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# Monocrotaline-Induced Cardiopulmonary Damage in Rats: Amelioration by the Angiotensin-Converting Enzyme Inhibitor CL242817 (42370)

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*Abstract.* Pulmonary injury induced by the plant alkaloid monocrotaline is partially prevented by the angiotensin-converting enzyme (ACE) inhibitor captopril. CL242817 [(S-[R*,S*])-1-([3-acetylthio]-3-benzoyl-2-methyl-propionyl)-L-proline] is a new orally active ACE inhibitor under evaluation as an antihypertensive agent. To determine whether CL242817 also can modify monocrotaline-induced pulmonary injury, male rats were divided into four groups: control; CL242817 (60 mg/kg/day, po); monocrotaline (2.4 mg/kg/day, po); or monocrotaline plus CL242817, and were sacrificed after 6 weeks of continuous treatment. Rats receiving monocrotaline alone exhibited occlusive medial thickening of the pulmonary arteries, cardiomegaly, and right ventricular hypertrophy. Electron micrographs of monocrotaline-treated lung revealed degeneration of both endothelial and Type I epithelial cells, as well as marked interstitial hypercellularity and fibrosis. Hydroxyproline (collagen) content of monocrotaline-treated lung also increased significantly, confirming the fibrosis observed in the electron micrographs. These structural changes were accompanied by decreased lung ACE and plasminogen activator (PLA) activities, indicative of pulmonary endothelial dysfunction. Concomitant CL242817 treatment ameliorated all anatomic manifestations of monocrotaline injury, particularly the right ventricular hypertrophy, pulmonary arterial occlusion, epithelial degeneration, and interstitial fibrosis. CL242817 also significantly prevented the monocrotaline-induced increase in lung hydroxyproline content. In contrast, concomitant CL242817 did not significantly influence the suppressed lung ACE and PLA activities in monocrotaline-treated rats. CL242817 alone produced retarded weight gain, decreased heart weight relative to body weight, decreased lung hydroxyproline content and ACE activity, and increased serum ACE activity and plasma AII concentration. Thus CL242817 resembles captopril, both in its ability to ameliorate monocrotaline-induced pulmonary injury in rats, and in many of its side effects. 

The pyrrolizidine alkaloid monocrotaline, derived from *Crotalaria spectabilis,* is hepato- and pneumotoxic, and induces pulmonary hypertension (1). The histologic and ultrastructural changes associated with monocrotaline-induced pulmonary vascular damage have been well documented (2–8). Vascular effects of monocrotaline in the lung include blebbing, degeneration and fragmentation of the endothelial cells, perivascular edema, extravasation of red blood cells, and muscularization of the pulmonary arteries and arterioles (2–8). The latter phenomenon results in progressive, occlusive medial thickening of the pulmonary vessels. These structural changes are accompanied by pulmonary endothelial dysfunction, including decreased clearance of 5-hydroxytryptamine (9, 10) and norepinephrine (10), transiently increased and then decreased angiotensin-converting enzyme (ACE) activity (11–13), decreased plasminogen activator (PLA) activity (13), and increased prostacyclin ($PGI_2$) production (13). While the pathogenesis of monocrotaline injury in the lung is not clear, the ACE inhibitor captopril (SQ14225) partially prevents monocrotaline-induced pulmonary hypertension in rats (14). Likewise, captopril and the nonorally active ACE inhibitor teprotide (SQ20881) ameliorate pulmonary hypertension produced by chronic hypoxia (15–17). These data suggest that inappropriate ACE activity may play a role in the development of experimental pulmonary hypertension.

CL242817 [(S-[R*,S*])-1-([3-acetylthio]-3-benzoyl-2-methyl-propionyl)-L-proline] is a new orally active competitive inhibitor of ACE (18). Compared to captopril, CL242817 is equally effective on an equimolar basis in inhibiting the pressor response to intravenous



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angiotensin I in normotensive rats and dogs, and in potentiating the depressor response to intravenous bradykinin in rats (18). Furthermore, intravenous CL242817 (1 mg/kg) lowers arterial blood pressure in aortic-coarcted hypertensive rats to the same degree as does 1 mg/kg of captopril (18). In the present study, the ability of CL242817 to ameliorate monocrotaline-induced pulmonary vascular injury in rats was tested in a model of lung damage in which we have previously demonstrated a beneficial effect of captopril (14). We sought to determine whether this therapeutic effect of captopril was unique, or was a property shared by other ACE inhibitors. This study is part of a structure–function analysis of ACE inhibitors as moderators of experimental pulmonary hypertension. The analysis eventually will include both sulfhydryl-containing ACE inhibitors such as captopril and CL242817, and nonsulfhydryl inhibitors such as MK421 (Merck Sharp and Dohme, West Point, Pa.) and CGS13945 (Ciba–Geigy, Summit, N.J.).

**Materials and Methods.** Male Wistar rats (Harlan Industries, Madison, Wisc.) weighing 250–300 g were housed at 23 ± 1°C and fed standard rat chow (Ralston Purina Co., St. Louis, Mo.) *ad libitum.* The animals were randomly assigned to one of four treatment groups: Group 1, controls, received tap water; Group 2, CL, received CL242817 (American Cyanamid Co., Pearl River, N.Y.) in their drinking water at a concentration delivering 60 mg CL/kg body wt/day; Group 3, Mon, received monocrotaline (S. B. Penick Co., Lindhurst, N.J.) in their water at a concentration delivering 2.4 mg Mon/kg/day; and Group 4, Mon + CL, received both monocrotaline and CL242817 in their water at the concentrations indicated above. Each group consisted of 15 animals. Water consumption among the four groups was similar throughout the study.

After 6 weeks of continuous treatment, six animals from each group were killed by decapitation. Blood was collected and centrifuged at 4°C, and serum and plasma samples were stored at −70°C. The left lung was ligated with thread at the main bronchus, removed, and dissected into three equal segments perpendicular to the spinal axis (termed the cephalic, central, and caudal segments). The three segments were weighed, frozen in liquid $N_2$, and then stored at −20°C. The right lung was perfused via the trachea with 10% phosphate-buffered Formalin (pH 7.4) at a pressure of 22 cm of water. The heart, kidneys, adrenals, liver, and spleen were weighed and fixed in Formalin. The fixed heart was dissected, and the right ventricle (RV) and the left ventricle plus septum (LV + S) were weighed separately. Right ventricular hypertrophy was evaluated on the basis of RV/LV + S weight ratios.

The middle lobe of the Formalin-fixed right lung was sectioned midsagittally at a 4-$\mu$m thickness, and was stained with hematoxylin–eosin. All arteries whose outer diameters were 20–200 $\mu$m were photographed, and the prints were evaluated on a digitizing graphics pad interfaced with a PDP 11/45 computer. The lumenal and outer perimeters of the artery were traced with an electronic cursor, and the data were analyzed by a program designed to calculate the surface area of irregular shapes. Appropriate geometric conversion permitted analysis of vessels cut at oblique angles, with their data normalized to a 90° cross-section of the idealized cylindrical artery. The mean wall thickness and outer diameter of the normalized arteries were obtained from the lumenal and total surface areas. A total of 676 pulmonary arteries were analyzed, and the data were expressed as percentage severely occluded arteries. A severely occluded artery was defined as one whose mean wall thickness was greater than 80% of the outer radius of the vessel. In a totally occluded artery, the wall thickness was 100% of the outer radius.

For electron microscopy, three additional animals per group were anesthetized with sodium pentobarbital (35 mg/kg, ip), and the lungs were fixed by injection of Karnovsky's paraformaldehyde–glutaraldehyde solution in the right heart ventricle (13). Specimens measuring approximately 4 × 6 × 10 mm were obtained from the central lateral portion of the left lung, then were cut into blocks of approximately 1 $mm^3$. The blocks were washed in neutral 0.1 *M* phosphate buffer, postfixed in 4°C osmium tetroxide (1%, v/v) for 30 min, and embedded in epoxy 812 resin. Sections (1 $\mu$m) were obtained from 3 to 5 blocks per lung and were stained with toluidine blue. Ultrathin sections were obtained from the areas of interest, and were stained with uranyl ace-

tate and lead citrate. Specimens were examined in a Hitachi HU-12 transmission electron microscope. In an attempt to minimize subjectivity of interpretation, an inherent limitation in ultrastructural analysis, 60 electron micrographs from monocrotaline-treated lungs, and 60 micrographs from the monocrotaline plus CL242817 group were number-coded, and were evaluated by three experimental pathologists unfamiliar with the code. Each observer evaluated each micrograph for six features: interstitial edema, hypercellularity, collagen accumulation, and abnormalities in Types I and II epithelial cells and endothelial cells. Each response was graded on a scale of "none, mild, moderate, or marked."

ACE activity in the central segment of the left lung and in the blood serum was measured within 48 hr after autopsy by the spectrophotometric method of Cushman and Cheung (19). Protein concentration in the lung homogenate and serum was determined by the buiret method. Plasma angiotensin II (AII) concentration was measured by radioimmunoassay (New England Nuclear Co., Boston, Mass.). PLA activity in the cephalic and caudal segments of the left lung was determined by the fibrin plate lysis method (20), and the data were expressed as area ($mm^2$) of fibrin plate lysed. Six animals per treatment group were sacrificed by pentobarbital overdose, and hydroxyproline (collagen) content in the lower lobe of the right lung was determined by the spectrophotometric method of Stegemann and Stalder (21), following delipidation of the lung tissue (22). Data were expressed as milligrams of hydroxyproline (HP) per right lower lung (RLL).

All samples were number-coded, and were processed by personnel unfamiliar with the code. The significance of treatment regimen on the several endpoints was determined by analysis of variance (23), and the differences between group means were subjected to the Sheffe analysis. Statistical significance was accepted at $P < 0.05$.

**Results.** *Body and organ weight.* Animals receiving either CL242817 or monocrotaline failed to gain weight at the normal rate, and after 6 weeks were significantly ($P < 0.05$) smaller than controls (Table I). When given in combination, the two drugs produced a subadditive retardation of weight gain. Expressed as a fraction of body weight, none of the treatments produced significant changes in liver, kidney, adrenal, or spleen weight (Table I).

*Cardiac changes.* Compared to controls, animals receiving CL242817 alone exhibited a significant ($P < 0.05$) reduction in heart

TABLE I. BODY AND ORGAN WEIGHTS IN MONOCROTALINE-TREATED RATS: EFFECT OF THE ACE INHIBITOR CL242817

| Endpoint | Control | CL242817 (CL) | Monocrotaline (Mon) | Mon + CL |
|---|---|---|---|---|
| Body weight (g) | 506 ± 12 | 434 ± 14* | 428 ± 18* | 384 ± 6* |
| Heart weight (g) | 1.67 ± 0.05 | 1.20 ± 0.04* | 1.82 ± 0.10 | 1.28 ± 0.04* |
| Heart weight (mg/100 g body wt) | 334 ± 6 | 278 ± 6* | 417 ± 15* | 336 ± 9 |
| Right ventricle (mg) | 204 ± 7 | 190 ± 9 | 313 ± 24* | 182 ± 12 |
| Right ventricle (mg/100 g body wt) | 41 ± 1 | 46 ± 3 | 73 ± 6* | 49 ± 3 |
| Left ventricle + septum (mg) | 827 ± 22 | 640 ± 27* | 620 ± 28* | 525 ± 18* |
| Left ventricle + septum (mg/100 g body wt) | 166 ± 5 | 148 ± 5 | 147 ± 5 | 140 ± 4* |
| Right ventricle/left ventricle + septum | 0.25 ± 0.01 | 0.30 ± 0.02 | 0.52 ± 0.05* | 0.35 ± 0.02* |
| Liver (g) | 21.9 ± 0.8 | 18.3 ± 0.7 | 18.4 ± 1.0 | 16.0 ± 0.5* |
| Liver (g/100 g body wt) | 4.25 ± 0.09 | 4.14 ± 0.09 | 4.28 ± 0.15 | 4.23 ± 0.08 |
| Left kidney (g) | 1.95 ± 0.08 | 1.86 ± 0.05 | 1.60 ± 0.07* | 1.56 ± 0.06* |
| Kidney (mg/100 g body wt) | 3.86 ± 0.24 | 4.22 ± 0.10 | 3.72 ± 0.14 | 4.14 ± 0.13 |
| Left adrenal (mg) | 67 ± 6 | 71 ± 6 | 73 ± 8 | 63 ± 6 |
| Adrenal (mg/100 g body wt) | 14.3 ± 1.0 | 17.6 ± 1.3 | 17.5 ± 2.0 | 17.6 ± 1.8 |
| Spleen (mg) | 898 ± 31 | 884 ± 26 | 948 ± 43 | 808 ± 30 |
| Spleen (mg/100 g body wt) | 1.78 ± 0.07 | 2.07 ± 0.06 | 2.19 ± 0.09 | 2.15 ± 0.07 |

*Note.* Rats were sacrificed after 6 weeks of treatment. Data are means ± SEM; $N = 6$.
* Different from control, $P < 0.05$.

weight relative to body weight (Fig. 1). In contrast, monocrotaline-treated animals developed a signifcant ($P < 0.05$) cardiomegaly, a response which was completely prevented by concomitant CL242817 administration. CL242817 alone had no effect on the weight ratio of the right heart ventricle (RV) to the left ventricle plus septum (LV + S). Monocrotaline produced a significant right heart enlargement, with an RV/LV + S more than twice that of control animals. In animals receiving both monocrotaline and CL242817, the right heart enlargement was significantly ameliorated (Fig. 2).

*Pulmonary arterial occlusion.* Severely occluded pulmonary arteries were rare in control rats, and in those receiving CL242817 alone. In contrast, almost 20% of the arteries from monocrotaline-treated lungs were severely occluded (Fig. 3). Concomitant administration of CL242817 significantly ($P < 0.05$) ameliorated this vasocclusive effect of monocrotaline (Fig. 3). An example of a normal and a severely occluded pulmonary artery can be seen in Fig. 4.

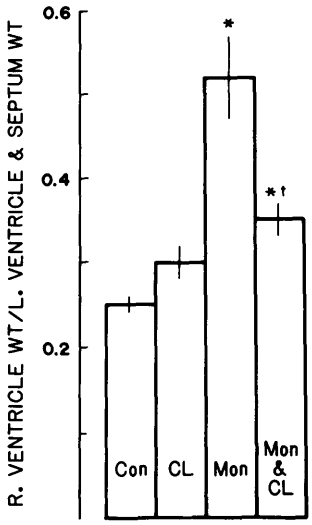


FIG. 2. Cardiac right ventricle weight divided by left ventricle plus septum weight as a function of treatment group. See legend to Fig. 1 for group identification. Mean ± SEM; $N = 6$. * = different from control, $P < 0.05$; † = different from monocrotaline, $P < 0.05$.

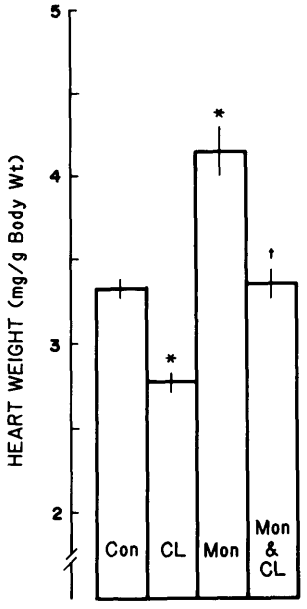


FIG. 1. Heart weight (mg/g Body Wt) as a function of treatment group: control (Con); CL242817, (CL), 60 mg/kg/day, po; monocrotaline (Mon), 2.4 mg/kg/day, po; monocrotaline plus CL242817 (Mon + CL), as above. Mean ± SEM; $N = 6$. * = different from control, $P < 0.05$; † = different from monocrotaline, $P < 0.05$.

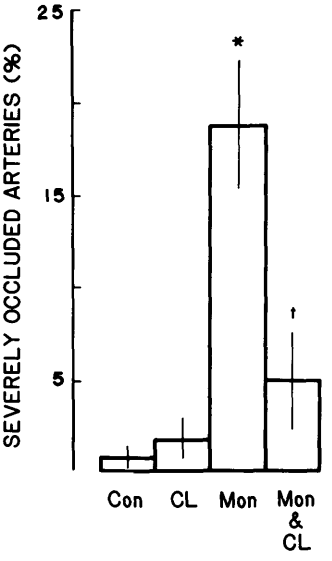


FIG. 3. Percentage severely occluded pulmonary arteries as a function of treatment group (see legend to Fig. 1 for group identification). An artery was defined as severely occluded when its mean wall thickness was more than 80% of the outer radius of the vessel. Mean ± SEM; $N = 6$. * = different from control, $P < 0.05$; † = different from monocrotaline, $P < 0.05$.

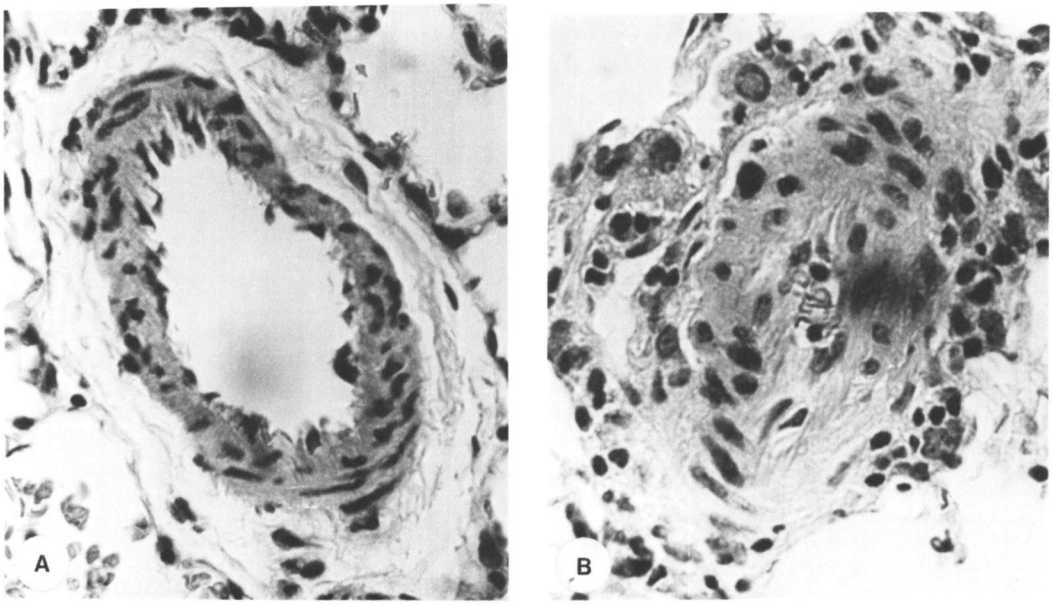


FIG. 4. An example of a normal (A) and a severely occluded (B) pulmonary artery.

| Group | Mean wall thickness ($\mu$m) | Outer diameter ($\mu$m) | Percentage occluded |
|---|---|---|---|
| (A) Control | 15 | 77 | 39 |
| (B) Monocrotaline | 31 | 76 | 83 |

*Pulmonary structure.* The gross anatomy and light microscopy of control and CL242817-treated rat lungs were similar. The lungs of animals receiving monocrotaline, however, exhibited gross congestion, petechial hemorrhages, and pleural exudates. Light microscopic evaluation of monocrotaline-treated lungs revealed hemorrhagic and inflammatory reactions, interstitial hypercellularity and fibrosis, and medial thickening of pulmonary arteries and arterioles. The severity of these monocrotaline reactions was reduced by concomitant CL242817 administration.

At the ultrastructural level, no significant changes from control were noted in the lungs of rats receiving CL242817 alone. Pulmonary changes in monocrotaline-treated animals included endothelial edema, blebbing and fragmentation, increased numbers of interstitial mast cells, plasma cells, fibroblasts, macrophages, and polymorphonuclear leukocytes, as well as interstitial collagen accumulation (Fig. 5). Monocrotaline-treated lungs also exhibited degenerative changes in Type I epithelial cells. Degenerating Type I pneumocytes were swollen and electron-lucent, and contained disorganized and abnormal organelles (Fig. 6). In animals receiving monocrotaline, Type II pneumocytes contained large, bizarre, fused lamellar inclusions. Analysis of 120 electron micrographs by three observers unfamiliar with the treatment history of the animal demonstrated that concomitant administration of CL242817 ameliorated this monocrotaline damage. Of 11 micrographs judged by all three observers to have moderate–severe interstitial fibrosis, 10 were from animals receiving monocrotaline alone, and only 1 from the combined drug group. Every instance of epithelial degeneration came from rats receiving monocrotaline alone. The lungs of animals receiving both drugs had the highest incidence of interstitial edema, however.

*Pulmonary ACE and PLA activity.* Lung

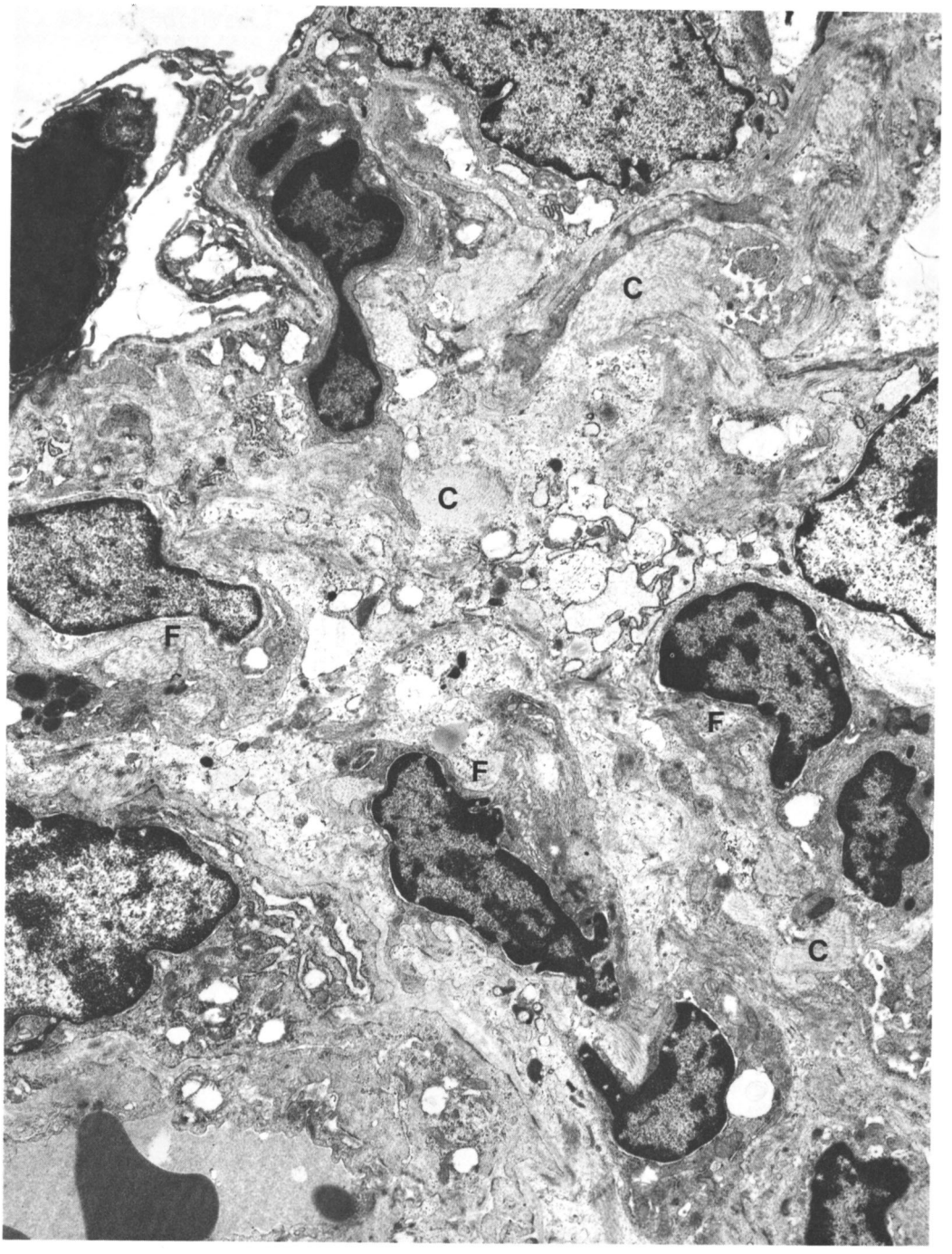


FIG. 5. Interstitial fibrosis in monocrotaline-treated rat lung. Note interstitial collagen accumulation (C) and fibroblasts (F). Interstitial hypercellularity and fibrosis was more extensive in rats receiving monocrotaline alone than in those receiving concomitant CL242817. ×6100

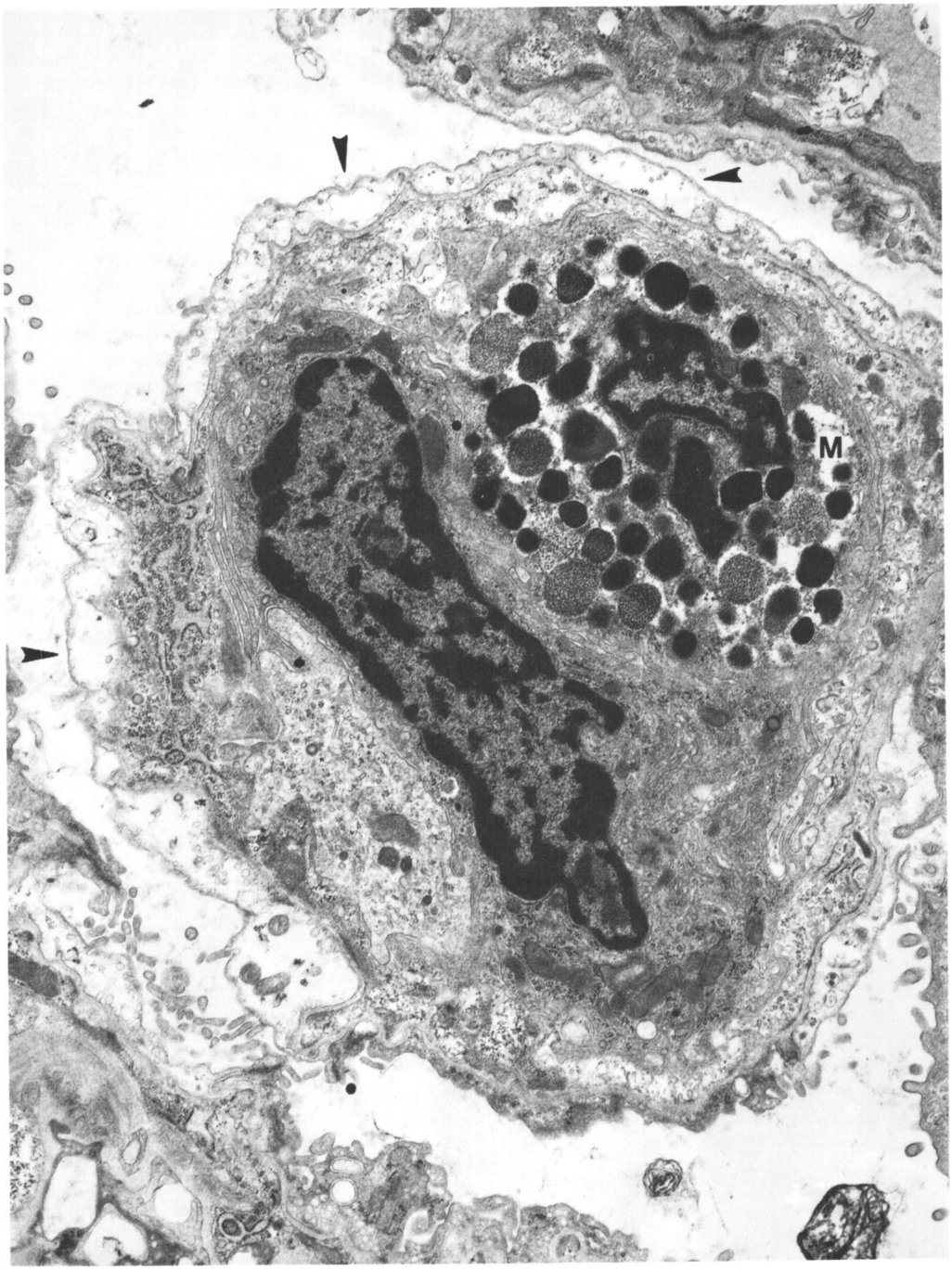


FIG. 6. Degeneration of Type I pneumocytes (arrows) in the epithelium of monocrotaline-treated rat lung. Degenerating Type I cells were swollen and electronlucent, with abnormal and disorganized organelles. This response was observed only in rats receiving monocrotaline alone, and not in animals receiving both drugs. Note interstitial mast cell (M). ×11,460.

TABLE II. LUNG FUNCTION IN MONOCROTALINE-TREATED RATS: EFFECT OF THE ACE INHIBITOR CL242817

| Endpoint | Control | CL242817 (CL) | Monocrotaline (Mon) | Mon + CL |
|---|---|---|---|---|
| Lung protein (mg/g wet) | 142 ± 12 | 139 ± 11 | 134 ± 14 | 129 ± 5 |
| Lung ACE (U/g protein) | 30.4 ± 2.6 | 17.8 ± 2.5* | 13.5 ± 1.4* | 12.0 ± 2.2* |
| Lung ACE (U/g wet) | 4.16 ± 0.25 | 2.37 ± 0.32* | 1.70 ± 0.13* | 1.52 ± 0.29* |
| Serum protein (mg/ml) | 94.4 ± 7.1 | 87.7 ± 3.4 | 87.1 ± 6.9 | 75.7 ± 4.3 |
| Serum ACE (mU/ml) | 70.2 ± 3.7 | 88.6 ± 3.4* | 57.4 ± 7.0 | 88.5 ± 5.1* |
| Serum ACE (mU/mg protein) | 0.74 ± 0.04 | 1.02 ± 0.05* | 0.72 ± 0.10 | 1.19 ± 0.07* |
| Plasma AII[c] (ng/ml) | 1.04 ± 0.06 | 3.86 ± 0.47* | 1.00 ± 0.07 | 3.77 ± 0.48* |
| Lung PLA ($mm^2$ lysed) | 87 ± 4 | 96 ± 6 | 73 ± 3* | 82 ± 4 |

*Note.* Rats were sacrificed after 6 weeks of treatment. Lung and serum angiotensin converting enzyme (ACE) activity was measured by the method of Cushman and Cheung (19) and expressed on the basis of lung protein or wet weight. Plasma angiotensin II (AII) was measured by radioimmunoassay. Data are means ± SEM; $N = 6$.

* Different from control, $P < 0.05$.

ACE activity was significantly inhibited by both CL242817 and monocrotaline, alone or in combination, whether enzyme activity was expressed on the basis of wet weight or protein concentration (Table II). The latter was not influenced by significant changes in lung protein concentration in any of the treatment groups (Table II).

PLA activity in the lung was slightly but not significantly increased in animals receiving CL242817 alone. In contrast, monocrotaline significantly decreased lung PLA activity, and this effect was slightly but not significantly ($P < 0.10$) reversed by concomitant CL242817 administration (Table II). PLA activity in the lungs of animals receiving combined drugs, however, was not significantly lower than the control level (Table II).

*Serum ACE activity and plasma AII concentration.* CL242817, either alone or in combination with monocrotaline, produced a significant increase in serum ACE activity and plasma AII concentration (Table II). Monocrotaline alone had no effect on either endpoint.

*Pulmonary hydroxyproline content.* CL242817 alone significantly reduced the hydroxyproline (HP) content of the lung, whereas monocrotaline alone increased HP content significantly (Fig. 7). Lung collagen content in animals receiving monocrotaline plus CL242817 was significantly ($P < 0.05$) lower than that of animals receiving monocrotaline alone, and, in fact, was not significantly increased over the control value (Fig. 7).

**Discussion.** These data confirm that monocrotaline induces pulmonary arterial wall thickening, cardiomegaly, and right heart enlargement, changes associated with pulmonary hypertension (13, 14). More importantly, the ACE inhibitor CL242817 significantly ameliorates all of these anatomic manifestations of monocrotaline-induced pulmonary injury.

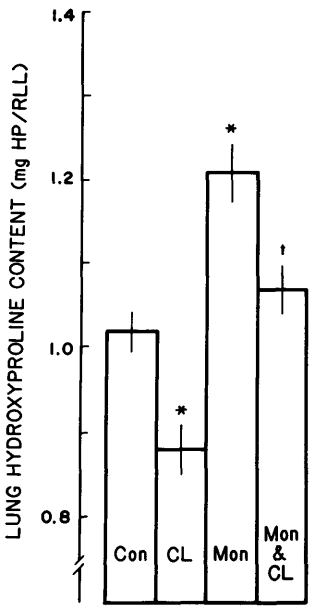


FIG. 7. Hydroxyproline (HP) content of the right lower lobe of the lung (RLL) as a function of treatment group. See legend to Fig. 1 for group identification. Mean ± SEM; $N = 6$. * = different from control, $P < 0.05$; † = different from monocrotaline, $P < 0.05$.

Captopril (SQ14225) has a similar protective effect in this model of lung damage (14). Monocrotaline injury in the lung is accompanied by well-documented vascular damage, including endothelial degeneration and muscularization of vessel walls (2–8, 13). Epithelial changes in monocrotaline-treated lung are less frequently described in the literature, and include abnormal lamellar inclusions and hyperplasia of Type II pneumocytes (3), as well as hypertrophy and cytoplasmic hydration of Type I pneumocytes (4). The present study confirms both the vascular (Fig. 4) and epithelial (Fig. 6) effects of monocrotaline in rat lung, and quantitates the former (Fig. 3). Interestingly, lung epithelial damage is observed only in rats receiving monocrotaline alone, not in animals given monocrotaline plus CL242817. While the present ultrastructural study is descriptive rather than quantitative, this observation suggests that CL242817 may ameliorate monocrotaline injury in both the epithelial and endothelial cells of rat lung. Interstitial fibrosis is perhaps the most prominent pulmonary reaction after 6 weeks of continuous monocrotaline administration. Evaluation of 120 number-coded electron micrographs by three investigators indicated that lung fibrosis is less striking in monocrotaline-treated rats receiving concomitant CL242817 than in those receiving monocrotaline alone. This ultrastructural impression is confirmed by biochemical data demonstrating a significant reduction in hydroxyproline (collagen) content in the lungs of rats receiving both monocrotaline and CL242817 compared to those given monocrotaline alone (Fig. 7). These data support the potentially important hypothesis, presently under study in this laboratory (14), that ACE inhibitors have antifibrotic activity in some models of lung injury.

The present data also confirm that monocrotaline-treated rats exhibit reduced lung ACE and PLA activities, indicative of pulmonary endothelial dysfunction (13). Chesney *et al.* (24) have suggested that monocrotaline-induced pulmonary hypertension is caused by capillary endothelial damage leading to obstructive thrombosis and fibrin deposition. While our pulmonary ultrastructural study failed to detect platelet aggregates or intravascular fibrin strands in any of the treatment groups, the present data demonstrating suppressed PLA activity after monocrotaline administration are consistent with a state of defective fibrinolytic capacity in the drug-treated lungs. Decreased ACE and PLA activity are not unique pulmonary responses to monocrotaline, since similar effects can be induced by ionizing radiation (25, 26).

Neither the pathogenesis of monocrotaline injury in the lung nor the mechanism by which ACE inhibitors ameliorate that damage are understood at this time. Pulmonary hypertension induced by both monocrotaline (13, 14) and chronic hypoxia (15) are preceded by transient increases in lung ACE activity. Thus the ability of ACE inhibitors to reduce lung damage produced by these two insults (14–17) may stem from the inhibition of this initial response. Alternatively, if monocrotaline-induced pulmonary hypertension is secondary to occlusive arterial medial thickening, it is clear that both CL242817 (Fig. 3) and captopril (14) significantly suppress this hypertrophy in monocrotaline-treated rat lung. Vascular occlusion of the magnitude analyzed in the present study (Figs. 3, 4) presumably restricts blood flow and/or contributes to pulmonary hypertension. McKenzie *et al.* (27) have reported that the ACE inhibitor teprotide (SQ20881) also reduces protein synthesis in pulmonary arteries of rats during the development of chronic hypoxia-induced pulmonary hypertension. While CL242817 was able to ameliorate the severely occlusive structural responses of the pulmonary vasculature to monocrotaline injury (Fig. 3), it had no significant effect on the functional responses of the endothelium to that alkaloid, at least as monitored by ACE and PLA activities.

It seems curious that CL242817, effective against both pulmonary (Figs. 1, 2) and systemic (18) hypertension, should elevate serum ACE activity and plasma AII concentration (Table II). The hypotensive agent captopril also elevates serum ACE and plasma renin activity (14). These blood changes, observed consistently in our animals receiving ACE inhibitors, are difficult to reconcile with the report that CL242817 inhibits serum ACE activity 1 hr after intravenous injection (18). The fact that monocrotaline reduced lung ACE without changing serum ACE activity, while CL242817 (Table II) and captopril (14) lower lung ACE and increase serum ACE activity,

demonstrates that the circulating level of the enzyme is not a reliable index of lung status in this model.

In addition to ameliorating monocrotaline-induced pulmonary injury, CL242817 (60 mg/kg/day, po) produces several side effects including retarded weight gain, reduced heart weight relative to body weight, decreased lung ACE activity, increased serum ACE and plasma AII concentration, and decreased lung hydroxyproline content. Captopril (60 mg/kg/day, po) induces a simlar spectrum of effects (14). The mechanism and biological significance of these changes should be pursued in animals receiving CL242817 for prolonged periods of time. In conclusion, CL242817, an orally active competitive inhibitor of ACE, resembles captopril (SQ14225) both in its ability to ameliorate monocrotaline-induced pulmonary injury in rats, and in many of its side effects.

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