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Gender and ARDS in Critically Injured Adults: A Prospective Study

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Abstract

Objective—The acute respiratory distress syndrome (ARDS) is a pro-inflammatory condition that often complicates trauma and critical illness. Animal studies have shown that both gender and sex hormones play an important role in inflammatory regulation. Human data is scant regarding the role of gender and sex hormones in developing ARDS. Our objective was to describe gender and hormonal differences in patients who develop ARDS in a large cohort of critically injured adults.

Methods—A prospective cohort study of adult trauma patients requiring ICU admission for at least 48 hours was performed. Demographic and clinical data was collected prospectively, and sex hormones were assayed at study entry (48 hours). The primary outcome was the development of ARDS. Multivariate logistic regression was used to determine the adjusted odds of death associated with differences in gender.

Results—648 patients met entry criteria and 180 patients developed ARDS (31%). Females were more likely to develop ARDS (35 % versus 25%, $p=0.02$). This association remained after adjusting for age, mechanism of injury, injury severity and blood product transfusion (OR 1.6 95% CI 1.1 – 2.4, $p=0.02$). Of patients with ARDS, there was no difference in mortality related to gender (22% mortality in females with ARDS versus 20% in males, $p=NS$). A pro-inflammatory sex hormone profile (low testosterone, high estradiol) was associated with ARDS in both males and females.

Conclusion—Females are more likely than males to develop ARDS following critical injury. Despite the increased incidence in ARDS, the mortality in patients with ARDS does not differ according to gender. The inflammatory properties of sex hormones may contribute to ARDS, but they do not fully explain observed gender differences.

Keywords

gender; sex hormones; ARDS; trauma; critical illness

Background

The Acute Respiratory Distress Syndrome (ARDS) was first described in 1967¹, and despite advances in both prevention and treatment, ARDS continues to contribute to significant mortality and morbidity in trauma patients after the initial injury stabilization. ARDS is among other mechanisms, a pro-inflammatory condition, but predicting which patients will develop ARDS remains difficult. Unpredictability in the inflammatory or immunologic response to traumatic injury is likely multi-factorial with demographic, clinical, environmental and genetic factors all contributing to observed variation²⁻⁴. Gender has often been considered an important contributor to this immunologic variation. Because sex hormones possess extensive and diverse inflammatory and immune mediating properties, the role of gender on outcomes after trauma has gained considerable attention, particularly in the laboratory setting. An extensive body of animal data points to the fact that the pro-estrous state is pro-inflammatory and is associated with improved survival, while the opposite is true for the pro-androgenic state⁵⁻¹¹. Results from human studies are less clear, with most studies reporting no difference in outcomes of infections or severe trauma related to gender^{9, 12-19}. However, two recent studies have demonstrated increased mortality in critically ill patients with elevated endogenous estrogens, regardless of sex.^{12, 20} Given the pro-inflammatory actions of estrogens, and the recent evidence linking elevated estrogens to increased mortality, we aimed to further understand the possible role of gender and sex hormones following severe traumatic injury on the development of ARDS.

Materials and Methods

Study population

A prospective cohort of critically ill or critically injured trauma patients was enrolled. Patients 18 years of age or older, admitted to the Trauma Intensive Care Unit (ICU) of Vanderbilt University Medical Center for at least 48 hours between October 2001 and May 2006 were eligible for enrollment. These patients were part of larger set of patients looking at the effect of gender on outcomes in critical illness (ROI – AI49989-01). Patients who died before 48 hours were excluded as were patients discharged from the ICU prior to 48 hours. This minimum length of stay was intended to exclude patients admitted for short observational stays, or patients with overwhelming injuries beyond the aid of modern critical care. Ventilator strategies used to minimize barotrauma were consistent among the patients, and between the treating physicians. This aimed for tidal volumes of 6mls/kg, both before and after the diagnosis of ARDS. Positive End Expiratory Pressure (PEEP) was preferred for improving oxygenation. Where available, invasive monitoring was used to minimize excess volume resuscitation. Demographic and clinical characteristics were collected by dedicated research nurses from patient or family interview or the electronic medical record. The following anatomic and physiologic severity scores were collected at the time of hospital admission—the Injury Severity Score (ISS), Trauma Related Injury Severity Score (TRISS), Abbreviated Injury Score (AIS) and the Acute Physiology and Chronic Health Evaluation (APACHE) II score. Patient care was at the discretion of the attending physician according to established critical care protocols.

Outcome classification

The primary outcome of interest was the development of Acute Respiratory Distress Syndrome (ARDS). ARDS was classified according to the following definition²¹: the acute onset of bilateral patchy infiltrates on chest radiograph, a $\text{PaO}_2/\text{FiO}_2$ ratio of less than 200 and the absence of cardiogenic pulmonary edema. All patients had to have at least 2 sequential $\text{PaO}_2/\text{FiO}_2$ ratios of less than 200 to be ascribed a diagnosis of ARDS. Patients were considered to have severe ARDS if both of the sequential $\text{PaO}_2/\text{FiO}_2$ ratios were less

than 100. All chest radiographs taken for up to 7 days following admission to the ICU were reviewed. These radiographs were classified by critical care specialists who were not a part of the patient treating team. Blood gases were obtained at the discretion of the treating physician. The ABG and PaO₂/FiO₂ ratios were matched to the concomitantly obtained chest X-ray. Once the diagnosis of ARDS was made, we did not follow sequential ABGs, and the course of the ARDS was often followed by clinical examination and pulse oxymetry rather than routine serial arterial blood gasses. Secondary outcomes included in-hospital mortality, and the number of ventilator days.

Hormone assays

Blood was collected upon entry into the study for analysis of sex hormones. Blood was separated, frozen and stored at -70°C until analysis. 17 β -estradiol and total testosterone assays were performed in the General Clinical Research Center at the University of Virginia Health Sciences Center. Estradiol was measured by kit EIA utilizing a competitive immunoassay strategy and alkaline phosphatase/p-Npp chromogenic reaction (Estradiol, catalog # 90108, Assay Designs, Inc., Ann Arbor, MI). Total testosterone was measured by ELISA kits and manufacturer's directions (testosterone EIA, catalog # 700C-081; Alfa Scientific Designs, Inc., San Diego, CA).

Statistical analysis

Normally distributed continuous variables were summarized by reporting the mean and standard deviation and compared using two sample *t*-tests for independent samples. Continuous variables that were not normally distributed were presented by reporting the median and interquartile ranges (IQR) and compared using the Wilcoxon Rank Sum test. Multivariate logistic regression was used to estimate independent relationships between gender and ARDS. Non-linear relationships between sex hormones and ARDS by gender were modeled using restricted cubic spline covariates. Stata version 9.2 (Stata Corp., College Station, Texas, USA) was used for analysis. Tests for statistical significance were two sided with an alpha of 0.05.

The study was approved by the Institutional Review Board of Vanderbilt University Medical Center. All data is maintained in a secure, password protected database that is HIPAA-compliant. All patient information is de-identified prior to analysis and reporting.

A waiver of consent was obtained from both institutional review boards for the blood draw at 48 hours and study inclusion since the study posed minimal risk to subjects. Families were assented during the critical illness phase, and patients were consented after their critical illness resolved when possible. Patients who died or were discharged prior to consent being obtained remained in the study, with IRB approval. Patients who were able to consent, but refused could either withdraw completely or refuse subsequent participation.

Results

The demographics and clinical characteristics of 648 enrolled patients are summarized in Table 1. Nearly 75% of the patients were males ($n=482$). Females were older, more severely ill by APACHE II, more likely to be victims of blunt trauma, and more likely to have chest trauma (as measured by mean AIS chest scores). The groups did not differ by BMI, ISS or TRISS. The overall mortality of the group was 12.5% ($n=81$), and in the univariate analysis there was no difference in mortality according to gender. The median number of ventilator days among the entire cohort was 3 days (IQR 2–4) with all but 2 (<1%) patients requiring some duration of mechanical ventilation. There was no difference in number of ventilator

days by gender. Male patients were less likely to receive blood product transfusions than females (77% versus 85% received blood products, $p=0.03$).

The overall rate of ARDS was 27% (180 patients). Females were more likely to develop ARDS than males (35% versus 25%, $p=0.02$). There was no difference in age, APACHE II score, or mortality between males and females. Among patients with ARDS, an equal percentage of males (13%) and females (14%) developed severe ARDS (PF ratio <100) ($p=0.68$). In a multivariable analysis adjusting for important clinical covariates including age, APACHE II, mechanism (blunt versus penetrating), transfusion (none versus any) and chest injury severity, the adjusted odds of developing ARDS for females as compared to males was 1.6 (95% CI 1.1 – 2.5, $p=0.02$). Despite a higher rate of ARDS in females, there was no difference in overall mortality from ARDS related to gender (OR of death for females with ARDS 0.80, 95% CI 0.25 – 2.5, $p=0.69$). There was no statistical difference in mortality between males and females who developed ARDS when divided by P/F ratio 100–200 (18% versus 25%; $p=0.9$) or P/F ratio <100 (severe ARDS) (30% versus 37.5%; $p=0.9$). The demographics of the patients who developed ARDS are presented in Table 2. The median number of ventilator days for patients with ARDS was 3 days (IQR 2 – 4) and this did not differ from patients without ARDS ($p=0.18$). The predominant cause of death in all patients in the series, irrespective of development of ARDS, was multi-organ failure. Of the 37 ARDS patients who died, factors were assessed that contributed to their mortality. Of these 37 patients, 7(19%) had an AIS head of 4 or 5, 13 (35%) developed pneumonia and 27 (37%) were septic (table 2). There were no statistical differences in these causes of death when reviewed either with respect to gender or severity of ARDS. Although the overall rate of death in patients with severe ARDS (PaO₂/FiO₂ <100) was higher than ARDS (PaO₂/FiO₂ 100–200), this did not reach statistical significance (33.3% versus 18.6%; $p=0.12$).

To investigate the contribution of sex hormones to the differences in the rate of ARDS between males and females, serum estradiol, testosterone, and the testosterone to estradiol ratio were analyzed with respect to the development of ARDS. The hormone and profiles stratified by gender and ARDS are summarized in Table 3. In the univariate analysis, there is no difference in estradiol by ARDS in either gender. In males, testosterone depression is more profound in those patients who develop ARDS, and these changes lead to a statistically different testosterone to estradiol ratio by ARDS among males. However, since the relationship between estrogens and mortality is non-linear, we further explored the relationship between sex hormones and ARDS using non-linear statistical models. The relationship between estradiol and ARDS stratified by gender is displayed in Figure 1a. For both genders, ARDS increases with increasing estradiol, but in males the increase is more profound, particularly outside the normal range for estradiol in males (0–54 pg/ml). The relationship between testosterone and ARDS stratified by gender is displayed in Figure 1b. For both genders, ARDS decreases with increasing testosterone, with testosterone levels less than 50 ng/ml associated with high rates of ARDS in both genders. The relationship between the ratio between testosterone and estradiol and ARDS is displayed in Figure 1c, where for both genders, the rate of ARDS increases sharply with ratios less than 50. Despite the development of ARDS, neither mortality nor ventilator days was different between males and females.

Discussion

The Acute Respiratory Distress Syndrome (ARDS) remains a considerable contributor to morbidity and mortality after critical injury. Several authors have hypothesized gender as accounting for differences in outcomes following trauma, particularly in animal models^{5, 6, 8, 10, 22, 23}, but few studies have specifically evaluated the relationship between gender and secondary outcomes such as ARDS. Our objective was to describe the

relationship between gender and ARDS, and to relate any observed differences to sex hormone levels. We hypothesized that the pro-inflammatory properties of estrogens would predispose females to developing ARDS.

Gender differences in the prevalence of asthma are well described with females being at a higher risk²⁴. In a recent analysis of patients hospitalized for an asthma exacerbation in England, women had a higher death rate²⁵. Female gender has also been identified as a risk factor for hospitalization in COPD patients²⁶. Our data adds support to the hypothesis that the female lung is more prone to injury and the deleterious effects of inflammation. The effect of female gender on the development of ARDS was independent of the older age and differing injury patterns in these patients. Despite higher rates of ARDS, females with ARDS did not die more frequently than their male counterparts with ARDS.

The fact that females are more prone to ARDS following trauma supports the hypothesis that sex hormones may contribute to the propensity to develop lung injury. Estrogens have diverse and extensive immunologic properties^{22, 27, 28}, giving plausibility to the fact that the pro-estrous state would be associated with exaggerated inflammation and ARDS. Our data confirms that higher levels of endogenous estrogens are associated with higher rates of ARDS in both genders. However, these differences do not fully explain the difference in ARDS rates by sex since females have a higher incidence of ARDS at all estradiol levels than males.

There is similar biologic plausibility for the association between lower testosterone and higher rates of ARDS since testosterone is generally considered immune depressing. Also, global hypothalamic-pituitary-gonadal axis suppression, and therefore, testosterone depression is related to illness severity. Our data confirms this relationship in both genders. This conflicts with an earlier report by Gee *et al*²⁹ who correlated high testosterone levels with the development of ARDS. Differences in patient populations may explain this contradiction since only 62 patients were enrolled in the study by Gee, with only 21 of these being mechanically ventilated and only 12 developing ARDS. The strengths of this study lie in its large sample size and the use of a standard case definition for ARDS. We did not rely on administrative coding, but rather systematically reviewed clinical data, including chest radiographs, to more accurately classify patients according to ARDS. Previous studies have reported significantly lower ARDS rates in blunt trauma (4.5%), most likely from relying on retrospective coding rather than actual review of the radiographs and clinical records³⁰.

Intriguingly there was no difference in ventilator days between patients who did and did not develop ARDS (approximately 3 days in each group). Although this was not a study pertaining to the management of ARDS and patient management was at the discretion of the treating physician, it is noted that ventilator strategies to minimize barotrauma were consistent among the patients. We believe that strict adherence to a high PEEP, low tidal volume (6mls/kg) ARDS management strategy definitely contributes to limiting the impact of ARDS. Furthermore, there are both direct pulmonary and indirect non-pulmonary causes of acute lung injury and ARDS. Therapies directed to the underlying etiology would shorten the inflammatory burden leading to ARDS.

The lack of a statistical difference in mortality between ARDS and severe ARDS was probably due to the relatively small numbers of patients who developed severe ARDS. There was no difference between the genders with relation to the risk of developing severe ARDS (13% versus 14%), or the associated mortality of severe ARDS (30% versus 37.5%; $p=0.9$). We postulate that this reflects a gender discrepancy with relation to the inflammatory environment which predisposes to the risk of developing ARDS. However, other factors are clearly involved with relation to the severity of the ARDS once it develops.

Despite these strengths, there are several important limitations. Conclusions regarding sex hormones are based on a single assay at study entry (48 hours after admission). We do not fully understand the relative importance of trends in sex hormones, nor whether absolute values or changes in sex hormones are most important. In this study it is impossible to determine whether or not estrogens specifically *cause* ARDS, or merely serve as a biomarker for injury or severity of illness. Another limitation is that while patients are cared for according to standard practice management guidelines, we cannot account for differences in fluid resuscitation or ventilator management that may influence rates of ARDS on a per patient level. While practice management guidelines support low tidal volume ventilation strategies and judicious use of fluids, we did not capture detailed information regarding these strategies. Presumably any differences in these strategies would be non-differential with respect to gender and sex hormones. The study was not designed to assess the association between duration of ARDS and gender or hormonal levels. Although others employ duration to establish the diagnosis of ARDS, we followed the definition as outlined by Ware et al which neither includes duration nor requires repeat PaO₂/FiO₂ ratios. Furthermore, once the diagnosis of ARDS was established the data were de-identified. This limited our ability to review medical records to re-assess repeated arterial blood gases, determine the duration of the acute lung injury or ARDS, and thus distinguish relatively short versus prolonged respiratory failure.

CONCLUSION

Females are more likely than males to develop ARDS following critical injury. Despite the increased incidence in ARDS, the mortality in patients with ARDS does not differ according to gender. These findings are not fully explained by sex hormones, but there is evidence that the relationship between pro-inflammatory estrogens and immune depressing testosterone and development of ARDS are important regardless of gender. These data may give consideration for gender based ventilator support strategies for critically ill patients, or sex hormone modulation.

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Figure 1.

The relationship between sex hormones and ARDS stratified by gender. Panel **a** demonstrates that for both genders, rates of ARDS increase with increasing estradiol. The higher rates of ARDS observed in women are not fully explained by estrogens, however, since for all estradiol levels, the rate of ARDS is higher in females. Panel **b** demonstrates that for both genders, rates of ARDS decrease with increasing testosterone. Panel **c** demonstrates the relationship between testosterone and estradiol (testosterone to estradiol ratio) and rates of ARDS. For both genders a higher ratio appears protective, with the lowest rates of ARDS being expected in patients with ratios greater than 50.

Table 1

Demographic and Clinical Characteristics by Gender.

	Males (n=482)	Females (n=166)	p value
Age (years)*	42 ± 17	45 ± 19	0.02
Body Mass Index (kg/m ²)*	28 ± 7	28 ± 8	NS
Injury Severity Score [^]	29 (24 – 38)	34 (24 – 41)	NS
TRISS [^]	0.855	0.804	NS
AIS Chest*	2.5 ± 1.7	3.0 ± 1.6	0.003
APACHE II*	17 ± 6	18 ± 5	0.03
Mechanism			
Blunt (%)	86	93	
Penetrating (%)	14	7	0.009
No Blood Product Transfusion n (%)	112 (23)	25 (15)	0.03
Mortality n (%)	67 (14)	14 (8)	NS
ARDS n (%)	122 (25)	58 (35)	0.02
P/F Ratio 100–200	106 (87)	50 (86)	NS
Severe ARDS (P/F Ratio <100)	16 (13)	8 (14)	NS

TRISS (Trauma Revised Injury Severity Score); AIS (Abbreviated Injury Score); APACHE II (Acute Physiology and Chronic Health Evaluation-II); ARDS (Acute Respiratory Distress Syndrome)

* compared using two sample t-test;

[^] compared using Wilcoxon Rank Sum test;

compared using chi-square test

Table 2

Demographic and Clinical Characteristics by ARDS.

	Males	Females	<i>p</i> value
Number of Patients	122	58	
Age (years)*	46.5	49.6	0.13
APACHE II*	17.1	19.5	0.27
ARDS patients			
Overall Mortality (%)	24 (20%)	13 (22%)	0.69
AIS Head 4 or 5	4/24 (16%)	3/13 (23%)	0.67
Pneumonia	9/24 (37.5%)	4/13 (30.7%)	0.73
Sepsis	18/24 (75%)	9/13 (69%)	0.71
Mortality P/F Ratio 100–200 [#]	19 (18%)	10 (25%)	0.9
Mortality Severe ARDS (P/F <100) [#]	5 (30%)	3 (37.5%)	0.9

APACHE II (Acute Physiology and Chronic Health Evaluation-II); ARDS (Acute Respiratory Distress Syndrome)

* compared using two sample t-test;

^ compared using Wilcoxon Rank Sum test;

compared using chi-square test

Table 3
Cytokines and Sex Hormones Stratified by Gender and Acute Respiratory Distress Syndrome (ARDS)

	Males (n=482)		p value *	Females (n=166)		p value *
	No ARDS (n=360)	ARDS (n=122)		No ARDS (n=108)	ARDS (n=58)	
Estradiol (pg/ml)	21	22	NS	24	29	NS
Testosterone (ng/ml)	41	32	0.007	34	34	NS
T:E ratio (ng/pg)	20	15	0.004	13	10	NS
IL-1	4.6	2.7	NS	3.9	6.4	NS
IL-2	8	2.7	0.001	3.6	2.7	NS
IL-4	22	37	0.03	14	30	NS
IL-6	87	234	<0.001	110	276	<0.001
IL-8	21	33	NS	17	38	0.03
IL-10	57	52	NS	68	72	NS
IL-12	9	5.6	0.009	5.5	3.4	0.05
TNF- α	5.6	6.2	NS	5.0	6.4	NS

T:E (testosterone:estradiol); IL (interleukin); TNF- α (tumor necrosis factor- α)

* Compared using Wilcoxon Rank Sum test; NS ($p > 0.05$)