PAPER

Standardized Trauma Resuscitation

Female Hearts Respond Better

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Hypothesis: Women respond better to standardized shock resuscitation compared with similarly severely injured men.

Design: Severely injured patients who met specific criteria were resuscitated using a standardized protocol with no adjustment for gender. The resuscitation protocol was used to attain and to maintain an oxygen delivery index of 600 mL/min·m^2 or greater ($DO_2I \geq 600$) for the first 24 hours in the intensive care unit (ICU). Interventions, responses, and outcomes for the 2 cohorts were compared. Data were analyzed using analysis of variance, χ^2, and *t* tests; $P<.05$ was considered significant.

Setting: A 20-bed regional level I trauma center ICU.

Patients: Patients at high risk of postinjury multiple organ failure (major organ or vascular injury and/or skeletal fractures, initial arterial base deficit of 6 mEq/L or greater, requirement for 6 units or more of packed red blood cells in the first 12 hours after hospital admission, or age ≥65 years with any 2 previous criteria).

Interventions: Pulmonary artery catheter, packed red blood cell transfusion, crystalloid fluid infusion, inotrope, and vasopressor support, as needed, in that sequence, to maintain $DO_2I \geq 600$.

Main Outcome Measures: Hemodynamic response to resuscitation, fluid, and packed red blood cell volume.

Results: During 2000, 58 patients (38 men, 20 women) met criteria and were resuscitated using our standardized protocol. Demographics and outcomes were similar for both cohorts. Requirements for and responses to standardized resuscitation were also similar, except for volume loading. The female cohort required less lactated Ringer solution volume (12±1 vs 8±2 L, $P<.05$), required less Starling curve intervention (42% vs 15%, $P<.05$), and maintained the DO_2I goal with average pulmonary capillary wedge pressure that was less than that of the male cohort.

Conclusion: Review of prospective data from standardized shock resuscitation for female and male cohorts demonstrates that women respond better to standardized resuscitation compared with similarly severely injured men.

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PATIENTS SUSTAINING major torso trauma without concomitant brain injury who survive the first 6 hours after injury are at risk of multiple organ failure (MOF) later in their hospital course. Multiple organ failure is the complication that most often prolongs intensive care or proves fatal. Statistical prediction models for MOF have identified age, Injury Severity Score (ISS), and severity of shock to be independent risk factors.[1] Severity of shock is the one determinant that can be affected by the clinician through effective shock resuscitation.[2,3] We have developed a shock resuscitation protocol that is presumptively applied to all major torso trauma patients who are at known risk for MOF.[4,5] This standardized process has become the standard of care in our intensive care unit (ICU) and is currently implemented using computerized decision support. This provides a unique opportunity to prospectively record structured shock resuscitation in a severely injured cohort, including indications for intervention, interventions made, and the individual patient's response.

Recent laboratory and clinical studies suggest that females tolerate shock better than males.[6-10] Because shock resuscitation is an outcome determinant and gender is a contributing host factor, we hypothesized that women would respond better to standardized resuscitation compared with similarly severely injured men.

PARTICIPANTS AND METHODS

Severely injured patients who met specific criteria were resuscitated using a standardized process with no adjustment for gender. We describe the response to this standardized resuscitation in an inception cohort study during a 12-month period ending December 31, 2000. Patients were admitted to the Shock Trauma ICU of Memorial Hermann Hospital, a level I regional trauma center and teaching affiliate of the University of Texas–Houston Medical School that serves the greater Houston area (southeast Texas), which has a population of 4 million.

The patients included in this study were those who required shock resuscitation. The criteria identifying need for resuscitation were (1) major injury (≥2 abdominal organs, ≥2 long bone fractures, complex pelvic fracture, flail chest, and/or major vascular injury), (2) blood loss (anticipated need for ≥6 units packed red blood cell transfusion during the first 12 hours after hospital admission), and (3) shock (arterial base deficit ≥6 mEq/L during the first 12 hours after hospital admission), or a trauma victim of 65 years or older with any 2 of the previous criteria. Patients with these criteria who also had incurred severe brain injury (defined as Glasgow Coma Scale score ≤8 in the Shock Trauma ICU and abnormal brain computed tomographic scan results) were not resuscitated by protocol, unless the patient's brain injury was assessed by the attending neurosurgeon to be at low risk of worsening cerebral edema with volume loading. There were no additional criteria for the patients described in this study. Injury Severity Score was determined by trauma registry coders. Consecutive patients during the 12-month period were reviewed as 2 cohorts, male and female.

The resuscitation protocol is a goal-directed, logical, rule-based process that emphasizes hemoglobin and volume loading to attain and maintain an oxygen delivery goal for the first 24 hours of hospital admission. Described previously,[4,5] a hierarchical sequence of therapy interventions and thresholds for intervention is uniformly applied to all patients. Resuscitation is data driven to tailor the standardized process to the needs and responses of the individual patient. The protocol comprises a hierarchy of 5 therapies and is described in **Table 1**. A pulmonary artery catheter with continuous cardiac output and mixed venous hemoglobin oxygen saturation monitoring, and a gastric tonometer-sump catheter (Datex-Ohmeda Inc, Helsinki, Finland) with gastric mucosal interstitial P_{CO_2} monitoring are placed. Current, essential measurements (hemoglobin concentration, cardiac index, arterial oxygen saturation, pulmonary capillary wedge pressure [PCWP]), are used in decision making for therapy intervention in real time. Based on these measurements and comparison with threshold rules for intervention, clearly described interventions are used in the hierarchy sequence (Table 1).

Data were obtained prospectively during the protocol resuscitation process. Through mid-2000, a detailed worksheet and flowchart algorithm was provided to the bedside clinician team for each patient, and diagnostic data and protocol interventions were recorded manually for later review. In October 2000, a computerized implementation was introduced. A computer with touchscreen and keyboard interfaces was used at bedside to enter necessary data, compare data with threshold rules, execute the logical process, and present instructions for intervention and/or monitoring. With the computer, both diagnostic data and interventions were recorded in real time for review. Retrospectively, the resuscitation response of female patients was compared with that of male patients. The hemodynamic variables oxygen delivery index (DO_2I), cardiac index, hemoglobin concentration, PCWP, and systemic vascular resistance index, and metabolic variables base deficit, serum lactate concentration, and gastric mucosal interstitial P_{CO_2}, and blood and fluid volumes were compared during the time course of the resuscitation process. Cohort demographics, length of stay, and survival outcomes were also compared.

Data are presented as mean ± SEM in the text and figures. Data were analyzed using analysis of variance, χ^2, and *t* tests. Analysis of variance was used to analyze and compare time sequence data for female and male cohorts and for changes within each cohort with time. The χ^2 test was used to compare ISS of the male and female cohorts, a nonparametric scale assessment. *t* Tests (unpaired, 2-tailed) were used to compare parametric quantities (eg, clinical laboratory measurements, fluid volumes, and stay times). A difference between or within the female and male cohorts with $P<.05$ was considered significant.

Table 1. Resuscitation Protocol: Summary of Therapy Intervention Hierarchy*

Intervention	Threshold	Method
Transfuse (PRBC)	$DO_2I<600$ mL/min · m^2 Hb<10 g/dL (<12, age ≥65 y)	1 g Hb/dL per unit PRBC; bolus transfusion, then Hb analysis (bedside), then calculate DO_2I
Volume load (LR)	$DO_2I<600$ mL/min · m^2 Hb≥10 g/dL (≥12, age ≥65 y) PCWP<15 mm Hg (<12, age ≥65 y)	1 L LR bolus infusion (0.5 L, age ≥65 y), then measure PCWP, then calculate DO_2I
Starling curve (NS)	$DO_2I<600$ mL/min · m^2 Hb≥10 g/dL (≥12, age ≥65 y) PCWP≥15 mm Hg (≥12, age ≥65 y)	0.5 or 0.25 L NS bolus infusion, then measure PCWP and CI: CI-PCWP optimal if change in CI ≤−0.3, change in PCWP ≤±4 with 2 consecutive boluses; then calculate DO_2I
Inotrope	$DO_2I<600$ mL/min · m^2 Hb≥10 g/dL (≥12, age ≥65 y) CI-PCWP optimized	Milrinone: 0.1 increment to 0.8 µg/kg · min or dobutamine: 2.5 increment to 20 µg/kg · min calculate DO_2I
Vasopressor	$DO_2I<600$ mL/min · m^2 MAP<65 mm Hg	Norepinephrine: 0.05 increments to 0.2 µg/kg · min measure MAP calculate DO_2I

*PRBC indicates packed red blood cells; DO_2I, oxygen delivery index; Hb, hemoglobin concentration; LR, lactated Ringer solution; PCWP, pulmonary capillary wedge pressure; NS, isotonic sodium chloride solution; CI, cardiac index; and MAP, mean arterial pressure.

Table 2. Cohort Demographics, Severity of Injury (ISS), and Shock,* Response to Resuscitation,† and Outcome‡

Characteristic§	Male (n = 38)	Female (n = 20)
Age, y	42 ± 3	39 ± 4
Mechanism, % blunt	72	80
ISS	24 ± 2	25 ± 3
Max BD 0-12 h, mEq/L*	7.3 ± 0.8	9.0 ± 1.2
Max lactate 12-24 h, mM†	4.9 ± 0.8	3.5 ± 0.4
PRBC 0-12 h (U)	10 ± 2	9 ± 2
Total crystalloid received during ED, OR, ICU shock resuscitation, L‡	28 ± 2	21 ± 2‖
Total PRBC received during ED, OR, ICU shock resuscitation, U	16 ± 2	17 ± 4
ICU LOS, d	16 ± 2	14 ± 2
Hospital LOS, d	24 ± 3	20 ± 2
Survival, %	77	85

*Maximum (max) arterial base deficit (BD) in the first 12 hours of resuscitation.

†Maximum serum lactate concentration in the second 12 hours of resuscitation.

‡Intensive care unit (ICU) length of stay (LOS), hospital LOS, and survival.

§ISS indicates Injury Severity Score; lactate, serum lactate concentration; PRBC, packed red blood cells; ED, emergency department; and OR, operating room. All values are given as mean ± SEM unless otherwise indicated.

‖$P = .03$.

RESULTS

During the 12-month study period, 58 patients admitted to the Shock Trauma ICU were resuscitated using our standardized protocol, of which 38 were men and 20 women. Demographic, injury and shock severity, and outcome data are summarized in **Table 2**. Male and female cohorts were not significantly different in age, injury severity, mechanism of injury, and initial severity of shock. There was no significant difference in survival outcome. The female cohort received significantly less crystalloid fluid during the first 24 hours of hospitalization (Table 2). The volume of crystalloid fluid infused in the emergency department, operating room, and during standardized resuscitation in the ICU was 21 ± 2 L for the female cohort and 28 ± 2 L for the male cohort ($P = .03$). The female and male cohorts had similar first hospitalization day PRBC transfusion requirements (17 ± 4 vs 16 ± 2 units PRBC in the emergency department, operating room, and during standardized resuscitation in the ICU).

Both cohorts had similar hyperdynamic response to the standardized ICU shock resuscitation protocol. Hemodynamic response to resuscitation is shown in **Figure 1**. The DO_2I increased to exceed the protocol goal of 600 mL/min · m^2 for both cohorts within approximately 12 hours. The cardiac index, systemic vascular resistance index, and hemoglobin concentration were remarkably similar for both cohorts throughout resuscitation. Metabolic response to resuscitation is depicted in **Figure 2**. Base deficit decreased to less than 2 mEq/L within approximately 12 hours of the start of resuscitation with similar time courses for both groups. Serum lactate concentration, similar for both cohorts in the first 8 hours, tended to be greater for the male cohort in the second 12 hours of resuscitation. The gastric mucosal interstitial P_{CO_2} was similar for both cohorts and tended to increase during the course of resuscitation.

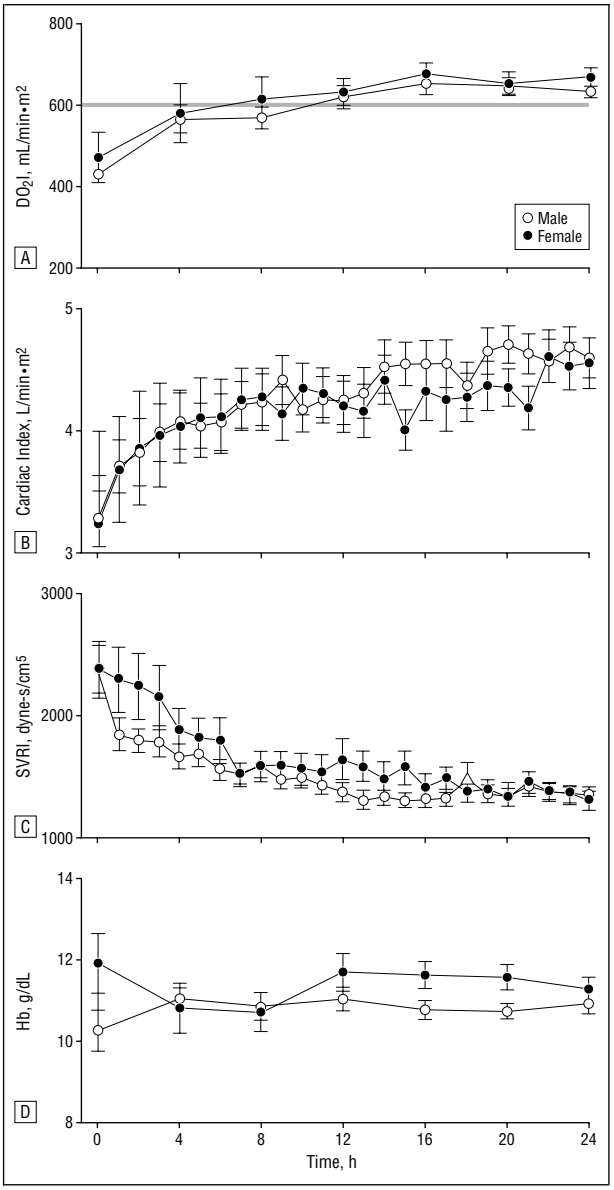

Figure 1. Hemodynamic response to standardized shock resuscitation of male (n = 38) and female (n = 20) cohorts during the first 24 hours in the intensive care unit. A, Systemic oxygen delivery index (DO_2I) vs time, showing increase to the goal of DO_2I of 600 mL/min · m^2 or greater within approximately 12 hours. B, Cardiac index vs time, showing similar time courses for both cohorts. C, Systemic vascular resistance index (SVRI) vs time, showing decrease to normal range within approximately 8 hours. D, Hemoglobin concentration (Hb) vs time, showing Hb goal of 10 g/dL or greater throughout resuscitation.

Protocol-directed resuscitation efforts (described in Table 1) are summarized for each cohort in **Table 3**. Although all patients met criteria for shock resuscitation on hospital admission, not all patients required any protocol-directed interventions, and few patients required all protocol interventions during shock resuscitation in the ICU to maintain the protocol DO_2I goal. Similar fractions of the male and female cohorts required PRBC transfusion (88% vs 95%), and the number of units of PRBC transfused were similar (5 ± 1 vs 6 ± 2 U). The fraction of the male cohort that required volume load-

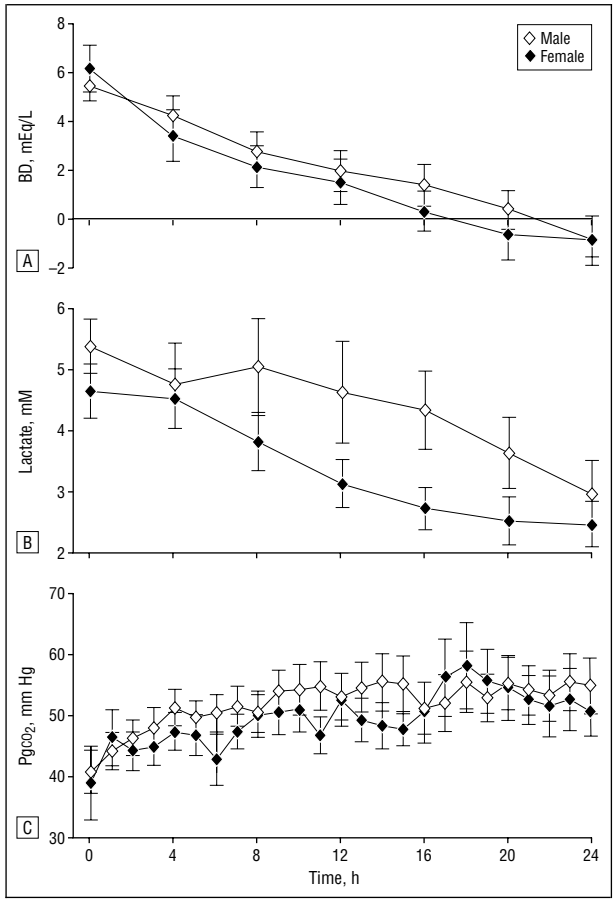

Figure 2. Metabolic response to standardized shock resuscitation of male (n=38) and female (n=20) cohorts during the first 24 hours in the intensive care unit. A, Arterial base deficit (BD) vs time, showing decrease to BD of 3 mEq/L or less within approximately 8 hours. B, Serum lactate concentration (Lactate) vs time, showing decrease to 2.5mM±0.4mM for the female cohort, and to 3.0mM±0.6mM for the male cohort at 24 hours. The time course of lactate for the male cohort tended to be greater than that for the female cohort during the second 12 hours of resuscitation. (To convert lactate from millimoles per liter to milligrams per deciliter, multiply by 0.1110.) C, Gastric mucosal interstitial P_{CO_2} (P_{gCO_2}) vs time, showing similar gradual increase for both cohorts with resuscitation.

ing with lactated Ringer solution (LR) tended to be greater than the female cohort fraction (95% vs 70%), and the number of protocol-directed liters of LR infused was significantly less for the female cohort (12±1 vs 8±2 L, $P=.04$). The female cohort required significantly fewer Starling curve interventions (optimization of cardiac index–PCWP operating point) than the male cohort (42% vs 15%, $P=.04$). Considered together, inotrope and/or vasopressor support was required significantly less in the female than the male cohort (36% vs 10%, $P=.02$).

The volume of crystalloid infusions and the PCWP measurements during the 24-hour resuscitation protocol are depicted in **Figure 3**. The increase in left ventricular preload necessary to increase cardiac index and DO_2I to meet or exceed the protocol DO_2I goal, measured as PCWP, was less for the female than for the male cohort ($P=.04$). During the first 3 to 4 hours, PCWP increased most rapidly for both cohorts. For the female cohort, the increase in PCWP from 10±1 to 15±2 mm Hg is consistent with protocol-directed interventions in response to instructions for volume loading as 1 L LR bolus infusions to increase vascular volume to a specific end point, monitored as PCWP of 15 mm Hg or greater, if DO_2I is less than 600 mL/min·m^2. For the male cohort, the increase in PCWP from 13±1 to 15±1 mm Hg showed the same response, consistent with protocol-directed interventions. During the first 4 hours, average LR volume of 4±1 L was adminis-

Table 3. Summary of Resuscitation Therapy Process*

Intervention	Male (n = 38)	Female (n = 20)
PRBC transfusion		
Patients who received, No. (%)	31 (88)	19 (95)
Units of PRBC/patient, mean ± SEM	5 ± 1	6 ± 2
LR volume load		
Patients who received, No. (%)	36 (95)	14 (70)
Liters of LR/patient, mean ± SEM	12 ± 1	8 ± 2†
Starling curve		
Patients who received, No. (%)	16 (42)	3 (15)†
Liters of NS/patient, mean ± SEM	1.2 ± 0.3	0.2 ± 0.2
Patients who received inotrope and/or vasopressor, No. (%)	14 (36)	2 (10)‡

*Number of patients in each cohort requiring each intervention therapy during standardized shock resuscitation protocol and amount of each therapy intervention. Combined, inotrope + vasopressor interventions were required in 14 (36%) of male and 2 (10%) of female cohort. PRBC indicates packed red blood cells; LR, lactated Ringer solution; and NS, isotonic sodium chloride solution.

†$P=.04$.

‡$P=.03$.

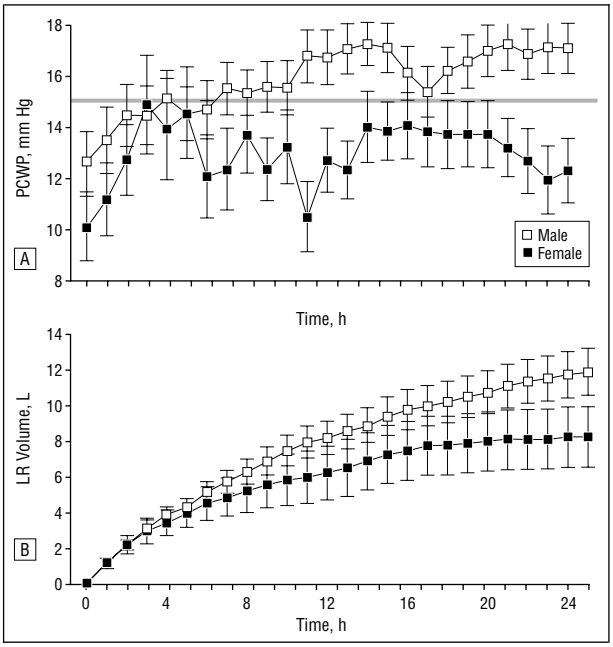

Figure 3. Left ventricular preload response to lactated Ringer solution (LR) volume load interventions directed by standardized shock resuscitation protocol during the first 24 hours in the intensive care unit. Volume load interventions during the first 4 hours show an increase to a mean pulmonary capillary wedge pressure (PCWP) of approximately 15 mm Hg, consistent with early protocol directed attempts to attain an oxygen delivery index (DO_2I) goal of 600 mL/min·m^2 or greater. A, Pulmonary capillary wedge pressure vs time, showing PCWP at approximately 13 mm Hg for the female cohort (n=20) and at approximately 16 mm Hg for the male cohort (n=38) to maintain a DO_2I goal of 600 mL/min·m^2 or greater ($P=.04$). B, Cumulative LR volume vs time, showing less volume requirement for the female cohort compared with the male cohort ($P=.04$).

tered to the female cohort and 4±0.4 L to the male cohort in early attempts to attain a DO_2I that was equal to or greater than the goal. After this initial start-up period, the PCWP time course of male and female cohorts differed. From 8 to 24 hours during the resuscitation process, mean PCWP was 13±0.3 mm Hg for the female cohort and 17±0.2 mm Hg for the male cohort. The female cohort maintained cardiac index and DO_2I without need to maintain PCWP of 15 or greater. In contrast, the male cohort required more volume load interventions to maintain PCWP of 15 or greater and DO_2I of 600 or greater. Corresponding with PCWP difference between cohorts, the volume of LR infused during the resuscitation protocol was significantly greater for the male than for the female cohort (12±1 vs 8±2 L, $P=.04$). The number of PRBC transfusions were similar for the female and male cohorts (6±2 vs 5±1 units PRBC during standardized resuscitation).

COMMENT

Our data support gender dimorphism in the response to traumatic shock resuscitation. Major torso trauma patients (excluding those with severe brain injury) were treated for shock using a standardized resuscitation protocol. The female cohort had a more efficient hemodynamic response to volume loading and required less intervention than did the similarly injured male cohort. The female cohort had less need for volume loading to increase the PCWP to achieve the same cardiac index as the male cohort.

This observation is consistent with the laboratory studies of Chaudry and coworkers). Comparison of male and female rats 24 hours after soft tissue trauma and hemorrhage insult and LR fluid resuscitation found males to have depressed cardiac performance compared with proestrus females.[11] Studies of male rats subjected to soft tissue trauma and hemorrhage insult and LR resuscitation and treated with flutamide, causing testosterone receptor blockade, found increased cardiac output and myocardial contractility after 20 hours compared with male rats not treated with flutamide.[12] Studies of male rats treated with 17β-estradiol as part of shock resuscitation have reported improved cardiac performance compared with those not treated with 17β-estradiol.[7] Increases in cardiac output, stroke volume, and contractility were reported with measurements 24 hours after completion of soft tissue trauma and hemorrhage, shock and resuscitation with LR fluid, and subcutaneous injection of 17β-estradiol compared with rats not treated with 17β-estradiol. Vasodilation through estrogen-stimulated activation of endothelial constitutive nitric oxide synthase is a possible cause of this difference. The mechanism for this rapid estrogen response is thought to be a non–transcription-regulated, mitogen-activated, protein kinase–dependent increase in expression or activity of constitutive nitric oxide synthase.[7,13] These animal studies have also investigated gender differences in inflammatory response and survival after hemorrhagic shock[8,14,15] and found results that encourage treatment of male trauma victims with female sex steroids to modulate cell and organ function.[7,9,16]

The clinical literature is inconclusive regarding the female sex advantage for survival and improved outcomes after major trauma. An early review by Morris et al[17] of host factors and mortality in approximately 200 000 trauma patients admitted to California hospitals in 1986 found that men of middle age (40-65 years) had risk of mortality greater than that of women and suggested that gender-related biochemical risk factors would need to be identified during the 1990s. Wohltmann et al[18] in a review of gender effect in outcomes of all trauma patients found the greatest gender difference in mortality in the younger (age <50 years), most severely injured (ISS >25). This difference, 28% mortality in women vs 33% in men, was not attributable to mechanism (blunt vs penetrating), severity, or pattern of injury. In a review of a large population of blunt trauma patients admitted to a level I trauma center from 1983 to 1995, Napolitano et al[10] found gender to have no relation to mortality in those patients who did not develop pneumonia but found males to have a greater incidence of pneumonia, with the most severely injured (ISS >30) males of middle age (46-65 years) having the strongest association with pneumonia. Offner et al,[19] in a study of sex differences in adult patient outcomes after major trauma (age >15 years, ISS >15, survival >48 hours), found major infection (pneumonia, abdominal and pelvic abscess; wound infection requiring surgical debridement; or meningitis) to have occurred in 40% of patients, and that men had 58% greater risk of developing a major infection than women. Similarly, in surgical intensive care patients studied prospectively for sepsis and/or septic shock, males were found to have greater incidence (due to greater incidence in elderly males aged 60-80 years), but gender had no effect on mortality.[20] Another study of gender differences in surgical sepsis found 70% mortality in men and 26% in women.[21]

These reports do not uniformly analyze clinical course for length of stay and onset of complications, but, overall, these results seem consistent with immune function that is more suppressed in male than in female trauma patients following initial resuscitation and early days of ICU care, leaving male patients at greater risk of infection, MOF, and other complications. This pattern seems consistent with a pattern of postinjury systemic inflammatory response syndrome, compensatory anti-inflammatory response, and delayed immunosuppression.[1] More severe and prolonged immunosuppression may occur in men than in women, starting with early systemic inflammatory response syndrome response to trauma.

The mechanism responsible for the difference observed in male and female cardiac performance of major torso trauma patients in this study is not clear from the data obtained. Estrogen-mediated vasodilation is conceptually consistent with the observed effect of more efficient use of fluid volume administered.[11] Although a difference in systemic vascular resistance index between cohorts was not apparent (Figure 1C), the effect of initial volume loading in the first 4 hours of resuscitation was sustained by the female cohort for the duration of the 24-hour resuscitation with significantly less further intervention than was required by the male cohort, including inotrope and/or vasopressor support (Table 3). The female cohort therefore maintained intravascular volume somewhat more persistently than the male cohort. Serum lactate concentration data suggest a tendency for

more rapid recovery of peripheral perfusion by the female compared with the male cohort, also consistent with estrogen-mediated vasodilation.

In summary, use of our standardized shock resuscitation protocol in a severely injured cohort provided a prospective record of the shock resuscitation process. Review of this prospective data for female and male cohorts for the 12-month period ending December 31, 2000, including indications for intervention, interventions made, and the individual patient's response, demonstrates that women respond better to standardized resuscitation compared with similarly severely injured men. Specifically, the female cohort required less fluid volume, less increase of PCWP, and less drug intervention to achieve the same hyperdynamic response.

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DISCUSSION

Felix D. Battistella, MD, Sacramento, Calif: Dr McKinley, your study is one of a growing number suggesting that the female response to injury is different than that of males. But before I discuss your findings, I want to compliment you on your resuscitation protocol. It is simple, logical, and easy to implement, and it is critical to the interpretation of your findings. We should all have similar resuscitation guidelines in our ICUs.

In your study, you were able to achieve similar cardiac resuscitation in males and females, but the resuscitation of males required more crystalloid infusion. You concluded from this that female hearts respond better. You compared total volume infused rather than volume index to body size. Women on average are smaller than men and therefore you would expect them to require less fluid to achieve similar resuscitation. Does the difference in volume persist if you index it to ideal body weight?

Having asked the question, I suspect the difference would persist, and in that case, I propose that the increased fluid requirement in men might be related to a difference in capillary permeability rather than cardiac function. Much of the work addressing gender-based dimorphic response to injury and hemorrhage has focused on the immune effects of testosterone. Perhaps, differences in cytokine production between the 2 sexes leads to differences in capillary permeability and increased third spacing in males. Do you have additional pulmonary artery catheter data, such as stroke work, cardiac power, or elastance that might support your conclusion?

Lastly, I was relieved, as I'm sure most of the audience was, to see that your conclusions did not include a recommendation for prophylactic castration.

Juan A. Asensio, MD, Los Angeles, Calif: Did the male group in your study undergo more trauma surgical procedures, as about 28% of them sustained penetrating injury vs 14% of females? That may account for increased third space requirements.

Question 2 is could you relate your findings to the females' smaller blood volume?

Third, although this is a prospective study, it was conducted over a very short period of time, just 1 year, with a small number of patients, 58. Do you think that the findings would have changed if you had extended your period of study?

Robert Stephen Smith, MD, Wichita, Kan: I would also like to congratulate the authors on a nice study. I have 3 questions regarding the preresuscitation physiologic status of these patients. At time "0," the hemoglobin for males and females appeared to be significantly different. Is this true?

Secondly, do you have any additional information about the prehospital physiologic status of the patients? You attempted to measure this with base deficits, but do you have RTS or Crams data on these patients?

Finally, was there any difference in cardiac comorbidities that predated the time of injury? I think that males are more likely to have cardiac dysfunction secondary to coronary artery disease in this age group.

James G. Tyburski, MD, Detroit, Mich: A follow-up on Steve's question. If I saw the slide correctly, the male hemoglobins were lower than the females, which usually is not com-

mon. Most laboratories would say that the females would have a lower base hemoglobin. Did this influence the timing for the transfusion, since you used a trigger of 10 g of hemoglobin? Likewise, did this influence the amount of crystalloids before transfusion of blood was started?

Gregory J. Jurkovich, MD, Seattle, Wash: Just 4 points, 2 of which were already mentioned, but I will reemphasize them. We really do need the fluid volumes indexed to either body surface area or weight rather than just volume of fluid.

Secondly, mechanism of injury has potentially a great impact, whether it is penetrating or blunt. Was there much difference between these males and females in that regard?

I would also like to ask about the standardized protocol, which I find fairly unique and of interest. First of all, how often is the protocol really followed to its conclusion and how often is the protocol broken, not followed, or aberrations in the protocol accomplished, either intentionally or unintentionally by either the nurses or the house staff taking care of the patients? You have attempted to standardize care and I wonder how effective you really were and what problems, if any, exist with the protocol.

Finally, I am curious as to why the outcomes, at least those presented to us, focused on cardiac index, when in fact the a priori assessment of adequacy of resuscitation was delivery of oxygen. Oxygen delivery and cardiac index are related, but not necessarily equal. So I would have liked to have seen at least a measure of oxygen delivery in both of the 2 groups and whether the resuscitation perhaps overshot oxygen delivery in 1 group.

Basil A. Pruitt, Jr, MD, San Antonio, Tex: Was the difference in fluid loading time related? That is, in the first few hours following injury, edema formation is primarily pressure related rather than permeability related. Consequently, if there is excessive early volume loading, that fluid will leave the circulation and cause more edema, which might account for the overall difference in fluid load.

Secondly, you noted there was a gender difference in circulating lactate levels. There are now data from both Cincinnati and Boston indicating that one can increase lactate just by infusion of catecholamines, and I wonder where there was a difference in catecholamine levels in the 2 groups of patients.

Thirdly, since you are attributing the differences to estrogen effect, did you measure estrogen levels? Finally, did it make any difference what part of the menstrual cycle the female patients were in when they were injured?

Dr Moore: In regards to Dr Battistella's concern about the difference in the weight of the women and men, I do not have the data analyzed by weight, but I would emphasize that the resuscitation protocol is simply a test of how well the heart can respond. When a patient arrives in the ICU, by using prediction models, we identify those people who are destined not to do well. We place appropriate monitoring devices, measure specific parameters, and then offer a series of interventions (ie, 5 steps) to get the heart to work. When we analyze the results of the protocol, the females require fewer steps. What they require is some early volume loading and once they get tanked up, their hearts work just fine. The males, on the other hand, require more volume loading, more Starling curves, and more drugs to get the same response. This may answer Dr Pruitt's question. In the men, we persist in giving fluids through the 24-hour period and go on to administer catecholamines in about 20%. It is conceivable that the delayed use of catecholamines are driving the increased lactate levels seen in the males late in resuscitation.

Dr Asensio, the males and females received an equal number of surgical interventions. Whether those surgical interventions were more intense or less intense, I cannot tell you.

The weakness in this study is that it is small, but its value is that the data are collected in real time based on a set of rules that are being applied uniformly. Dr Jurkovich asked, how often are the recommended interventions followed? Eighty-seven percent of the time, the bedside clinician follows what the computer recommends. It's airtight if the clinician does not do what the computer says. They just need to write down why they did not want to follow the instruction and what they did. By analyzing these data, we hope to improve the robustness of our decision support tool. But, unlike other studies, we can actually look back and say, we know what happened last night. This is unique for shock resuscitation studies.

Dr Smith and Dr Tyburski, the hemoglobin levels at baseline were not different and both groups received the same amount of blood transfusions based upon our transfusion trigger rules.

Dr Jurkovich asked about oxygen delivery as an outcome. The oxygen deliveries were quite similar for the 2 groups. Oxygen delivery is the product of cardiac index × hemoglobin level × arterial hemoglobin saturation. We can generally keep the hemoglobin level and saturation in a normal range, so that our resuscitation protocol really does drive cardiac index. Unfortunately, we do not have other indices of cardiac function.

Dr Pruitt, we do not have data on the menstrual cycle. This analysis was spurred by some recent studies suggesting that there was a difference in outcome between males and females after major trauma. Because shock is an important determinant outcome following trauma, we analyzed our available database as a first pass to assess whether there is an obvious gender difference in the response to resuscitation. Of course, in a future study, it would be important to clarify this issue.