Multiple Organ Dysfunction During Resuscitation Is Not Postinjury Multiple Organ Failure

David J. Ciesla, MD; Ernest E. Moore, MD; Jeffrey L. Johnson, MD; Angela Sautaia, MD, PhD; Clay C. Cothren, MD; John B. Moore, MD; Jon M. Burch, MD

Hypothesis: Multiple organ dysfunction (MOD) within 48 hours of injury is a reversible physiologic response to tissue injury and resuscitation.


Setting: Regional academic level I trauma center.

Patients: One thousand two hundred seventy-seven consecutive trauma patients at risk for postinjury multiple organ failure (MOF). Inclusion criteria were being 16 years and older, being admitted to the trauma intensive care unit, having an Injury Severity Score higher than 15, and surviving more than 48 hours after injury. Isolated head injuries were excluded.

Interventions: None.

Main Outcome Measures: Development of postinjury MOD as defined by a Denver MOF score of 4 or higher within 48 hours of injury and MOF as defined by a Denver MOF score of 4 or higher more than 48 hours after injury.

Results: Postinjury MOD and MOF were diagnosed in 209 (16%) and 300 (23%) patients, respectively. Age, Injury Severity Score, and 12-hour blood transfusion requirements were significantly higher among patients who developed MOD and MOF. Of the 209 patients who developed MOD, 134 (64%) progressively developed MOF while 75 (36%) had MOD resolve within 48 hours.

Conclusion: Multiple organ dysfunction during resuscitation is a reversible response to severe injury and often resolves during the resuscitation period.

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POSTINJURY MULTIPLE ORGAN failure (MOF) is a leading cause of late postinjury deaths and morbidity despite more than 25 years of intensive study. The etiology is proposed to be a result of uncontrolled systemic inflammation leading to secondary organ injury and dysfunction. Clinical manifestations can range from a mild systemic inflammatory response to overt organ failure. The initial magnitude of the postinjury inflammatory response is dependent on the amount of tissue injury, the degree of shock, and the presence of host factors such as age and comorbid disease. We developed an MOF scale in 1987 as a descriptive end point for clinical studies. A slightly modified scale (the Denver MOF scale) has since been used in generating predictive models of postinjury MOF based on early physiologic responses to injury and resuscitation. Our definition of MOF did not include organ dysfunction scores obtained within 48 hours of injury because it was thought that organ dysfunction during this period reflects reversible derangements induced by the inciting event or incomplete resuscitation.

Cryer et al have recently questioned this rationale in a study of patients at high risk of developing postinjury MOF where it was concluded the MOF was established within 24 hours of injury. Recognizing differences in study design, this article prompted us to reevaluate our definitions of postinjury MOF. We undertook this study to define the relationship between multiple organ dysfunction (MOD) that occurs during resuscitation and MOF that persists beyond the resuscitation period. We hypothesized that organ dysfunction during resuscitation is not postinjury MOF.

METHODS

Trauma patients admitted to the Rocky Mountain Regional Trauma Center surgical intensive care unit at Denver Health Medical Center, Denver, Colo, were studied prospectively from 1992 until September 2003. The Denver
Health Medical Center is a state-designated level I trauma center verified by the American College of Surgeons Committee on Trauma, Chicago, Ill. Inclusion criteria were having an Injury Severity Score (ISS) higher than 15, surviving more than 48 hours after injury, being admitted to the surgical intensive care unit within 24 hours of injury, and being 16 years and older. Patients with isolated head injuries were excluded. Daily physiologic and laboratory data were collected through surgical intensive care unit day 10, and clinical events were recorded thereafter until death or hospital discharge. The data collection and storage processes were in compliance with Health Insurance Portability and Accountability Act of 1996 regulations and were approved by our institutional review board. The database was maintained on an IBM-compatible computer using Microsoft Access 97 (Microsoft Corp, Redmond, Wash).

Organ dysfunction was defined using the Denver MOF scoring system. In brief, 4 organ systems (pulmonary, hepatic, renal, and cardiac) were evaluated daily throughout the patient’s intensive care unit stay and organ dysfunction was graded on a scale from 0 to 3 (Table 1). The pulmonary score was simplified to assign a dysfunction grade based on the partial pressure of carbon dioxide–fraction of inspired carbon dioxide ratio. The values that determine the division points have been adjusted for altitude by multiplication of the value by the ratio of atmospheric pressure in Denver to that at sea level (630 mm Hg:760 mm Hg). The MOF or MOD score was calculated as the sum of the simultaneously obtained individual organ scores on each hospital day. Single organ failure was defined as an organ failure grade greater than 0, and MOF was defined as the total score of 4 or higher. Postinjury day 0 was defined as the first 24 hours following injury. An MOF score within 48 hours of injury was defined as MOD. For patients who died before postinjury day 10, the MOF score on the day of death was carried out to day 10.

Statistical analyses were performed using SAS for Windows (SAS Institute, Cary, NC). Categorical variables were compared using a χ² test with the Yates correction for continuity or the Fisher exact test when expected cell values were smaller than 5. For continuous variables with normal distribution, analysis of variance or t tests (with the appropriate modification when the assumption of equal variances did not hold) were used. Continuous variables without a normal distribution were analyzed using the Wilcoxon Two-Sample Test. P<.05 was considered significant. The predictive power of the initial organ dysfunction for subsequent MOF was evaluated by calculating its sensitivity, specificity, and predictive value.

### RESULTS

Data were collected on 1277 patients during a 10-year period ending September 2003; 921 (72%) were men, and the mean age ± SD was 37.3 ± 16.5 years. Blunt mechanisms accounted for 72% of injuries with an overall ISS of 37.3 ± 16.5. The mortality rate was 9% (110 patients). Three hundred seventy-five patients (29%) had at least 1 daily MOD score of 4 or higher. The distribution of MOD scores 4 or higher according to ISS is shown in Figure 1. Seventy-two (17%) of 430 patients with ISSs between 16 and 25 had at least 1 MOD score of 4 or higher. Characteristics of patients who developed an MOD score of 4 or higher are compared with those who did not in Table 2. Patients who developed an MOD score of 4 or higher during the study period were older, more se-

### Table 1. Postinjury Multiple Organ Failure Score

<table>
<thead>
<tr>
<th>Dysfunction</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary PaCO₂/FiO₂ ratio</td>
<td>&gt;208</td>
<td>208-165</td>
<td>165-83</td>
<td>&lt;83</td>
</tr>
<tr>
<td>Renal creatinine level, mg/dL</td>
<td>&lt;1.8</td>
<td>1.8-2.5</td>
<td>2.5-5.0</td>
<td>&gt;5.0</td>
</tr>
<tr>
<td>Hepatic total bilirubin level, mg/dL</td>
<td>&lt;2.0</td>
<td>2.0-4.0</td>
<td>4.0-8.0</td>
<td>&gt;8.0</td>
</tr>
<tr>
<td>Cardiac</td>
<td>No inotropes and cardiac index</td>
<td>Minimal inotropes or cardiac index</td>
<td>Moderate inotropes</td>
<td>High inotropes</td>
</tr>
<tr>
<td>&gt;3.0 L/min per meter squared</td>
<td>&gt;3.0 L/min per meter squared</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Characteristics of Patients With and Without Multiple Organ Failure (MOF)*

<table>
<thead>
<tr>
<th>MOF Score</th>
<th>&lt;4</th>
<th>≥4</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 902)</td>
<td>(n = 375)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>71</td>
<td>74</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>35.5 ± 15.4</td>
<td>41.8 ± 18.1†</td>
</tr>
<tr>
<td>Older than 55 y</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Blunt mechanism</td>
<td>82</td>
<td>84</td>
</tr>
<tr>
<td>Injury Severity Score, mean ± SD</td>
<td>27.2 ± 9.7</td>
<td>34.4 ± 13.2†</td>
</tr>
<tr>
<td>Injury Severity Score ≥25</td>
<td>48</td>
<td>70</td>
</tr>
<tr>
<td>12-h RBC count, mean ± SD</td>
<td>0.16 ± 0.87</td>
<td>0.68 ± 1.93†</td>
</tr>
<tr>
<td>Received &gt;0 U of blood</td>
<td>6</td>
<td>22†</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>2</td>
<td>24†</td>
</tr>
</tbody>
</table>

Abbreviation: RBC, red blood cell.

*Values expressed as percentages unless otherwise indicated. †P<.05.
Forty-eight hours postinjury is the standard time limit.

The temporal distribution of the onset and prevalence of multiple organ dysfunction and multiple organ failure (MOF) according to postinjury day is shown in Figure 2. The onset is defined as the day on which the condition resolve within 72 to 96 hours following injury. Mortality was also higher among severely injured, and received more blood in the first 12 hours following injury. Mortality was also higher among patients with an MOD score of 4 or higher.

The temporal distribution of the onset and prevalence of MOF according to postinjury day is shown in Figure 2. The onset is defined as the day on which the condition resolves within 72 to 96 hours following injury. Of the 209 patients who developed an MOF score of 4 or higher, 56% occurred within 48 hours of injury. The sensitivity increased and the negative predictive value increased while the specificity decreased as the defined resuscitation time limit increased from 24 hours to 96 hours. The sensitivity or proportion of patients with MOF that had antecedent MOD was only 45%, and the positive predictive value or the proportion of patients with MOD that progressed to MOF was only 64%. Table 4 presents the effect of varying the resuscitation time limit by 24-hour increments from 24 hours to 96 hours. The sensitivity and the negative predictive value increased while the specificity and positive predictive value decreased as the resuscitation time was extended.

The trends in Table 4 are not unexpected because increasing the resuscitation time allows larger numbers of patients with MOD and decreases the number of patients with MOF. Alternatively, Table 5 compares the effects of increasing the resuscitation time on the presence of MOD on or after postinjury day 3. In this table, MOD denotes an MOF score of 4 or higher occurring within the resuscitation period and MOD96 to denote an MOF score of 4 or higher occurring after the resuscitation period. Table 3 presents the relationship between MOD and MOF using this definition in a 2 × 2 contingency table. Although χ² analysis shows a strong relationship between MOD and MOF (P < .001), the sensitivity or proportion of patients with MOF that had antecedent MOD was only 45%, and the positive predictive value or the proportion of patients with MOD that progressed to MOF was only 64%.

Our previous work defined the resuscitation period limit as 48 hours postinjury. To distinguish MOF during the resuscitation period from the postresuscitation period, we use the term MOD to denote an MOF score of 4 or higher occurring within the resuscitation period and MOF to denote an MOF score of 4 or higher occurring after the resuscitation period. Table 3 presents the relationship between MOD and MOF using this definition in a 2 × 2 contingency table. Although χ² analysis shows a strong relationship between MOD and MOF (P < .001), the sensitivity or proportion of patients with MOF that had antecedent MOD was only 45%, and the positive predictive value or the proportion of patients with MOD that progressed to MOF was only 64%.

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The sensitivity increased and the specificity decreased as the defined resuscitation time limit was extended. However, there was no change in positive and negative predictive values as the resuscitation time was extended.

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Results from Table 4 and Table 5 demonstrate that a significant proportion of patients with MOD will have the condition resolve within 72 to 96 hours following injury. To examine this further, we followed the course of MOF in patients who developed an MOF score of 4 or higher within 48 hours of injury through postinjury day 10. Figure 3 shows the prevalence of MOF according to postinjury day in patients who developed MOD within 48 hours of injury. Of the 209 patients who developed...
an MOF score of 4 or higher within 48 hours of injury, 75 (36%) had MOD resolve within 72 hours and 93 (44%) had MOD resolve within 96 hours.

Finally, we compared the characteristics of patients who developed MOD that progressed to MOF with those with MOD that had resolved within 48 hours following injury. Table 6 shows that there were no differences in sex, age, or ISSs between the 2 groups. Patients who progressed from having MOD to having MOF tended to receive more units of blood during the first 12 hours of resuscitation than the patients whose MOD resolved within 48 hours (P = .059), although the proportion of patients receiving 1 or more units of blood during the first 12 hours was not different. Mortality was higher among patients in whom MOD progressed to MOF.

**COMMENT**

The working definition of MOF that we developed previously did not include MOD scores obtained during the first 48 hours following injury because organ dysfunction during this period was thought to reflect the host response to injury and effects of incomplete resuscitation. As a result, we were potentially ignoring a population of patients with MOD that resolved within 48 hours. In this study, we considered an MOF score of 4 or higher at any time during the first 10 days following injury to define postinjury MOF. The onset of MOD occurred within 48 hours of injury in 209 patients (56%) who developed an MOD score of 4 or higher during the study period. Cryer et al found similar results in a study of high-risk patients where 67% of those with a maximum daily MOF score of 3 or higher had an MOF score higher than 0 within 24 hours of injury. While we do not consider MOD scores lower than 4 to represent MOF, the study by Cryer et al illustrates the finding that organ dysfunction after injury often begins early in the hospital course of the severely injured patient.

Risk factors for postinjury MOF include age, injury severity, degree of shock, and blood transfusion. Although the risk of postinjury MOF increases with injury severity, a significant proportion of patients who develop MOD have moderate injuries (ISS, 16-25). In this study, we found that 72 (17%) of 430 patients with an ISS indicating moderate injury developed an MOF score of 4 or higher within 10 days of injury. In contrast, 303 (36%) of 847 patients with an ISS of 25 or higher developed an MOD score of 4 or higher within 10 days of injury. This risk is increased to 46% if more than 6 U of blood are transfused during the first 12 hours of resuscitation. Nonetheless, patients with moderate injuries account for 34% of the population at risk and 17% of the cases of MOF.

Organ dysfunction during resuscitation does not invariably progress to MOF beyond the resuscitation period. The difficulty then is to distinguish between transient organ dysfunction that occurs as a result of injury and resuscitation from durable organ failure that persists once shock is reversed and homeostasis is reestablished. Defining the end point of complete resuscitation based on clinical parameters continues to be debated in the literature. However, most strategies attempt to meet resuscitation goals within 24 hours of injury. In this study, we defined resuscitation periods according to postinjury days. We varied the time limits for resuscitation in 24-hour increments and found that moving the limit closer to injury decreases the proportion of patients who develop MOD during the resuscitation period and increases the proportion of MOF following resuscitation. Since the total number of patients with an MOF score of 4 or higher remains constant, the net result is an increase in sensitivity and negative predictive value with a concomitant decrease in specificity and positive predictive value. Specificity and negative predictive value remain high because the majority of the patients (902 [71%] of 1277 patients) had daily MOD scores lower than 4 at all times during the first 10 days following injury. Although the value of MOD for predicting MOF (positive predictive value) was highest for the 24-hour time limit, the sensitivity was only 14%. If used as a predictive test, a patient with MOD during the first 24 hours has a 75% probability of developing MOF. However, only 14% of
patients with MOF will have had MOD during the first 24 hours following injury. Thus, a screening test for MOF based only on an MOF score of 4 or higher within 24 hours of injury would miss the 76% of MOF cases where onset occurs after 24 hours.

One problem with this method is that the predictive power of the initial organ dysfunction for subsequent MOF relies on a variable time definition that affects both the resuscitation and postresuscitation periods simultaneously. As an alternative, we considered the effect of varying the resuscitation time limit on predicting the presence of MOF at or after 96 hours from injury. Results are similar in that sensitivity increases and specificity decreases as the resuscitation time is extended and the negative predictive value remains relatively high. However, the positive predictive value remains relatively constant near 50%. This illustrates that MOD will resolve in half of the patients within 96 hours of injury.

Of the 209 patients with MOD, 121 (58%) had improved before the second postinjury day and 75 (36%) remained free of MOF until postinjury day 10. Forty-seven patients who initially improved worsened at some point before postinjury day 10. Thus, although almost 60% of patients with MOD improve by the second postinjury day, many develop MOF within 10 days. This may represent the resolution of MOD and subsequent development of late MOF owing to a second insult such as pneumonia or sepsis. Alternatively, this may reflect a deficiency in the MOF scale where a patient with organ dysfunction falls below the MOF threshold. Patients with MOD that resolved within 48 hours did not differ in sex, age, injury severity, or blood transfusion requirements in the first 12 hours following injury. Further study is needed to delineate risk factors that are associated with the progression of MOF beyond the resuscitation period.

In summary, MOD that develops during the first 48 hours following injury often resolves during the resuscitation period. Moreover, organ dysfunction during resuscitation is not a prerequisite for subsequent development of MOF. While a strong relationship between transient organ dysfunction and postinjury MOF exists, organ dysfunction during resuscitation likely represents a manifestation of the postinjury hyperinflammatory response. The findings in this study support our prior definitions of postinjury MOF with respect to time of onset. We submit that MOD that occurs within 48 hours of injury represents reversible physiologic responses to injury and resuscitation that have the potential for resolution once resuscitation is complete.

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REFERENCES


DISCUSSION

Donald E. Fry, MD, Albuquerque, NM: I want to thank the association for the invitation to address a subject about which I have been writing for 25 years. I’m not convinced that I know any more today than I did 25 years ago. Could we have my discussion slide, please?

I’d like to distill the data down into one very usable slide. I do want to congratulate the Denver group again on continuing to pursue this subject, because I think it is an extraordinarily interesting one. The data are intriguing, the numbers are large, and the description of the population is excellent. My only problem is that I come up with a 180-degree opposite conclusion. Let me amplify if I may.

They have identified early MODs within the first 48 hours as occurring in 200 patients. That means that of the population of 1277 patients, 1068 did not develop MODs. They have identified the 288 patients (23%) that developed multiple organ failure longitudinally across the entire study. Of those 288 patients, 134 were in the early MODs group. We see that 64% of the early MOD patients, in fact, develop multiple organ failure; if you didn’t have early MODs, only 14% developed organ failure. I did a hand-calculated chi squared in the back of the room and came up with 180; that is still a P value very, very much less than .001. At lunchtime, I tried to find a chi squared table on the Internet and was unsuccessful, but I would certainly agree that that is a highly statistically significant variable. So I would say to the opposite of what has been presented, that a 64% probability of early MOD equaling ultimately MOF is pretty good. I’ll take 64% to the racetrack everyday.

So I actually would suggest that early organ dysfunction is in fact a very significant variable in predicting that a patient is going to have organ failure for the balance of their course and would suggest that their data actually supports very nicely that of Dr Cryer’s, which seemed to have stimulated this study.

Now, obviously 154 patients did not have early MODs and 154 patients had other variables that were clearly responsible for these patients developing organ failure. Let me recount a few of those variables. Age; injury severity; shock; volume resuscitation; blood transfusions; specific injury of long bone, head
injury or soft tissue, head injury patients were all excluded from this study; infection and sepsis; the integrity of the host; pre-existing disease; intrinsic host defense; hyperalbuminemia, whether it's acquired or whether it's intrinsic second to malnutrition or underlying disease; nutritional support interventions; oxygenation; blood sugar control; temperature control; and others.

If I've learned anything about sepsis and organ failure over 25 years, it is that there is no silver bullet. We must abandon the concept of looking for a single variable or a single marker to invariably predict. Nothing will invariably predict. So it certainly would be my observation to amplify further on remarks I made this morning, that we need complexity theory or chaos theory analysis of the multiple variables that we involved in these patients. I would surely argue that the evidence for early dysfunction being a major contributor is apparent to me, but it is not the only variable to be sure, so I guess I would ask the question of our essayists if they could show me the wisdom that I have failed to appreciate in evaluating their manuscript. I would like to see the evidence that it doesn't predict organ failure because to my analysis it clearly does, and I would certainly love to see a multicenter longitudinal study with high-performance computational science applied to a vast number of patients to help us try to ultimately answer this very complex question.

Dr Moore: Thank you, Dr Fry. We have similarly struggled for 25 years to understand this disease, as you know, and we seem to spar about every other year based on a differing perspective. We agree this is a very complex arena. But today we are addressing a relatively simple aspect. The LA County experience reported by Gill Cryer indicated that if you are going to study MOF, it is already established on the first day of injury. Organ dysfunction within that first 48 hours is a risk factor for multiple organ failure consistent with the central mechanistic role of the hyperinflammatory state. What concerns us is targeting that group exclusively for therapy because to my analysis it clearly does, and I would certainly love to see a multicenter longitudinal study with high-performance computational science applied to a vast number of patients to help us try to ultimately answer this very complex question.

Dr Moore: Dr Pruitt also provides an interesting perspective; his platform is that we have created MOF in trauma/burn care because of overzealous resuscitation and, in fact, I think he is absolutely correct that we need to reconfigure early resuscitation. In this analysis, I don’t think we can answer whether cardiac reserve is pivotal in determining trajectory, but certainly age is an independent risk and for organ failure it may well be their relative intolerance to injudicious fluid loading.

David H. Wisner, MD, Sacramento, Calif: Gene, I wonder if what you are seeing here is just a result of the use of what really is a multiple organ failure score for both of your definitions. The score you are using for MODs is something derived to define multiple organ failure down the line, and you sort of arbitrarily used it as the same score for multiple organ dysfunction. I wonder if you used different kinds of physiologic scores the correlation might be somewhat better.

Dr Moore: We haven’t dissected out the individual components to see their correlation but as you are suggesting, an injury score principally related to cardiac and pulmonary dysfunction within the first 48 hours may be quite different than a change in bilirubin or creatinine. Thank you for your suggestion.