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EVALUATION OF (1-SARCOSINE,
8-ISOLEUCINE) ANGIOTENSIN II AS A
THERAPEUTIC AGENT FOR OLEIC
ACID-INDUCED PULMONARY EDEMA

TETSUO YUKIOKA, M.D.,
NORIKO YUKIOKA, M.D.,
L. HOWARD AULICK, Ph.D.,
CLEON W. GOODWIN, M.D.,
ARTHUR D. MASON, JR., M.D.,
TSUYOSHI SUGIMOTO, M.D.,

and

BASIL A. PRUITT, JR., M.D.,
Fort Sam Houston, Texas, and Osaka, Japan

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Evaluation of (1-sarcosine, 8-isoleucine) angiotensin II as a therapeutic agent for oleic acid-induced pulmonary edema

Tetsuo Yukioka, M.D., Noriko Yukioka, M.D., L. Howard Aulick, Ph.D., Cleon W. Goodwin, M.D., Arthur D. Mason, Jr., M.D., Tsuyoshi Sugimoto, M.D., and Basil A. Pruitt, Jr., M.D., Fort Sam Houston, Texas, and Osaka, Japan

(1-Sarcosine, 8-isoleucine) angiotensin II was assessed as a therapeutic agent for acute respiratory distress syndrome with oleic acid pulmonary edema in sheep used as an experimental model. Under general anesthesia with controlled mechanical ventilation with 100% oxygen, 32 sheep received oleic acid (0.075 ml/kg) intravenously. After oleic acid infusion, 20 animals were treated with continuous intravenous infusion of the angiotensin II analogue; nine received 300 ng/kg/min, six received 600 ng/kg/min, and five received 2000 ng/kg/min. Cardiopulmonary measurements were repeated every 30 minutes for 270 minutes. According to time-integrated PaO_2 , six of 15 animals of the groups given 300 and 600 ng/kg/min (43%) did not respond to the treatment. All animals responded in the group given 2000 ng/kg/min. Animals in the latter group had lower $\dot{Q}_s/\dot{Q}_t$, PaCO_2 , and airway resistance than had the control animals. Elevation of pulmonary vascular resistance was limited and mean arterial blood pressure was well maintained. These results reveal that (1-Sar, 8-Ile) angiotensin II is effective in the treatment of oleic acid-induced pulmonary edema.

From the US Army Institute of Surgical Research, Fort Sam Houston, Texas, and the Department of Traumatology, Osaka University Hospital, Osaka, Japan

ANGIOTENSIN II (A II), AN OCTAPEPTIDE, is thought to be the most potent naturally occurring vasoconstrictor. Some of its analogues (A II As) antagonize A II pressor activity and have been developed as diagnostic agents for angiotensinogenic hypertension. Clinical trials indicate that these A II As have value in the differential diagnosis of hypertension.¹⁻³ Recent studies have shown that two kinds of A II A may be effective in the treatment of respiratory disease.

Yukioka et al.^{4,5} used (1-sarcosine, 8-isoleucine

[1-Sar, 8-Ile] A II (Fig. 1) for the treatment of acute respiratory distress syndrome (ARDS). They found that PaO_2 increased and PaCO_2 and $\dot{Q}_s/\dot{Q}_t$ decreased during continuous intravenous infusion of the drug. No changes were detected in systemic or pulmonary circulation. They speculated that the main effect of the A II A was on the airway. Mookherjee et al.⁶ have reported the effects of saralasin, (1-Sar, 8-Ala) A II, in chronic lung disease. They observed an increase of PaO_2 with no change of PaCO_2 or airway resistance and concluded that saralasin had no effect on the airway. The mechanism by which these A II As increase PaO_2 remains uncertain. The purpose of this study was to evaluate the therapeutic effectiveness of one A II A, (1-Sar, 8-Ile) A II, on a form of ARDS.

MATERIAL AND METHODS

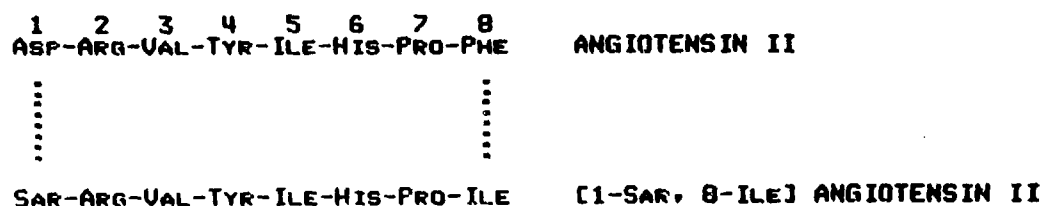
Thirty-two healthy adult male sheep (28 to 40 kg) were studied. All sheep were fasted for 24 hours before the study. They were anesthetized with intravenous pentobarbital (20 mg/kg) and intubated with a cuffed endotracheal tube. The animals were placed in the supine position and ventilated with a volume limited

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

In conducting the research described in this report, the investigators adhered to the *Guide for the Care and Use of Laboratory Animals*, as promulgated by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

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(control group, $n = 5$; 2000 group, $n = 5$). For this purpose, an esophageal balloon was inserted to obtain intrathoracic pressure.⁷ Transpulmonary pressure (pressure difference between the airway and esophageal pressure) was monitored by a differential pressure transducer (Model MP45-1, Validyne Engineering Corp., Northridge, Calif.). Respiratory gas flow was monitored by a pneumotachygraph (Model 17212, Gould Inc., Oxnard, Calif., with flow transducer, model 2, Fleish). Pressure-flow curves were obtained with a Wavetek oscillograph (Model 1901C; Wavetek Indiana, Inc., Beech Grove, Ind.). The static compliance was calculated as the ratio of the tidal volume to transpulmonary pressure when the breath was held at the end of inspiration. Pulmonary resistance was calculated as the ratio of transpulmonary pressure to the peak inspiratory flow rate. The peak flow rate was usually around 0.50 L/sec.

Two-way analysis of variance (repeated-measures design) was used to interpret the data. $P < 0.05$ was defined as statistically significant.

RESULTS

Fig. 2 presents the effect of the A II A treatment on integrated PaO_2 (I- PaO_2). All treated animals were divided into two groups, responders and nonresponders. We defined a responder as any animal whose I- PaO_2 was at least 3 SDs above the mean of the control animals (mean $\pm$ SD = $15.8 \times 10^3 \pm 3.08 \times 10^3$ torr min). Four of nine sheep in the 300 group and two of six sheep in the 600 group were identified as nonresponders. All animals in the 2000 group were responders. To determine whether responders and nonresponders could be identified before treatment, baseline cardiopulmonary variables of responders ($n = 9$) and nonresponders ($n = 6$) of the 300 and 600 groups were compared (Table I). There were no significant differences between them (Student t test).

Since the 300 and 600 group contained some nonresponders, only the data from the 2000 group was used for detailed analysis. Figs. 3 through 11 show changes of the mean and SE of each variable of the 2000 and control groups. PaO_2 decreased after oleic acid infusion in both groups (Fig. 3). While the PaO_2 of the control group remained low, that of the 2000 group increased significantly over time ($p < 0.01$). $\dot{Q}_s/\dot{Q}_t$ of the 2000 group was lower than that of the control group after oleic acid infusion (Fig. 4; $p < 0.05$). The PaCO_2 of the control group increased after oleic acid infusion and remained high during the experiment. In the 2000 group, PaCO_2 increased transiently after oleic acid infusion and then decreased toward baseline values

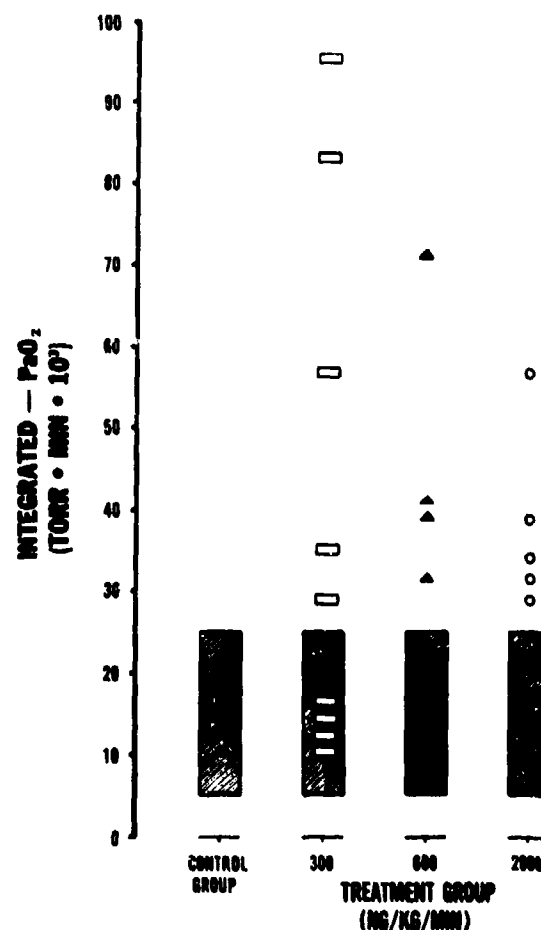


Fig. 2. The effect of (1-Sar, 8-Ile) A II on I- PaO_2 after oleic acid-induced pulmonary edema. Shaded area represents mean $\pm$ 3 SD of the control group. In the 2000 group ($\circ$) all five cases were above this range, in the 600 group ($\blacktriangle$) four out of six were above this range, and in the 300 group ($\square$) five out of nine were above the range.

(Fig. 5). After 120 minutes, PaCO_2 was significantly lower in the 2000 group ($p < 0.05$).

Changes in PVR are shown in Fig. 6. Although the mean values of PVR were not different between the two groups, the PVR of the control group increased continuously from 90 minutes after oleic acid infusion to the end of the experiment while the PVR of the 2000 group did not change in the same period. The changes of PAP were essentially the same as those of PVR. PWP was 3 to 7 mm Hg and identical in both groups.

Static compliance was not different between the two groups (Fig. 7). Pulmonary resistance increased immediately after oleic acid infusion in both groups; in the control group, pulmonary resistance increased again after a temporary decrease (Fig. 8). On the other hand, in the 2000 group it continuously decreased and pulmonary resistance of the 2000 group was signifi-

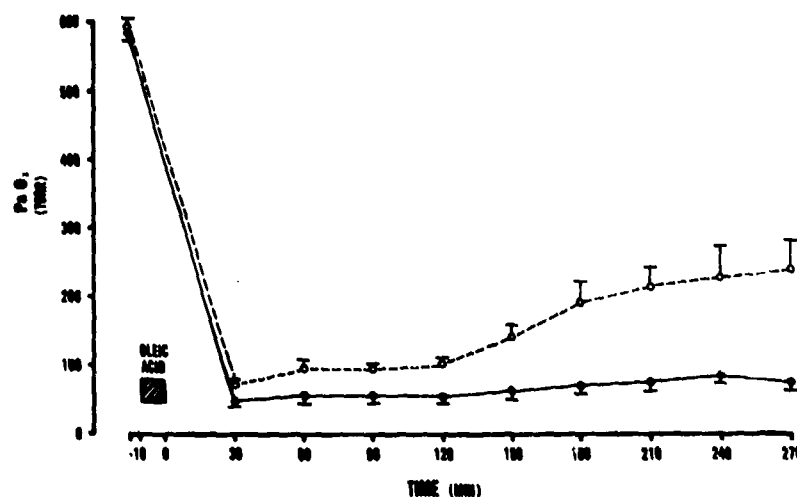


Fig. 3. The effects of (1-Sar, 8-Ile) A II (2000 ng/kg/min) on PaO_2 after oleic acid-induced pulmonary edema. Arterial blood oxygenation was significantly greater in the treated animals ($\circ$ -- $\circ$) throughout the period of observation (mean $\pm$ SE).

Table I. Baseline measurements of responders and nonresponders

	Responder (n = 9)	Nonresponder (n = 6)	Student t test	p Value
Weight (kg)	34.6 $\pm$ 1.9	37.8 $\pm$ 2.9	1.90	0.080
PaO_2 (torr)	552 $\pm$ 19.3	571 $\pm$ 9.0	0.75	0.465
PaCO_2 (torr)	29.9 $\pm$ 1.7	29.8 $\pm$ 1.2	0.11	0.918
MBP (torr)	107 $\pm$ 3.7	104 $\pm$ 3.8	0.62	0.547
CI (L/min $\cdot$ m ²)	3.06 $\pm$ 0.27	3.74 $\pm$ 0.16	1.85	0.087
TPR (dyne $\cdot$ sec/cm ⁵)	3342 $\pm$ 275	2575 $\pm$ 217	2.00	0.067
MPAP (torr)	8.1 $\pm$ 0.71	8.7 $\pm$ 0.47	0.65	0.524
PVR (dyne $\cdot$ sec/cm ⁵)	226 $\pm$ 26.1	160 $\pm$ 20.0	1.84	0.089
LVS WI (g $\cdot$ m/beat $\cdot$ m ²)	33.1 $\pm$ 1.9	37.9 $\pm$ 1.2	1.90	0.080

Legend: TPR, total peripheral resistance.

cantly lower during the last 90 minutes of the experiment ($p < 0.05$).

In the systemic circulation, hypotension and CI depression were observed in both groups after oleic acid infusion. Hypotension was limited in the 2000 group ($p < 0.01$) where MBP increased over time and returned to baseline value by the end of the experiment (Fig. 9). Although the mean values of CI did not differ between the groups, that of the 2000 group increased continuously in the latter half of the experiment while CI of controls did not change (Fig. 10). The pulse rate was 120 to 140/min in both groups. Fig. 11 shows the change of LVS WI. LVS WI was immediately depressed after oleic acid injection in both groups. However, in the 2000 group it increased over time and was significantly higher than that of the control group ($p < 0.01$).

Anatomic findings were consistent in all sheep. On gross examination the lungs were severely congested

and edematous, particularly the diaphragmatic lobes. The severity of congestion was identical in the control and treatment groups. Light microscopic examination revealed that there was massive pulmonary edema and congestion in the lung tissue. Alveoli were filled with pink proteinaceous material and parts of the terminal and respiratory bronchioles were flooded with the same material. There was minimal to moderate infiltration of inflammatory cells with a mixture of polymorphonuclear leukocytes and lymphocytes. The most consistent findings at electron microscopy were edematous changes in the type 1 pneumocyte and increased pinocytotic vesicles in the endothelium.

DISCUSSION

In the present study we produced severe, histologically confirmed pulmonary edema that was associated with significant deterioration of pulmonary function and systemic hypotension. Continuous intravenous

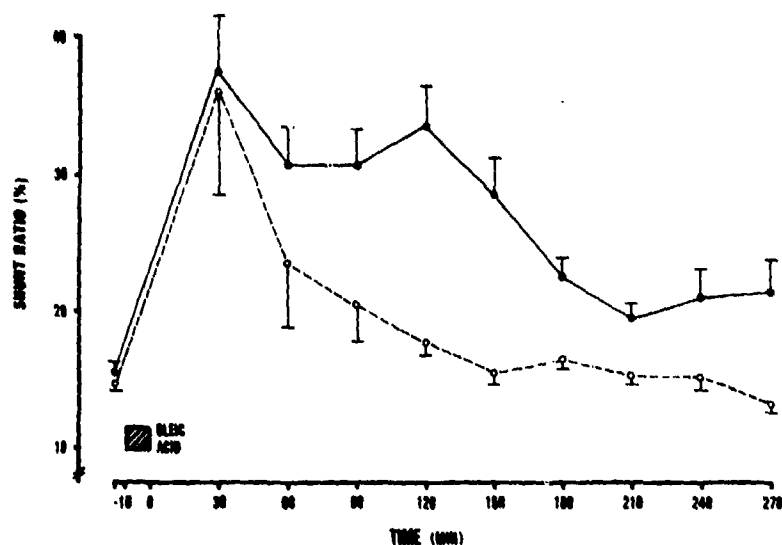


Fig. 4. The effect of (1-Sar, 8-Ile) A II (2000 ng/kg/min) on the shunt ratio after oleic acid-induced pulmonary edema. The mean shunt ratio of the treated animals (○--○) was lower than that of controls (●--●).

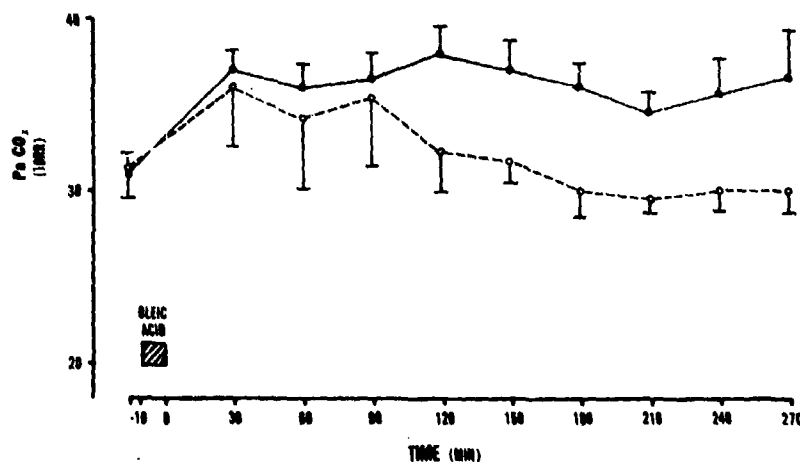


Fig. 5. The effects of (1-Sar, 8-Ile) A II (2000 ng/kg/min) on PaCO_2 after oleic acid-induced pulmonary edema. PaCO_2 of the treated animals (○--○) was lower than controls (●--●) from 120 to 270 minutes after oleic acid infusion (mean $\pm$ SE).

infusion of (1-Sar, 8-Ile) A II improved respiratory function and limited the duration of systemic hypotension after oleic acid infusion.

Oxygen toxicity must be considered in any experiment using 100% oxygen. In preliminary studies with the same respiratory management but without either oleic acid or A II A, no deterioration of respiratory function could be detected up to 7 hours. Since the animals were exposed to 100% oxygen less than 7 hours in the present study, the effect of oxygen toxicity on the measured variables is assumed to be minimal.

Characteristic differences of pulmonary function in the treated animals included higher PaO_2 , lower $\dot{Q}_s/\dot{Q}_t$, lower PaCO_2 , and lower pulmonary resistance.

Since $\dot{Q}_s/\dot{Q}_t$ represents true intrapulmonary shunt under 100% oxygen, A II A appears to ameliorate true intrapulmonary shunt after oleic acid administration. Since minute ventilation did not change throughout the experiment, the decreased PaCO_2 in the treated animals suggests increased effective alveolar ventilation.

To analyze the effect of this drug on pulmonary function, it is necessary to consider not only ventilatory status but also circulatory changes. If the drug redistributes some shunt flow to alveoli previously ventilated but without blood flow, the lower $\dot{Q}_s/\dot{Q}_t$ and PaCO_2 and higher PaO_2 could be the result of alteration of circulatory status. No drug effect on pulmonary circulation was clearly identified in the present study, but

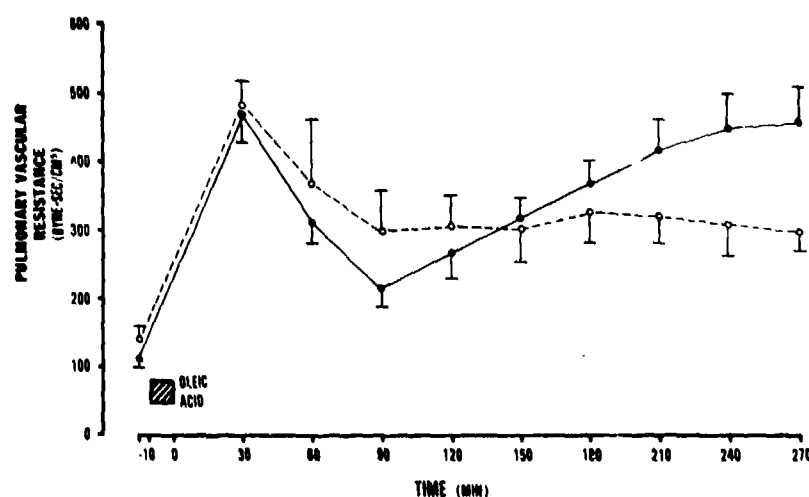


Fig. 6. The effect of (1-Sar, 8-Ile) A II (2000 ng/kg/min) on PVR after oleic acid-induced pulmonary edema. PVR of the control animals (●-●-●) increased continuously 90 minutes after oleic acid infusion. PVR of the treated animals did not change.

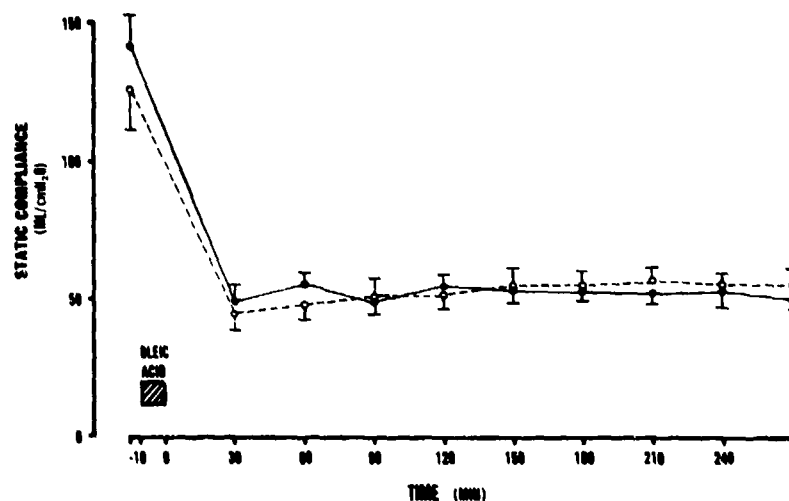


Fig. 7. The effect of (1-Sar, 8-Ile) A II (2000 ng/kg/min) on static compliance. The static compliance was identical in the two groups (○-○-○, treated animals; ●-●-● controls) (mean $\pm$ SE).

since the PVR of the treated animals did not increase in the latter half of the experiment, some drug effect should not be ruled out (Fig. 6). We do not have data concerning intrapulmonary blood distribution and further study is necessary for more detailed analysis of an effect on pulmonary circulation.

The pulmonary resistance of the treated animals was lower than that of the control group during the later stages of the experiment despite the fact that both groups had identical static compliance (Figs. 7 and 8). Pulmonary resistance is the sum of airway resistance and tissue resistance.⁸ Since compliance has a close relationship with tissue resistance,⁹ both groups should have identical tissue resistance. If this is so, the lower

pulmonary resistance of the treated animals can best be explained by lower airway resistance. These results suggest a drug effect on ventilatory status and are compatible with higher PaO_2 , lower $\dot{Q}_s/\dot{Q}_t$, and lower PaCO_2 .

Airway resistance is related to the tone of bronchial smooth muscle as well as edema of bronchial tissue and mucosal congestion. Since histologic examination revealed an equal severity of lung injury in all sheep, the lower airway resistance of the treated animals may result from a decrease in smooth muscle tone. Thus the relationship between A II and bronchial smooth muscle is important in analyzing the effect of A II A on respiratory function. Türker and Ercan¹⁰ have reported

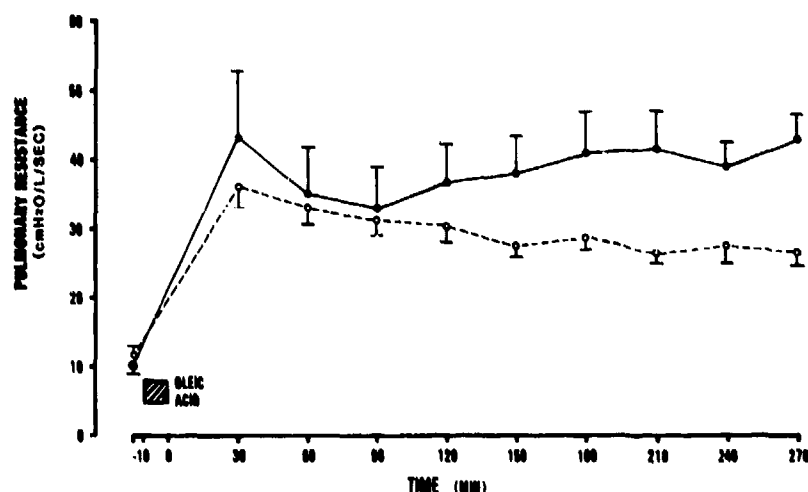


Fig. 8. The effect of (1-Sar, 8-Ile) A II (2000 ng/kg/min) on pulmonary resistance after oleic acid-induced pulmonary edema. Pulmonary resistance of the treated animals (○ - - ○) was lower than controls (● - - ●) from 180 to 270 minutes after oleic acid infusion (mean $\pm$ SE).

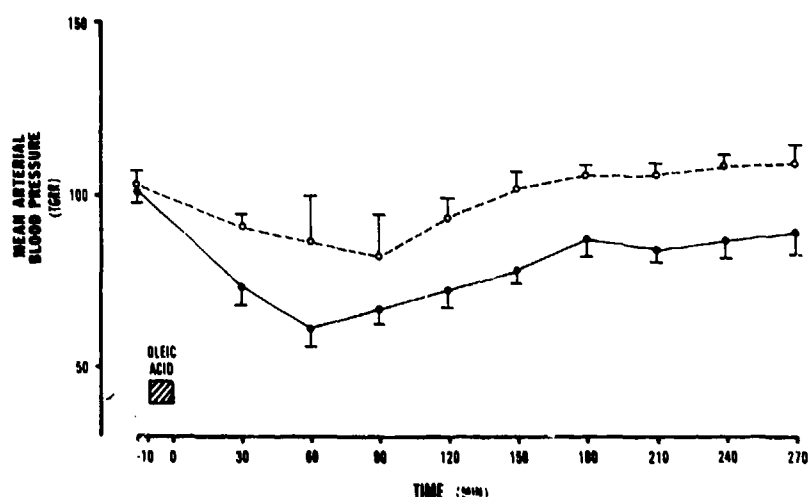


Fig. 9. The effect of (1-Sar, 8-Ile) A II (2000 ng/kg/min) on MBP after oleic acid-induced pulmonary edema. MBP of the treated animals (○ - - ○) was higher than that of the controls (● - - ●) throughout the observation period.

that A II relaxed bronchial smooth muscle in the cat and that the action of A II was blocked by aspirin. Conversely, Lung and Souhrada¹¹ reported that A II constricted bronchial smooth muscle of both the guinea pig and the rat. Such constriction was blocked by (1-Sar, 8-Ala) A II (saralasin) but not by aspirin. It thus appears that the effect of A II on bronchial smooth muscle varies according to species. In our study, however, the changes in PaCO₂ and airway resistance strongly suggest that (1-Sar, 8-Ile) A II causes airway dilatation.

In the 300 and 600 groups, according to our criterion of I-PaO₂, six of 15 animals (40%) did not respond to

the drug (Fig. 2). These are the usual dosages employed in clinical studies.^{12, 13} Since we could not detect any difference in the baseline data between responders and nonresponders (Table I), it was impossible to predict which subjects would respond to the A II A.

We cannot explain why some animals responded and others did not, but altered drug metabolism could be responsible for part of the interanimal variation. Angiotensinase inactivates not only A II but also A II As.¹⁴ This enzyme is ordinarily found in lung tissue, especially in the lysosomal fraction.¹⁵ Although A II is not metabolized in the pulmonary circulation under

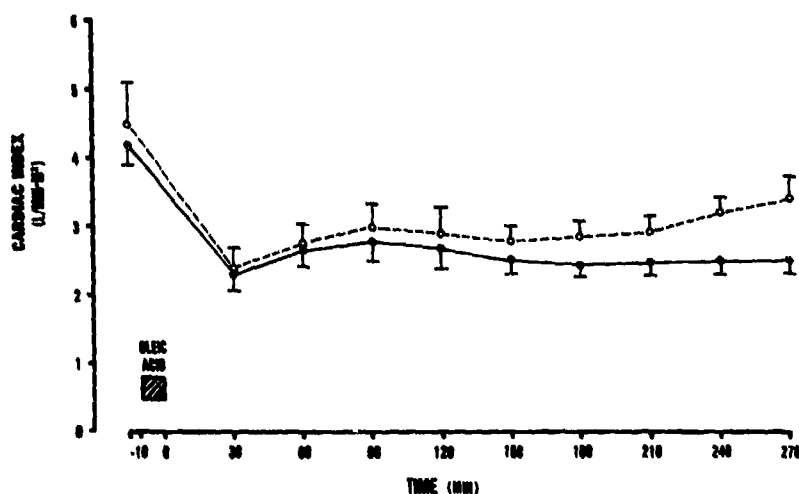


Fig. 10. The effect of (1-Sar, 8-Ile) A II (2000 ng/kg/min) on CI after oleic acid-induced pulmonary edema. CI of the treated animals (○-○) increased in the latter 2 hours of the experiment, while that of the controls (●-●) did not change.

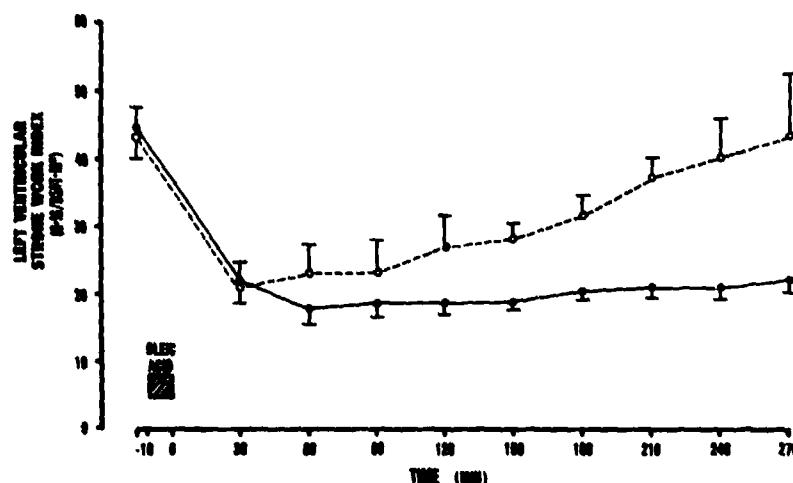


Fig. 11. The effect of (1-Sar, 8-Ile) A II (2000 ng/kg/min) on left ventricular stroke work index. LVSWI of the treated animals (○-○) was greater than controls (●-●) throughout the observation period.

normal conditions, when the lung becomes edematous A II is inactivated while passing through the lung.¹⁶ Since oleic acid pulmonary edema is a typical permeability type edema,¹⁷ (1-Sar, 8-Ile) A II may also be degraded in the pulmonary circulation and its concentration maintained at levels too low to be effective. This speculation is consistent with the observed dose response.

In the systemic circulation, hypotension was limited in the treated animals despite an initial decrease in CI comparable to that of the untreated animals. This suggests greater vasoconstriction in the treatment group at this stage of the experiment (Figs. 9 and 10). (1-Sar, 8-Ile) A II not only acts to antagonize the A II

pressor effect but can also act agonistically to increase blood pressure.¹⁸ Administration of A II A has also been reported to release catecholamines,¹⁹ and this action of the drug might be responsible for limitation of hypotension in the treatment group.

In the latter half of the experiment, the increased CI of the treated animals played some part in increasing blood pressure. This improvement of the CI was associated with increased cardiac performance as measured by a significant increase of LVSWI (Fig. 10). Some factors in the treatment group, such as improvement of blood oxygenation and limited elevation of PVR, which limits the increase in right-heart afterload, might indirectly improve cardiac performance

during the latter half of the experiment. The direct effect of the drug on cardiac function is uncertain. These results suggest that (1-Sar, 8-Ile) A II may have some desirable effects on the systemic circulation when used as a therapeutic agent for ARDS.

Information concerning the pulmonary effects of A II As is limited.⁴⁻⁶ The only consistent observation is an increase in PaO_2 after infusion of A II A. Yukioka et al.^{4,5} used 300 ng/kg/min of (1-Sar, 8-Ile) A II in the treatment of patients with ARDS. They found that PaO_2 increased while PaCO_2 decreased. No changes occurred in the pulmonary or systemic circulation. However, the patients in that study had relatively stable circulation with normal blood pressure. In such patients, (1-Sar, 8-Ile) A II at that dose could increase PaO_2 without pronounced effects on the circulatory system.

Mookherjee et al.⁶ used saralasin in the treatment of chronic lung disease. They reported no change of PaCO_2 or airway resistance. The differences between that study and ours include not only the differences between acute and chronic lung disease and species but also the A II A used. The pharmacologic effect of (1-Sar, 8-Ile) A II on patients with hypertension is different from that of saralasin. The depressor effect of saralasin is usually accompanied by reduction of cardiac output with or without a decrease of peripheral resistance.^{20,21} (1-Sar, 8-Ile) A II has less of a depressive effect on cardiac function and reduces blood pressure and peripheral resistance without changing cardiac output.²² In the treatment of chronic lung disease with saralasin, increase in PaO_2 correlated with decrease in cardiac output.⁶ In the present study we found no depressive effect of (1-Sar, 8-Ile) A II on cardiac function or systemic circulation. Since patients with severe ARDS may also exhibit circulatory instability, (1-Sar, 8-Ile) A II might be preferred to saralasin in the treatment of such patients.

Other drugs have been studied as therapeutic agents for ARDS. Nitroprusside decreases PVR but also decreases $\text{P}\dot{\text{V}}\text{O}_2$. Glucagon improves oxygenation but increases PVR.²³ Prostacyclin has been reported to have some useful effects in the treatment of pulmonary embolism²⁴; however, prostacyclin depresses the systemic circulation and this may limit its clinical application. Compared with these drugs, (1-Sar, 8-Ile) A II improved not only blood gas data but also the pulmonary circulation while maintaining or even improving systemic circulation. These effects suggest that this A II A may have some promise as a therapeutic agent for the clinical treatment of ARDS.

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