

Treatment of Severe Acute Respiratory Distress Syndrome

Robert M. Hardaway, MD

Yvonne Vasquez, BS

Department of Surgery

Texas Tech University Health Science Center

4800 Alberta Avenue

El Paso TX 79905 USA

Abstract

Twenty patients suffering from acute respiratory distress syndrome were treated with plasminogen activator. They were treated only if they had failed to respond to respirator therapy with 100% oxygen. They responded with significant improvement in pO_2 levels. None bled or had any change in coagulation parameters.

Key words: acute respiratory distress syndrome, septic shock, disseminated intravascular coagulation, multiple organ failure

Introduction

Trauma is associated with two types of shock: hemorrhagic or hypovolemic shock and shock resulting from multiple trauma. These types of shock are separate and distinct, although they may occur together, probably in synergy. Hemorrhagic (hypovolemic) shock is characterized by blood loss (e.g., knife wound to an artery). Traumatic shock is associated with severe tissue damage. Septic shock is associated with infection, which may or may not be secondary to trauma. Primary treatment of hypovolemic shock is administration of intravenous fluids. Treatment of traumatic shock and septic shock is very unsatisfactory.

Both traumatic and septic shock often produce multiple organ failure (MOF), especially acute respiratory distress syndrome (ARDS). ARDS has a high mortality. Its only effective treatment is ventilator therapy. If this fails, mortality is probably 100%. No other treatment for ARDS, including "magic bullets," has proved effective. We postulate that ARDS may be caused by disseminated intravascular coagulation (DIC), which may obstruct the pulmonary microcirculation.¹ DIC may be initiated by the destruction of red cells, tissue cells, or bacterial cells. Cell destruction exposes the inner layer of cell membranes. This inner layer is composed of thrombogenic aminophospholipids, which do not occur on the outer layer. These aminophospholipids may initiate DIC, acting as an autotoxin. Traumatic and septic shock are often accompanied by DIC. Red cells and tissue cells may be broken by trauma, cold, heat, anoxia, viruses, or plasmodia. Bacterial cell walls may be broken by antibiotics, heat, or antibodies.

A more detailed report of this study was published in the April 2001 issue of *The American Surgeon*.²

Materials and Methods

Twenty patients suffering from ARDS secondary to trauma and/or sepsis were treated with a plasminogen activator after giving informed consent. All patients who were entered into the study had severe ARDS secondary to trauma and/or sepsis and had a decreasing PaO_2 of less than 65 mmHg after 24 hours of full treatment with oxygen, volume-cycled ventilator, and positive end-expiratory pressure (PEEP). Normal clotting mechanism as well as normal values on liver and kidney function test were required. Patients could not have a history of bleeding or trauma within 48 hours. Other exclusion criteria included age less than 18 years, kidney or liver disease, history of coagulopathy, peptic ulcer, stroke, diabetes, and head injury.

Patients were given a 10-minute intravenous infusion of urokinase, 1000 units/lb of body weight, followed by 1000 units/lb/hr for 24 hours. In the event of relapse, urokinase infusion was repeated. Blood samples were obtained every 4 hours to measure fibrin split products, prothrombin time, partial thromboplastin time, platelet count, fibrinogen level, fibrinolysis, and clotting time. The following parameters were measured every 2 hours: arterial and venous pH, PCO_2 , PO_2 , urine output, fluid intake, arterial pressure, and central venous pressure. Treatment was discontinued if any clotting abnormality occurred.

Table 1. PaO_2 Values Before and After Plasminogen Activator (PA)*

Case	Before PA Therapy†	After PA Therapy
1	61	80
2	52	51
3	62	282
4	65	500
5	52	180
6	47	381
7	33	256
8	46	376
9	39	52
10	35	206
11	65	318
12	43	54
13	44	380
14	61	360
15	63	238
16	65	419
17	40	110
18	45	90
19	39	150
20	60	110

PaO_2 showed a significant difference before and after PA therapy ($P=0.0001$).

*Patients 1 through 16 received streptokinase. Patients 17 through 20 received urokinase.

† PaO_2 values after 24 hours of 100% oxygen respirator therapy but before the start of PA therapy.

From Hardaway RM, Harke H, Tyroch AH, Williams CH, Vasquez Y, Krause GF. Treatment of severe acute respiratory distress syndrome: a final report on a Phase I study. *Am Surg* 2001; 67(4):377-82.

Table 2. Coagulation and Hemodynamic Parameters

	Day after Admission to ICU		
	11	12	14
		(Treatment 1)	(Treatment 2)
Platelets (x10 ⁹ /μl)	381	483	600
Fibrogen (mg/dl)	948	501	119
Prothrombin time (sec)	15.2	14.7	17.1
Activated prothrombin time (sec)	28.4	26.8	29.1
Heart rate (bpm)	123	114	121
Cardiac output (L/min)	10.2	9.7	11.5
Pulmonary vascular resistance (dyne sec/cm ²)	141	132	111
Left ventricular stroke work index (dyne sec/cm ²)	36.8	33.3	41.1

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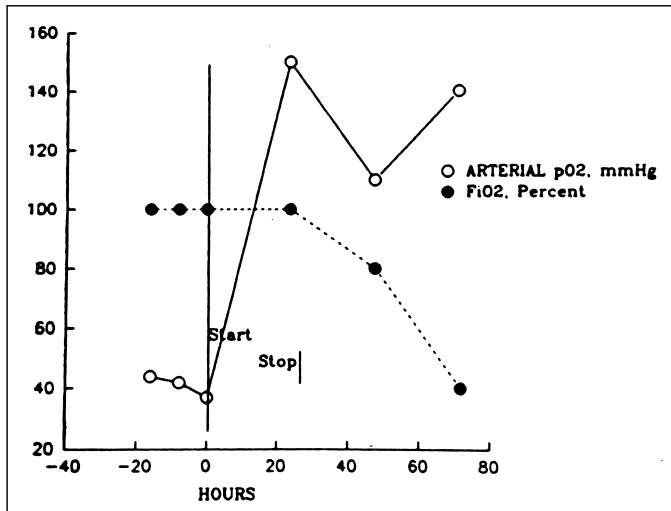


Figure 1. Arterial pO₂/FiO₂ ratio response to urokinase in case 19. Figures on abscissa represent number of hours before or after administration of urokinase. (From Hardaway RM, Harke H, Tyroch AH, et al. Treatment of severe acute respiratory distress syndrome: a final report on a Phase I study. *Am Surg* 2001; 67[4]:377-82.)

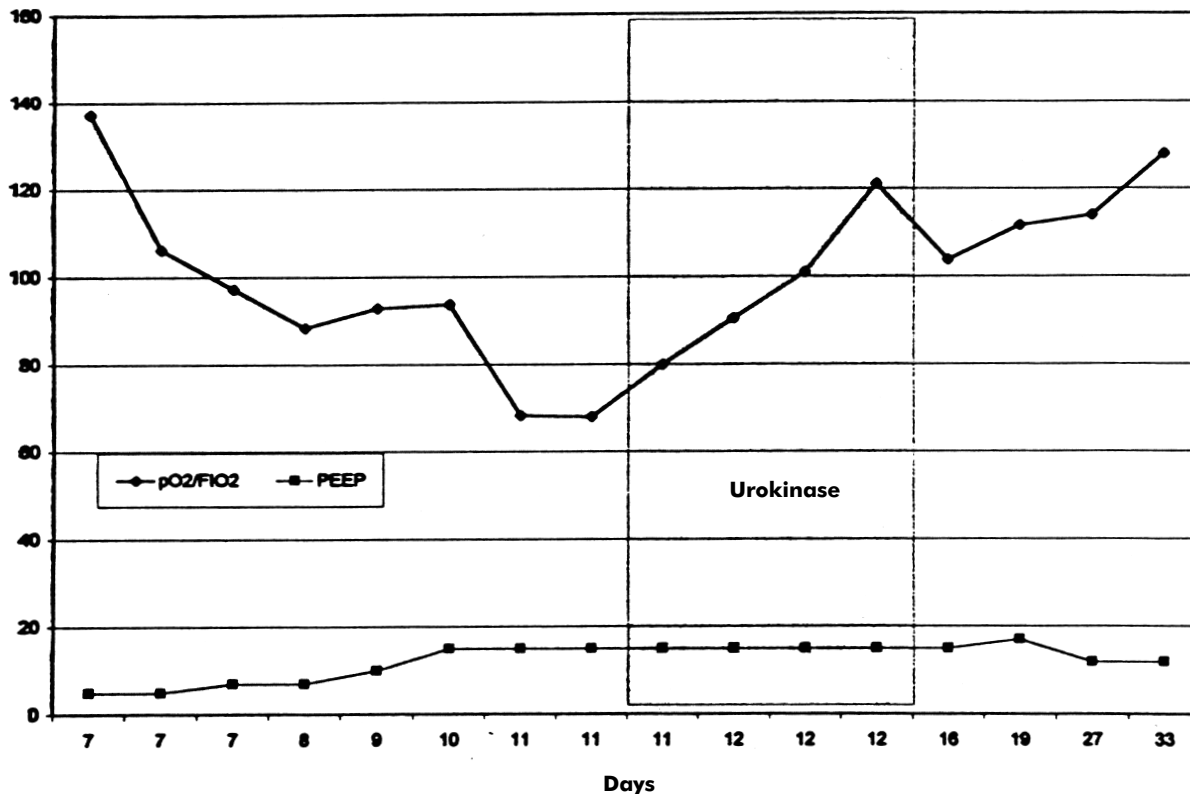


Figure 2. Arterial pO₂/FiO₂ ratio response to urokinase in case 20. Figures on abscissa represent days after original injury. (From Hardaway RM, Harke H, Tyroch AH, et al. Treatment of severe acute respiratory distress syndrome: a final report on a Phase I study. *Am Surg* 2001; 67[4]:377-82.)

Results

A total of 20 patients were enrolled in this study. Table 1 illustrates the PaO₂ levels before and after plasminogen activator (PA) therapy for each patient. Nineteen of the 20 patients showed an increase in PaO₂ value after PA therapy (Table 1). PaO₂ values showed a significant difference (P=0.0001) before and after PA therapy. No patient bled or had any abnormalities in clotting parameters.

Two patients are reported in detail: A 30-year-old woman (case 19) was admitted to the intensive care unit with aspiration pneumonia after a drug overdose and subsequent gram-positive septicemia and ARDS. Despite support with 100% oxygen, her PaO₂ dropped to 39 mmHg. Death seemed imminent. Within a few hours of urokinase therapy, PaO₂ rose to 150 mmHg. FiO₂ was then decreased progressively to 40% while PaO₂ continued to rise (Fig. 1). Her PaO₂ value remained

normal thereafter, and she recovered. No bleeding or disturbance in coagulation parameters occurred.


A 58-year-old man (case 20) was admitted to the intermediate care unit with a broken ninth and tenth left rib, a bruised left lung, and a ruptured spleen incurred during a fall. The patient was watched closely to see if bleeding from the spleen progressed. It did, and the patient had a splenectomy on the second day after injury. The patient developed severe ARDS, which was unresponsive to 100% O₂ and PEEP of 15 cm H₂O. The patient was comatose and death seemed imminent. Oxygenation continued to decline and the patient was entered in the protocol. The patient was given three treatments. After the first treatment with urokinase, his PaO₂ rose to 110 mmHg but relapsed the following day (Fig. 2). The patient remained comatose. A second treatment of streptokinase was administered. Streptokinase was used in lieu of urokinase because of shortage of the latter drug. Once again, the patient's oxygenation improved but started to deteriorate 3 days after the second treatment. A third and final treatment of streptokinase was given. Oxygenation gradually improved, and the patient woke up. Continual progress marked the patient's hospital course and he recovered fully. During all three treatments, no problems with bleeding or change in clotting parameters occurred (Table 2).

Conclusions

The major finding of this study is that the infusion of PA consistently improves PaO₂ levels without affecting clotting parameters or causing bleeding. Patients nonresponsive to respi-

rator therapy probably have a mortality of 100%. Of the 14 patients who did not survive, the majority died of either liver and/or kidney failure. Hardaway et al¹ have shown that liver and kidney damage may be prevented if fibrinolytic therapy is initiated before significant necrosis occurs. The lungs, on the other hand, are not subject to rapid necrosis as much as are the parenchymal organs. The lungs consist largely of connective tissue and endothelium, neither of which has the high metabolic activity of, for example, liver and kidney cells. In addition, oxygen is present in lung tissue. Therefore, if circulation is restored to capillaries occluded for 12 to 24 hours, lung function will resume. In contrast, obstruction of microcirculation to liver and kidney for 12 to 24 hours will probably result in cellular death in these organs, despite restoration of circulation. Survival may depend on how early the treatment is administered after the onset of DIC. The improvement of PaO₂ levels demonstrated in this study provides a new possibility in the treatment of patients with trauma- and/or sepsis-induced ARDS.

References

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The following abstract was submitted to the ITACCS Research Committee for TraumaCare 2001 in San Diego but inadvertently not included in the spring/summer issue of TraumaCare. ITACCS and TraumaCare regret the error.

The Use of Hypertonic-Saline Dextran (HSD) in a Prehospital Setting

Joel Olsson, MD, PhD,

Department of Anesthesiology, Gällivare Sjukhus, Gällivare, Sweden

Christer Svensén, MD, PhD,

Assistant Professor, Department of Anesthesiology,
University of Texas Medical Branch at Galveston, Texas, USA

Advanced Trauma Life Support guidelines¹ for the initial treatment of hemorrhage and trauma are to control hemorrhage by hemostasis and the use of crystalloid solutions. The most commonly used solution is lactated Ringer's. Internal hemorrhage can rarely be immediately stopped, as this requires in-hospital treatment, which is often surgery. Therefore, in most cases, fluid infusion is started before hemorrhage is controlled. However, if hemorrhagic shock develops, it is considered necessary to infuse fluid to increase blood volume and secure perfusion to end organs in order to downregulate the eventually life-threatening systemic inflammatory response. The timing and amount of volume are controversial, but a sufficient amount of volume needs to be infused that can provide enough venous return to produce a cardiac output that allows adequate blood flow to vital organs to preserve their function. The volume effect of existant crystalloid solutions are negligible.² The concept of trauma care is that prompt early restoration of cardiovascular function in the first hour after injury can be critical to prevent subsequent morbidity or development of irreversible shock. This has led to early aggressive fluid infusion protocols.

In recent years, there has been less emphasis on aggressive resuscitation, particularly after penetrating injury. Animal experiments mimicking uncontrolled internal hemorrhage due to aortotomy and arterial resection have shown that rapid increases in blood pressure secondary to rapid infusion can in some cases cause internal bleeding and increased mortality. The Bickell study,³ performed on trauma patients and using crystalloids, has shown higher survival rates when substantial fluid therapy was delayed until time of surgery. This study, however, was done in a scenario with very short prehospital times. Currently, there is no definitive means to guide fluid therapy.

In the prehospital setting, guidelines for fluid therapy often mimic in-hospital guidelines. Because storage capacity for fluids is limited, there has been interest in smaller volume therapy. Hypertonic saline dextran (RescueFlow®) has

been registered in Sweden since 1998 for the indication of hypotension during trauma. This solution has been tested in clinical trials for trauma patients during the past 10 years. It has shown slight benefit for trauma patients overall without statistical significance due to lack of power. In meta-analysis⁴ of these studies, two groups of trauma patients—those with head trauma and those with penetrating trauma—requiring surgery had statistically lowered mortality. There have been no side-effects in these clinical studies.

The following is a description of a clinical protocol launched as a joint effort between the Prehospital Sections of the Karolinska Hospital and Stockholm Söder Hospital, Stockholm, Sweden together with Gällivare Sjukhus, Gällivare, Sweden. The intention has been to use this solution in both urban and rural settings.

Group A

Head trauma with
Glasgow Coma Scale score <8
and/or

Severe shock
-unconscious

-carotid but no radial pulse

Treat with 250 ml HSD during five minutes

Group B

Other trauma
If prehospital time >30 min
And blood pressure <90 mmHg,
pulse >100 beats/min

Treat with 250 ml HSD during five minutes

Group C

Other trauma
If prehospital time <30 min

Treat with NO fluid

References

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