APE. Other outcome measures were the incidence of respiratory failure necessitating intubation and the change in mean arterial pressure (MAP).

Setting and Population

The study was performed at an urban teaching hospital that has 140,000 annual ED visits. All patients with the clinical appearance of APE (acute onset of dyspnea, diaphoresis, and rales > 50% of posterior lung fields), as judged by the ED attending physician or the PGY4 emergency medicine (EM4) resident, were eligible for this study. Patients were excluded for a systolic BP < 90 mm Hg, pregnancy, known ACE inhibitor allergy, or age < 18 years. By a-priori design, patients who were intubated within 15 minutes of arrival were disqualified from the study because there would be insufficient time to obtain a meaningful number of observations. Patients were enrolled between August 1993 and January 1994.

Human Subject Committee Review

The Albert Einstein College of Medicine Committee for Clinical Investigation approved this study to enroll patients using three different forms of consent: 1) full consent, 2) abbreviated consent, and 3) "deferred consent." The committee used predetermined guidelines as well as the guidance of its full time ethicist to determine whether the study met criteria for deferred consent. Full consent was used for patients who were sufficiently comfortable to read a complete consent form or for obtaining consent from next of kin available. These patients were enrolled in the study and consent was obtained when their conditions improved enough to allow them to comfortably read and sign a full deferred consent form. The term "deferred consent" reflected the ethical position of the board at the time the study was approved. If we were to submit the same protocol for approval in 1995, the committee would determine whether the critically ill patients who gave "deferred consent" would be eligible for waived consent.

Experimental Protocol

The investigators were given a numbered data collection instrument with a prepackaged set of four unmarked capsules that had previously been randomized to be either placebo (lactose powder) or captopril (lactose plus 12.5 mg captopril). The code was to be broken only at the end of the study or in the case of an adverse event (anaphylaxis, cardiac arrest). On arrival, the patient was assessed for enrollment criteria. If the criteria were met, consent was obtained from the patient or next of kin, or was deferred at the judgment of the attending physician. The patient was then enrolled in the study with the randomized data collection instrument.

Once enrolled, the patient’s clinical distress was measured with a composite score of four measurements developed for this study. The first set of measurements were taken on arrival, and when complete, the patient was given the study drug. The contents of two capsules (a total of 25 mg of captopril or placebo) were emptied sublingually for patients who had a systolic BPs ≥ 110 mm Hg; one capsule (a total of 12.5 mg of captopril or placebo) was administered for those who had systolic BPs between 90 and 110 mm Hg.

Blood pressure, pulse, and the four measurements of the composite score were measured every 5 minutes for 120 minutes. The study drug was readministered at 60 minutes, following the same dose-to-BP guidelines used initially. Treatment otherwise followed the standard protocol used to manage APE in this ED. During the first 15 minutes of treatment and evaluation, the patient received supplemental O₂ 100% by mask, nitroglycerin (0.4 mg) sublingually every 5 minutes for a total of three doses, IV morphine in 2-mg increments titrated against symptoms and BP, and IV furosemide (40-mg minimum dose). Over the following 15 minutes, the patients were evaluated for the need for IV nitroglycerin, repeat sublingual nitroglycerin, or nitropaste. After 30 minutes, the patients were evaluated for repeat doses of furosemide, morphine, or nitrates. The attending physician or the EM4 resident was permitted to alter dosing, frequency, or route of administration at his or her discretion. However, in no case were medications or treatments other than O₂, nitrates, morphine, or furosemide given. The
decision to intubate a patient was based on the clinical assessment by the attending or the EM4 resident.

All the patients arrived by emergency medical services (EMS) transport. Patients who were transported by basic life support (BLS) units received O2 therapy and rapid transport. Patients who were transported by advanced life support (ALS) units were treated according to the APE protocol of the New York City EMS. This protocol uses supplemental O2, sublingual nitrates, IV morphine and furosemide, and a maximum on-scene time of 20 minutes. The percentage of patients receiving ALS field treatment is listed in Table 1.

Measurements

Attending emergency physicians and EM4 residents functioned as the bedside investigators and other residents and medical students functioned as the data recorders. All the participating physicians and students attended a special presentation on data collection and had their initial data collections supervised by one of the authors (RJH).

The clinical measurement of APE severity was derived from four measurements—three visual analog scales (VASs) and a measurement of the lowest head-of-bed angle the patient could tolerate without worsening his or her dyspnea. These measurements were obtained every 5 minutes after the administration of the study drug (time 0) for 120 minutes or until intubation. An unweighted composite raw score for measuring the clinical manifestations of APE was created by simply adding the raw scores of the four component variables gathered at a particular point in time. Thus, each patient had a raw composite score computed every 5 minutes. Each raw composite score was then converted to a percentage of the initial score to produce an APE distress score (APEX) expressed as a percentage of the initial raw score. Therefore, all patients present with 100% APEX and either improve toward 0% distress or deteriorate toward an APEX > 100% distress.

The first VAS was a patient-reported dyspnea scale. Patients were told that 0 mm indicated "I can breathe as I normally do" and 100 mm represented "I can't breathe at all." The patients were asked to make a mark on the continuous line where their particular respiratory difficulty was represented. This mark was later measured and recorded as a raw score in mm.

The second VAS was obtained from the attending physician or EM4 resident scoring the respiratory distress. A mark at 0 mm on the scale indicated "No respiratory distress" and a mark at 100 mm indicated "The patient must be intubated." This mark was later measured and recorded as a raw score in mm.

The third VAS was a score of the patient's diaphoresis. The forehead was wiped dry and then the amount of diaphoresis was evaluated by the data collector. A mark at 0 mm indicated "The skin remained dry" and a mark at 100 mm indicated "The skin was persistently diaphoretic" despite wiping. This mark was later measured and recorded as a raw score in mm.

The final measurement was obtained after the patient was told that the head of the stretcher was going to be lowered. The patient was told to indicate to the investigator when the head was as far back as he or she could comfortably tolerate. If the patient could not tolerate that position after 30 seconds, the head was moved forward until a position was found that he or she could tolerate. This angle (0°-90°) was measured and converted to a 0- to 100 scale by multiplying by 1.11.

If the patient was obtunded on arrival, he or she was moved to the maximum head-of-bed angle and automatically given a respiratory difficulty score of 100 mm ("I can't breathe at all"). The patient was questioned every 5 minutes until the mental status improved enough for the patient to indicate his or her respiratory distress and a comfortable head-of-bed angle. Figure 1 is an example of typical data collection.

Analytical Methods

The primary target outcome variable, established a priori, was the APEX. Based on previous experience and information about the pharmacokinetics of captopril, we estimated that patients given placebo would have a 30-minute APEX of 90% (i.e., only 10% improvement). Furthermore, we estimated that an improvement to an APEX of 70% (i.e., 30% improvement) by the addition of sublingual captopril would represent the smallest clinically important difference worth detecting. Using 20% as our Δ, a two-tailed α of 0.05, a power of 80% (one-tailed β of 0.20), and assuming equal numbers of patients randomized to the treatment groups, we estimated

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<th>TABLE 1 Characteristics of the Study Group*</th>
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<tr>
<td>Initial raw APE distress score—</td>
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<td>mean</td>
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<td>Age—mean</td>
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<td>Gender—male</td>
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<td>Furosemide</td>
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<td>Myocardial infarction</td>
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*p-value > 0.05 for all comparisons. APE = acute pulmonary edema; ALS = advanced life support; MAP = mean arterial pressure.
that we would need approximately 60 patients in each arm of the trial to demonstrate a 20% difference if it existed.\textsuperscript{8}

One-way analysis of variance (ANOVA) (repeated-measures) (SAS Institute Inc., Release 6.04, Cary, NC) and multiway ANOVA (True Epistat, 1989, Epistat Sigma Services, Richardson, TX) were used to compare the APEXs over the first 40 minutes and to compare the APEXs as individual endpoints, respectively. Residuals were tested for normal distribution. A multiple-comparisons test using the Newman-Keuls procedure was performed to determine the 95% confidence overlap of the repeated measures.

The groups were compared for a secondary endpoint, the proportion of intubations performed, using Fisher’s exact test (Epistat). Multiple logistic regression (Epistat) was performed to determine whether the initial raw score and the use of captopril (the independent variables) predicted the need for intubation (outcome variable). Other variables, including baseline features at randomization, uses of medications other than captopril, and maximum changes in MAP, were compared using Student’s t-test for continuous data, and chi-square or Fisher’s exact test for categorical data, as appropriate. In addition to p-values, 95% confidence intervals (CIs) are used where relevant.

All charts underwent blinded retrospective review by the authors after completion of the study to ensure that the admitting diagnosis of APE was correct based on previously reported guidelines for clinical investigations of CHF.\textsuperscript{9-12}

\section*{RESULTS}

Of the 110 patients who arrived in APE in this ED, 57 were enrolled. Patients were not enrolled when the num-

\begin{figure}[ht]
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Sample data collection at time 15 minutes and creation of raw composite score. APEX calculated based on a sample initial raw score of 300.}
\end{figure}

Time 15 minutes

\begin{itemize}
\item Measured orthopnea scale
  0° flat ... 90° upright
  Corrected to a 0-to-100 scale

\item Patient-reported dyspnea scale
  0° flat ...
  90° upright
  Corrected to a 0-to-100 scale

\item Observer-reported respiratory distress scale
  0
  100 mm
  \textit{No respiratory distress}
  \textit{Intubation distress}

\item Observer-measured diaphoresis scale
  0
  100 mm
  \textit{Skin is dry}
  \textit{Persistent diaphoresis}
\end{itemize}

Sample measurement

\begin{itemize}
\item 90°
\item 75-mm mark
\item 50-mm mark
\item 25-mm mark
\end{itemize}

Converted score

\begin{itemize}
\item 100
\item 75
\item 50
\item 25
\end{itemize}

Sample data collection at time 15 minutes and creation of raw composite score. APEX calculated based on a sample initial raw score of 300.

Initial raw composite score = 300

\begin{itemize}
\item \textit{I can breathe as I normally do}
\item \textit{I can’t breathe at all}
\end{itemize}

\begin{itemize}
\item Time 15 raw composite score = 250
\item Time 15 APEX = 83.3%
ber of patients in the ED prevented proper data collection or when a research assistant was not available. Patients were otherwise enrolled 24 hours a day. Three patients were disqualified because they were intubated upon arrival. Five patients were eliminated due to incomplete data collection (e.g., no available interpreter, documentation deficiency). One patient who had chronic obstructive pulmonary disease had dyspnea but no rales and was mistakenly enrolled in the study and after 40 minutes of treatment was later disqualified. All such patients were disqualified prior to unblinding of the study. All other patients entered into the study had cardiogenic pulmonary edema later confirmed by record review. The etiology of the APE was determined (by discharge diagnosis) to be acute myocardial infarction (AMI) (31%) or exacerbation of chronic CHF (69%).

Forty-eight patients were available for data analysis—25 in the placebo group and 23 in the captopril group. The two groups of patients did not differ significantly in sex, age, initial MAP, field treatment by ALS, incidence of AMI, initial raw APE composite score, or use of sublingual nitrates, furosemide, morphine, and IV nitroglycerin (Table 1). The placebo and the captopril patients received the same total dose ranges of sublingual nitrates (three to six 0.4-mg tablets) and IV furosemide (80–200 mg). Those in the groups given morphine received similar dose ranges (4–10 mg).

The APEX, which was calculated after the study was completed, was concordant with the need for intubation (all patients with rising APEXs required intubation) and with general clinical condition (no patient was noted to deteriorate clinically or require intubation when the APEX was falling, i.e., improving).

The APEXs vs time are graphed in Figure 2. The addition of sublingual captopril resulted in a reduction of APEX to 57% (95% CI 47% to 67%) of initial distress by 30 minutes, compared with the placebo patients, who had only reduced to 75% (95% CI 65% to 85%) of their

![Figure 2: APEX vs time (minutes). *Denotes p < 0.05, multiway analysis of variance.](image-url)
initial distress (p = 0.03, multiway ANOVA). The 95% CI for this 18% difference is 3% to 33%. The first significant difference (p = 0.03) occurred at 25 minutes, when the captopril patients had improved to a 65% APEX (95% CI 55% to 75%) and the placebo patients were still at 79% APEX (95% CI 71% to 87%). After 40 minutes, the improvement with captopril was sustained but no longer statistically significant. By 75 minutes, there was no difference in APEXs. The repeat dose of sublingual captopril at 60 minutes had no clinically measurable effect. However, the number of patients with persistent distress at one hour was small.

The patients who received sublingual captopril experienced a more significant improvement of APEX over the first 40 minutes of therapy (one-way ANOVA, repeated-measures p < 0.001, F = 14.5). Using the Newman-Keuls procedure for multiple comparisons, the APEXs between 25 and 40 minutes demonstrated no 95% CI overlap between the captopril and the placebo groups.

There was a trend toward less respiratory failure necessitating mechanical ventilation for the captopril patients (9%) vs the placebo patients (20%); 95% CI for difference of 11% (−8% to 31%). This difference was not significant (p = 0.10, Fisher's exact test). Multiple logistic regression determined that the initial raw composite score (reflecting severity of presentation) and the use of captopril could not predict intubation outcome (p = 0.08). All the patients who had respiratory failure were mechanically ventilated by 40 minutes. Finally, the addition of captopril did not result in a significant change in MAP over placebo (Table 1).

I DISCUSSION

While ACE inhibitors have a clear role in chronic disease states such as hypertension and CHF, their utility in the acute management of APE is undefined. The pathophysiology of APE secondary to myocardial ischemia begins with an impairment of LV contractility and a decrease in cardiac output. This results in an early sympathetic response and a late sustained stimulation of the renin–angiotensin–aldosterone axis, which produces systemic vasoconstriction and sodium and water retention. Although this ensures vital organ perfusion, it creates a cycle of volume expansion and systemic vasoconstriction that exacerbates LV dysfunction, increases filling pressures, and causes transudation of fluid into the pulmonary capillary bed.13 ACE inhibitors correct this spiral at several different points.

Although categorically vasodilators and afterload reducers, ACE inhibitors actually provide more specific redistribution of blood flow by dilating splanchnic beds of the kidneys, heart, and brain. In addition, ACE inhibitors increase sodium excretion. This characteristic produces a synergism between ACE inhibitors and loop diuretics.14 Furthermore, angiotensin II promotes release of norepinephrine from the synapse, and ACE inhibitors become sympatholytic when high angiotensin II levels exist in pathologic states such as in APE.8,14,15 Indeed, studies show that ACE inhibitors may act by reducing local production of angiotensin II in coronary arteries.16 There is strong evidence that ACE inhibitors can even offer improvement in anephric patients.17 ACE inhibitors block the breakdown of tissue bradykinin (a potent vasodilator) by kininase II as well as increase the level of renal prostaglandin.14

The use of captopril in the early management of APE was previously untested. However, previous studies have established that sublingual captopril acts rapidly and is effective in improving hemodynamics in patients with elevated LV diastolic pressures. Haude et al.5 performed a randomized, crossover study of sublingual nitrates vs sublingual captopril in patients with New York Heart Association classes II–IV CHF, cardiac indexes < 2.5 L/min/m², and diastolic pulmonary artery pressures > 20 mm Hg. Haude et al. demonstrated that captopril and nitroglycerin each produced a rapid sustained improvement in cardiac index, stroke volume index, and stroke work index that began 20 minutes after administration. However, captopril achieved a later peak effect (at 47–84 minutes postadministration) and a longer sustained improvement (117–162 minutes) in these values. While these patients did have severe chronic CHF, they were hemodynamically stable and had been treated with digoxin and/or diuretics prior to the administration of captopril.

Barnett et al.6 electively hospitalized patients with CHF and withheld all vasodilators and diuretics for 48 hours. These patients demonstrated a decrease in elevated pulmonary capillary wedge pressure that began 10 minutes after administration of sublingual captopril and reached plateau at 30 to 40 minutes. Langes et al. reproduced these results7 with IV captopril in a similar study of 13 patients who had LV failure, electively undergoing right heart catheterization. These patients were taking all their usual CHF medications (except for ACE inhibitors). However, none of these studies examined the effectiveness of captopril when added to an aggressive regimen of diuretics, nitroglycerin, and morphine.

Using the APEX as our endpoint, we demonstrated that the addition of captopril to the current standard regimen results in a more rapid resolution of the clinical manifestations of APE. The clinical data reported here demonstrate that sublingual captopril had a clinical effect within 25 minutes of administration. This conforms with the pharmacodynamic data reported elsewhere,4–7 which show that serum levels of captopril and plasma...
renin activity increase significantly within 30 minutes of sublingual administration, with a correspondent reduction in BP.

It is remarkable that there was no difference detected in the change in MAP between the captopril and the placebo groups. This may be explained by the observation that patients who develop dramatic hypotension after captopril have been treated first with an increasing or prolonged course of high-dose diuretics. It is theorized that these patients may have angiotensin II levels that are extremely high and decrease precipitously with ACE inhibition. Perhaps the same patients started on ACE inhibitors in the early phase of APE do not experience this precipitous BP change.

**LIMITATIONS AND FUTURE QUESTIONS**

Investigating APE is limited by the severe initial manifestation of this disease. Satisfactory consent is problematic, pulmonary artery catheterization is technically difficult, and there is no clinometric tool to measure outcome. We attempted to overcome these challenges by using a type of study design known as a "split plot," or repeated measures. It is used, e.g., to compare two therapies that have effects that are measured over time. A "split plot" study takes repeated measurements over time and expresses them as a change from study entry (such as measuring the efficacy of a new antihypertensive as the mean change in arterial pressure over time).

The two groups can then be compared despite variation in the degree to which the disease process is present among the study participants. This approach follows the principle that controlling for the variation in the severity of a disease with experimental design is superior to post-hoc statistical manipulation (such as covariant analysis). This was the goal in designing the APEX. This score makes repeated measurements of four clinical manifestations that physicians use to assess APE at the bedside and expresses them as a percentage of the initial manifestations. Ultimately, the APEX and the study design are tools to detect the effect of captopril in a disease state that does not have an established clinical endpoint.

We did not assess the impact on the individual components of the APEX, to avoid a post-hoc search for significance that was not part of the experimental design (sometimes called data "torturing"). We observed that the individual components of the APEX changed in the same direction but at different rates. This reflects the clinical experience that patients often report feeling "better" before they appear improved to the treating physician, and vice versa.

The inferences that can be drawn from this study are limited by two additional features. First the APEX has never been compared with invasive monitoring. The APEX appears to have face validity because it appears appropriate to the entity measured (i.e., it makes clinical sense). It has content validity because each of its components is appropriate to the entity measured (the four components are established clinical characteristics of APE). Finally, it has construct validity because it adheres to the theoretical construct of the pathophysiology of APE (the degrees of orthopnea, diaphoresis, dyspnea, and respiratory failure reflect the severity of the underlying disease process).

However, the APEX lacks concurrent criterion validity (i.e., it was not simultaneously compared with invasive monitoring). However, predictive criterion validity (whether the APEX predicts such aspects of APE as respiratory failure) may be a useful proxy for concurrent criterion validity. If so, there is some suggestion that the scale may be truly measuring clinical severity of APE, since no patient who had falling scores (i.e., improving) and all patients who had rising scores deteriorated and required intubation.

Finally, we did not reach our calculated sample size, nor did we achieve our Δ of an absolute difference of 20% in APEXs between the captopril and the placebo groups at 30 minutes following study entry. To a certain extent, this reflects the imprecision inherent in sample size calculations, which require estimation of three different variables. Nevertheless, we did reach an 18% difference in APEXs favoring captopril, which was significant over the first 40 minutes, and most marked at 30 minutes.

The proportion of patients experiencing respiratory failure and requiring intubation was larger in the placebo-treated group. Multiple logistic regression with the initial raw composite score (since the sickest patients are more likely to require intubation) may indicate a captopril effect on preventing respiratory failure. Although not statistically significant, this trend may prove to be reproducible in larger studies. Of note is the observation that all the patients deteriorated within the first 40 minutes of arrival. This points to a role for more aggressive therapy in the field, and sublingual captopril would be an ideal drug.

**CONCLUSION**

The addition of sublingual captopril to a regimen of nitrates, furosemide, and morphine appears to result in a rapid improvement of APE. Since these test results are based on a reduction in the APEX, a new, nonvalidated clinometric test of APE, further study is required to confirm these findings.

**REFERENCES**

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