

Effects of Heat Illness on Hospitalization for Exertional Rhabdomyolysis in the Military

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Abstract

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Exertional rhabdomyolysis and exertional heat illness are common in military populations due to frequent high intensity physical training. Exertional rhabdomyolysis (ER) is a syndrome of muscle breakdown following exercise and is also a known complication of exertional heat illness. The behavior and clinical course of exertional rhabdomyolysis is not well described, and it is unclear if ER behaves differently in the setting of concomitant heat illness. This study describes laboratory and demographic trends of servicemembers hospitalized for exertional rhabdomyolysis and examines the impact of associated heat illness. 321 hospitalized cases of exertional rhabdomyolysis were reviewed from 2010-2013 and stratified into groups based on the presence of associated heat illness or medical comorbidities. 193 (60.1%) were associated with heat illness. Initial creatine kinase (CK) levels were significantly lower in heat illness-related cases. Length of hospital stay was moderately positively correlated to maximal CK. The presence of comorbid medical conditions resulted in longer lengths of stay. Most hospitalizations for exertional rhabdomyolysis (60.1%) were associated with heat illness and these cases had lower initial values of creatine kinase (mean 6,528 U/L).

DEDICATION

For the warfighters
who secure our freedom
around the world

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INTRODUCTION

Exertional rhabdomyolysis (ER) typically occurs in a generally health population following vigorous exercise.¹⁻⁸ ER is a syndrome of muscle injury and its related sequelae which include acute kidney injury, myoglobinuria, compartment syndrome, electrolyte abnormalities, and coagulopathy. Diagnosis of exertional rhabdomyolysis is made when there is laboratory evidence of myonecrosis following excessive physical activity.^{3,9} Creatine kinase (CK) of at least five times the upper limit of normal reflects significant muscle breakdown. Severity ranges from mild to life-threatening and prognosis is poorly described in the literature.^{1,3} In mild cases, outpatient management is appropriate.^{8,9} Hospitalization is often recommended for severely elevated CK levels or the presence of high-risk markers including myoglobinuria, acute kidney injury, elevated troponin, or other metabolic abnormality. There are no established limits for CK that warrant hospitalization, though some guidelines suggest outpatient management of rhabdomyolysis may be appropriate if the serum CK levels are between 20,000 and 50,000 U/L in the absence of high-risk markers.⁹

Inpatient treatment typically involves aggressive hydration, reversing metabolic disturbances, and laboratory monitoring until creatine kinase trends downward and renal function improves. The literature does not report standard regimens for intravenous hydration or universal criteria for appropriate hospital discharge. In studies on rhabdomyolysis requiring hospitalization, CK was consistently downtrending at time of discharge with wide variation in the median CK level at time of discharge.^{1,2,7} There are no consistent trends reported for length of stay, mortality, and readmission.^{2,4} Follow-up and guidelines for return to physical activity are also inconsistent. Three studies recommended that in typically circumstances patients can return to physical activity following resolution of clinical symptoms and major laboratory abnormalities.^{3,5,10}

Early recognition and treatment of exertional rhabdomyolysis is particularly important in military servicemembers, as ER related to military training activities can significantly affect long-term health and impair performance of military duties and training..^{3,5,6} Military training is often implicated as a common cause of exertional rhabdomyolysis..^{3,5,6} ER in the military occurs most frequently among males younger than 20 years old.¹¹ A 2015 case series characterizing trends of 30 servicemembers hospitalized for ER describes a mean admission CK of 61,000 U/L, mean discharge CK of 23,000 U/L, and correlations of higher CK predicting longer length of stay and higher creatinine correlated to lower CK.²

Rhabdomyolysis may present as a distinct clinical diagnosis or in conjunction with exertional heat illness (EHI). Strenuous physical activity and military training place servicemembers at simultaneous risk for both ER and EHI and the two are often encountered in tandem..^{2,3,5} Exertional heat illnesses include a spectrum of disorders including heat cramps, heat syncope, heat exhaustion, heat injury, and heat stroke.

We previously reported a case series of 30 servicemembers hospitalized for exertional rhabdomyolysis.. This retrospective cohort study expands on the study and describes laboratory trends of all servicemembers and correlations to length of hospitalization for exertional rhabdomyolysis. In addition, since there are little data comparing the behaviors of CK, serum creatinine, and hospital length of stay in exertional rhabdomyolysis with and without associated heat illness, this study will also examine the relationship of ER and heat illness.

METHODS

This was a retrospective cohort study using data from the Armed Forces Health Surveillance Center. Study subjects included all active duty servicemembers admitted for rhabdomyolysis (ICD-9 code 728.88) from January 2010 through July 2013. There is no ICD-9

code for rhabdomyolysis secondary to exertion. For inclusion, subjects must have been diagnosed and hospitalized for rhabdomyolysis as determined with a discharge diagnosis in any position of: “rhabdomyolysis” (ICD-9-CM: 728.88) and/or “myoglobinuria” (ICD-9-CM: 791.3); plus a diagnosis in any position of “volume depletion/dehydration” (ICD-9-CM: 276.5) and/or “effects of heat” (ICD-9-CM: 992.0-992.9) and/or “effects of thirst (deprivation of water),” “exhaustion due to exposure,” and “exhaustion due to excessive exertion (overexertion)” (ICD-9-CM: 994.3-994.5). Subjects with ICD-9 codes for traumatic injuries, intoxications, or adverse drug reactions were excluded.

403 cases of exertional rhabdomyolysis were identified, and 15 cases were excluded for incomplete data. 67 additional cases were excluded for maximal CK levels of <1,000 U/L. ICD-9 codes associated with each case were reviewed by a team of study investigators, comprised of two family medicine physicians and one family and sports medicine physician. All cases were stratified into categories by consensus of study investigators: exertional rhabdomyolysis without a heat-related illness (ER-NonHeat, n=104); exertional rhabdomyolysis with a comorbid heat-related illness (ER-Heat, n=193); and ER associated with other medical conditions (ER-Medical, n=24). ER-Medical included subjects with comorbid active infectious diseases (e.g. pneumonia, gastroenteritis) and other significant chronic medical conditions.

Data analysis was performed in RStudio 1.2.5042. The Mann-Whitney-Wilcoxon rank sum test was used to compare median length of stay, creatine kinase, and creatinine. Differences by category and military grade were assessed by Kruskal-Wallis test. Spearman's rank correlation coefficients were calculated to assess correlations between age, length of stay, and laboratory data. The Institutional Review Board at Uniformed Services University reviewed and approved the study as an exempt protocol; the Human Subjects Division at the University of Washington (UW) determined that this study did not require additional review by the UW IRB.

RESULTS

We identified 321 cases of exertional rhabdomyolysis admitted to the hospital from 2010-2013, of which 94% were male and 6% were female with an average age of 25.2 years (range 17-52). By military grade, 87% were enlisted and 13% were Officers. There were no readmissions for rhabdomyolysis within 30 days identified. Of the 321 cases, 193 (60.1%) were associated with heat (ER-Heat), 104 (32.4%) were not associated with heat (ER-NonHeat) and 24 (7.5%) were classified as medical-related exertional rhabdomyolysis (ER-Medical). Additional demographics are listed in Table 1.

Length of Stay

The median length of stay was 2 days with a range of 0-25 days (see Table 1). Stratified by category, median length of stay was 2 days in the ER-Heat and ER-NonHeat groups, and 4 days in the ER-Medical group (Kruskal-Wallis $\chi^2 = 13.52$, p-value = 0.001). There were significant differences between median length of stay in the ER-NonHeat and ER-Medical groups (2 vs. 4; 95% CI -3.00 – -1.00; p < 0.001) and between the ER-Heat and ER-Medical groups (2 vs. 4; 95% CI -3.00 – -1.00; p < 0.001). There was no significant difference in median length of stay between the ER-NonHeat and ER-Heat groups (2 vs. 2; 95% CI -0.00007 – 0.000009; p-value = 0.955). . There was no difference in median length of stay by gender (2 vs. 2; 95% CI -0.00005 – 1.00001; p-value = 0.267). Median length of stay did not differ by military grade (Kruskal-Wallis $\chi^2 = 2.50$, p-value = 0.474).

Laboratory Data

Mean, and median, and range CK and creatinine levels are reported in Table 2 and Table 3, respectively. Median initial, maximum, and minimal CK were higher in the ER-NonHeat group versus the ER-Heat group (p < 0.001, p = 0.015, and p < 0.0001, respectively). Median initial and maximal CK were higher in the ER-Medical group compared to the ER-Heat group (p = 0.020, p = 0.040). There were no statistically significant differences in median CK levels between ER-NonHeat and ER-Medical.

Table 1. Demographics.

	Total	ER-NonHeat	ER-Heat	ER-Medical
Subjects (n)	321	104	193	24
Mean Age (years)	25.2	25.5	25.2	24.6
Length of stay (days)	2.65	2.50	2.56	4.04
Readmissions	0	0	0	0
Gender				
Male	302 (94%)	98 (94%)	186 (96%)	18 (75%)
Female	19 (6%)	6 (6%)	7 (4%)	6 (25%)
Grade				
E1-E4	204 (64%)	70 (67%)	116 (60%)	18 (75%)
E5-E9	75 (23%)	22 (21%)	47 (24%)	6 (25%)
O1-O5	41 (13%)	12 (12%)	29 (15%)	0 (0%)
O6-O10	0 (0%)	0 (0%)	0 (0%)	0 (0%)
WO	1 (0%)	0 (0%)	1 (1%)	0 (0%)

Table 2. Laboratory Data: Creatine Kinase (CK)

	Initial CK (U/L)			Maximal CK (U/L)			Minimal CK (U/L)		
	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range
ER-NonHeat	19,247 (37,097)	4,092	299-271,000	22,201 (38,667)	4,927	1,081-271,000	10,321 (29,124)	2,537	100-271,000
ER-Heat	6,528 (12,010)	2,000	118-113,024	13,146 (25,257)	3,434	1,037-245,248	3,618 (6,201)	1,611	27-41,721
ER-Medical	9,731 (11,862)	4,228	555-45,047	13,304 (12,821)	10,174	1,322-47,784	5,923 (7,105)	1,768	380-29,785
Total	10,888 (24,027)	2,597	118-271,000	16,092 (29,969)	2,597	1,037-271,000	5,962 (17,645)	2,000	27-271,000

Table 3. Laboratory Data: Creatinine

	Initial Creatinine (mg/dL)			Maximal Creatinine (mg/dL)		
	Mean (SD)	Median	Range	Mean (SD)	Median	Range
ER-NonHeat	1.71 (1.23)	1.10	0.54-5.80	1.80 (1.33)	1.10	0.54-5.80
ER-Heat	1.50 (0.62)	1.42	0.40-3.20	1.51 (0.67)	1.40	0.50-4.10
ER-Medical	1.90 (2.36)	1.05	0.50-8.10	2.26 (2.39)	1.10	0.51-8.10
Total	1.61 (1.12)	1.27	0.50-8.10	1.68 (1.20)	1.20	0.50-8.10

CK levels varied by gender and military grade. Mean initial CK was different between female and male, 6,268 U/L versus 11,179 U/L, respectively (95% CI -8,802 to -1019; $p = 0.014$). Mean maximal CK was also different between female and male, 9,155 U/L versus 16,528 U/L (95% CI -12,977 to -1,768; $p = 0.011$). There were no statistically significant differences between military grade and initial CK (Kruskal-Wallis $\chi^2 = 7.618$, p -value = 0.055) or between military grade and maximal CK (Kruskal-Wallis $\chi^2 = 5.044$, p -value = 0.169).

The initial median creatinine in all groups was 1.27 mg/dL (range 0.50-8.10) and maximal medial creatinine of 1.20 mg/dL (range 0.51-8.10). There were no statistically significant differences by category.

Exploratory correlations

Correlations were explored to examine the relationship between CK, creatinine, length of stay, and demographic data (see Table 4). Length of stay was weakly positively correlated to both initial CK (Spearman's $\rho = 0.29$; $p < 0.001$) and moderately positively correlated to maximal CK (Spearman's $\rho = 0.44$; $p < 0.001$). Maximal CK was not correlated to initial creatinine (Spearman's $\rho = -0.14$; $p = 0.185$) or maximal creatinine (Spearman's $\rho = -0.14$; $p = 0.163$). Age was weakly negatively correlated to initial CK (Spearman's $\rho = -0.16$; $p = 0.005$), but not to

maximal CK (Spearman's $\rho = -0.10$; $p = 0.074$) or length of stay (Spearman's $\rho = -0.06$; $p = 0.261$).

Correlations were explored in the ER-Heat and ER-NonHeat groups separately. In the ER-NonHeat group, length of stay was moderately positively correlated to maximal CK (Spearman's $\rho = 0.52$; $p < 0.001$). In the ER-Heat group, length of stay was also weakly positively correlated to maximal CK (Spearman's $\rho = 0.38$; $p < 0.001$). Length of stay was more positively correlated to initial CK in the ER-NonHeat group (Spearman's $\rho = 0.48$; $p < 0.001$) compared to the ER-Heat group (Spearman's $\rho = 0.21$; $p = 0.003$). There were no statistically significant correlations found between length of stay and creatinine in either group.

Table 4. Spearman's rank correlation coefficient matrix for selected variables.

Creatinine, max	-0.14 $p = 0.163$		
Length of Stay	0.44 $p < 0.001$	0.10 $p = 0.309$	
Age	-0.10 $p = 0.074$	0.24 $p = 0.014$	-0.06 $p = 0.261$
	CK, max	Creatinine, max	Length of Stay

DISCUSSION

This is the largest retrospective cohort study of exertional rhabdomyolysis that we are aware of in the literature. In the 321 cases of ER, the majority (60.1%) were associated with heat illness and 32.4% as pure exertional rhabdomyolysis. The intense physical training and occupational demands of military servicemembers place them at higher risk for exertional illness and injury. Not surprisingly, exertional rhabdomyolysis is more common in physically active

populations such as military servicemembers and athletes.⁴⁻⁶ In another recent cohort study of 430 rhabdomyolysis cases, only 21 had exertional rhabdomyolysis. Similar to our study, 90% of the 21 cases were male and the mean length of hospitalization was two days.¹³ Other studies on exertional rhabdomyolysis have helped to characterize laboratory trends associated with ER hospitalization. CK is typically normalized or trending downward at time of discharge, though median CK at time of discharge varies widely.^{1,2,7} No standard criteria for hospital discharge have been identified but this study informs the practice patterns of clinicians. This study supports prior studies, with downtrending CK levels observed throughout hospitalization and a median minimal CK of 2,000 U/L (interquartile range 954 – 4,607).

Few correlations were identified among laboratory and demographic data. This study found moderately positive correlations between CK and length and stay, and correlations within ER-NonHeat and ER-Heat groups were similar. Length of stay was more positively correlated to initial CK in the ER-NonHeat group versus the ER-Heat group. A prior study has identified stronger correlations.² This study was a smaller cohort at one institution and may have been related to institutional practice. Age was weakly negatively correlated to initial CK but not to maximal CK or length of stay. This study describes significantly lower mean CK values in females and no differences based on military grade.

When stratified by category based on the presence of heat illness or other medical conditions, only few differences were observed. Initial CK and minimal CK levels were higher in the ER-NonHeat group compared to the ER-Heat group, with no difference in maximal values. This may represent pathophysiological differences between pure exertional rhabdomyolysis (direct injury to muscles leading to necrosis) and exertional heat illness (muscle injury secondary to systemic inflammation).^{14,15} Further analysis may test this hypothesis by examining this interval as well as measuring time to peak CK in heat and non-heat groups.

There are several limitations to this study. First, as there is no ICD-9 code for exertional rhabdomyolysis, and inclusion and exclusion criteria were utilized to help distinguish exertional

cases from other types of rhabdomyolysis. Second, grouping into categories by the presence of heat illness or other medical comorbidities was completed only by review of ICD-9 codes and adjudicated by expert opinion. Third, this study only included subjects with maximal CK levels of at least 1,000 U/L which is consistent with ER diagnostic guidelines.⁸ The initial data pull included 67 subjects who were diagnosed with rhabdomyolysis (ICD-9 728.88) but whose maximal CK levels were less than 1,000 U/L; these subjects were excluded from our analysis and indicate non-standard diagnostic criteria for exertional rhabdomyolysis. One study in a military population even contends that a CK greater than 50 times the upper limit of normal is more specific for a diagnosis of rhabdomyolysis rather than a lower multiple.⁶

In conclusion, this study described trends and correlations in 321 cases of exertional rhabdomyolysis cases and investigated the relationship of accompanying heat illness. Heat illness with associated rhabdomyolysis warranting hospitalization in servicemembers appear to present more frequently than ER not associated with heat illness. Exertional rhabdomyolysis as a sequela of heat injury presents with lower initial CK levels. The presence of other medical conditions or comorbidities is associated with a longer length of stay. This data may help clinicians better understand the presentation and course of exertional rhabdomyolysis with and without associated heat illness.² Further research should explore the impact of heat illness severity on ER, disease prognosis, and continue to differentiate and define heat versus non-heat-related rhabdomyolysis.

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