Cigarette Smoking and ARDS After Blunt Trauma

The Influence of Changing Smoking Patterns and Resuscitation Practices

Farzad Moazed, MD; Carolyn Hendrickson, MD; Amanda Conroy, BA; Lucy Z. Kornblith, MD; Neal L. Benowitz, MD; Kevin Delucchi, PhD; Mitchell J. Cohen, MD; and Carolyn S. Calfee, MD, MAS

BACKGROUND: Cigarette smoking is associated with an increased risk of developing ARDS. However, whether changes in smoking patterns or processes of care impact this relationship is unclear.

RESEARCH QUESTION: Are changes in smoking and resuscitation patterns associated with changes in the relationship between smoking and ARDS?

STUDY DESIGN AND METHODS: We conducted a prospective cohort study of critically injured adults with blunt trauma from 2005 to 2015. Plasma cotinine, a tobacco biomarker, was measured to categorize patients by smoking status. We used regression to assess the relationship between smoking, resuscitation practices, and ARDS over time.

RESULTS: In the overall cohort, active (OR, 1.9; 95% CI, 1.0-3.5; $P = .046$) and passive (OR, 2.6; 95% CI, 1.4-4.8; $P = .002$) smoking were associated with an increased risk of developing ARDS in multivariate analyses. In contrast to the dose-response relationship in patients enrolled from 2005 to 2008, passive cigarette smoke exposure was associated with the highest risk of developing ARDS in patients enrolled from 2009 to 2015, suggesting a threshold effect. Packed RBC (pRBC) and fresh frozen plasma (FFP) transfusions were associated with an increased risk of developing ARDS, particularly in active smokers (pRBC: OR, 5.6; $P < .001$; FFP: OR, 4.5; $P < .001$) compared with passive smokers or nonsmokers. Blood product transfusion and smoking patterns changed over time.

INTERPRETATION: Despite changes in resuscitation and smoking patterns, cigarette smoking remains associated with an increased risk of developing ARDS. However, this relationship changed over time, with passive smokers at particularly increased risk of developing ARDS in later years, which may be related to changes in smoking patterns or transfusion practices over time. These findings highlight the need for additional mechanistic and epidemiologic studies of the effects of low levels of cigarette smoke exposure on lung health.

CHEST 2020; 158(4):1490-1498

KEY WORDS: ARDS (acute respiratory disease syndrome); smoking; transfusion; trauma

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ABBREVIATIONS: FFP = fresh frozen plasma; ISS = Injury Severity Score; pRBC = packed RBC; TBI = traumatic brain injury

AFFILIATIONS: From the Department of Medicine (Drs Moazed, Hendrickson, Benowitz, and Calfee) and the Center for Tobacco Control Research and Education (Drs Moazed, Benowitz, Delucchi, and Calfee), University of California San Francisco, San Francisco, CA;

Department of Medicine (Dr Moazed), Highland Hospital, Oakland CA; Zuckerberg San Francisco General Hospital (Ms Conroy; and Drs Kornblith and Benowitz), San Francisco, CA; the Department of Psychiatry (Dr Delucchi), University of California San Francisco, San Francisco, CA; the Department of Surgery (Dr Cohen), University of Colorado, Denver, CO; the Department of Anesthesia and the

Cigarette smoking has been identified as a risk factor for ARDS in several populations. In blunt trauma patients, we previously reported that active and heavy passive smokers have an increased risk of ARDS.¹ Similarly, smoking is associated with an increased risk of ARDS after blood transfusion,² in nonpulmonary sepsis,³ and after lung transplantation.⁴

Our initial report that active and passive cigarette smoking were associated with an increased risk of ARDS after trauma included patients enrolled between 2005 and February 2009.¹ Since this initial report, there have been significant changes in trauma-related resuscitation practices, including decreased crystalloid administration and a shift toward balanced blood product administration.^{5,6} Furthermore, changes have occurred

in cigarette use patterns. Although the number of daily smokers in the United States is decreasing, the number of intermittent smokers is increasing.⁷⁻⁹ In the last decade, the proportion of smokers in the United States who smoke one to nine cigarettes daily increased from 16.4% to 25%, whereas those who smoke more than a pack daily decreased from 47.6% to 35.9%.^{9,10} The impact of these changes in cigarette use patterns and trauma resuscitation on the relationship between cigarette smoke exposure and ARDS is unknown.

In this study, we examined the relationship between cigarette smoke exposure and ARDS over time, with a focus on how changes in smoking exposure and resuscitation practices may impact ARDS development.

Methods

Subjects

We studied 635 blunt trauma patients admitted to the ICU in a prospective observational cohort study at a level 1 trauma center. Median dispatch to ED transit time was 25 minutes. Adult patients meeting criteria for full trauma activation between 2005 and 2015 were included. We divided patients into those enrolled in our prior analysis (2005-2008) and since (2009-2015). Data collection for this cohort has been described previously.¹¹ Patients underwent blood draw within 10 minutes of ED arrival. Comprehensive demographic and clinical information were obtained until discharge or death. Injury Severity Score (ISS) was used to assess injury severity.¹² Alcohol use history was obtained from chart review, and whenever possible, from patients or surrogates, using the previously validated Alcohol Use Disorders Identification Test.¹³ Blood product usage included intraoperative products. Recreational drug use was obtained from chart review or urine toxicological studies when available. ARDS adjudication was performed by two-physician review during the first 7 days of hospitalization according to the Berlin definition¹⁴; physicians were blinded to smoking and resuscitation status of each patient. The San Francisco General Hospital Committee of the University of California at San Francisco Research Protection Program and Institutional Review Board approved the protocol and granted a waiver of consent for blood sampling as a minimal risk

intervention (approval #10-04417). Informed consent was subsequently obtained from patients or surrogates for continued study participation.¹

Measurements

Plasma cotinine, a metabolite of nicotine with a half-life averaging 16 hours that quantifies recent cigarette smoke exposure,¹⁵ was measured on baseline plasma samples via liquid chromatography-tandem mass spectrometry.^{16,17} The limit of quantification for cotinine was 0.02 ng/mL. Based on previous analyses, passive smokers were defined as those with a plasma cotinine level of 0.02 to 3.08 ng/mL.¹⁸ A cutoff of 0.19 ng/mL, representing the median cotinine level among passive smokers in our prior study, was used to differentiate between low and high passive exposure.¹ Active smokers were those with cotinine levels above 3.08 ng/mL.¹⁸

Statistical Analysis

We used Pearson χ^2 test to compare categorical variables, Student *t* test, or analysis of variance to compare normally distributed variables, and Mann-Whitney Wilcoxon *U*-test or Kruskal-Wallis test to compare non-normally distributed variables. Normal variables were presented as mean with SD, whereas non-normally distributed variables were presented as median with interquartile range. Logistic regression was used to assess the relationship between cigarette smoking status and the outcome of ARDS in the overall cohort and during the two previously described periods within our study. Multivariate logistic regression was performed to adjust for potential confounders; we selected confounders that differed between smoking groups and had known relevance to ARDS, including age, sex, race, diabetes, alcohol misuse, ISS, and traumatic brain injury (TBI). We hypothesized that cigarette smoking may predispose cigarette smokers to develop ARDS after trauma, particularly in the setting of resuscitation with crystalloid or blood products, via subclinical alveolar epithelial or endothelial dysfunction. Thus, we performed logistic regression with an interaction term between cigarette smoke exposure and blood products or crystalloid for the outcome of ARDS to assess whether the relationship between administration of these products and ARDS differed based on cigarette smoke exposure status. Log transformation using a small positive constant was used for analyses as needed. *P* ≤ .05 was considered statistically significant. Statistical analyses were performed with STATA 15.0 (StataCorp LP).

Cardiovascular Research Institute (Dr Calfee), University of California San Francisco, San Francisco, CA.

Presented in abstract form at the American Thoracic Society International Conference, May 18-23, 2018, San Diego, CA.

FUNDING/SUPPORT: NHLBI HL110969, HL140026 (to C. S. C.); NHLBI HL136844 (to F. M.), Department of Defense W911NF-10-1-0384 (to M. J. C.), P30 DA102393 (to N. L. B.), NIGMS GM130892 (to L. Z. K.).

CORRESPONDENCE TO: Farzad Moazed, MD, UCSF Department of Medicine, Division of Pulmonary and Critical Care Medicine, 505 Parnassus Ave, M1097, San Francisco, CA 94143; e-mail: farzad.moazed@ucsf.edu

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DOI: <https://doi.org/10.1016/j.chest.2020.05.603>

Results

Demographics

In the overall cohort, both active ($n = 291$, 46%) and passive ($n = 190$, 30%) cigarette smokers were more likely to be young, male, and black, to use illicit drugs, to misuse alcohol, and to have lower rates of diabetes compared with nonsmokers (Table 1). Active smokers also had lower rates of TBI and malignancy than nonsmokers (Table 1). No significant differences were seen in ISS, chest abbreviated injury scale, or shock.

Cigarette Smoking and ARDS

We first compared the risk of developing ARDS in passive and active smokers with that of nonsmokers in the overall cohort (2005-2015). In multivariate analyses adjusting for age, sex, race, diabetes, TBI, ISS, and alcohol misuse, both

passive (OR, 2.6; 95% CI, 1.4-4.8; $P = .001$) and active (OR, 1.9; 95% CI, 1.0-3.5; $P = .046$) smoking were associated with increased odds of developing ARDS (Table 2).

Given that passive smokers were at particularly increased risk of developing ARDS, we divided patients into those with and those without detectable cotinine levels. We found that any exposure to cigarette smoke was associated with increased odds of developing ARDS in multivariate models (OR, 2.3; 95% CI, 1.3-4.0; $P = .004$) in the overall cohort (e-Table 1). We did not detect any significant relationship between log-transformed plasma cotinine as a continuous variable and ARDS in the overall cohort. These results suggest a threshold effect in the relationship between cigarette smoke exposure and ARDS rather than a dose-response relationship, as we had previously observed (e-Fig 1).

TABLE 1] Overall Demographics

Characteristic	Nonsmokers ($n = 154$)	Passive Smokers ($n = 190$)	Active Smokers ($n = 291$)	P
Plasma cotinine, ng/mL	0 (0-0)	0.18 (0.10-0.44)	120.0 (41.6-203.7)	.0001
Age, y	59 (21)	48 (22)	40 (15)	< .0001
Male, No. (%)	93 (60%)	137 (72%)	243 (84%)	< .001
Race				< .001
White	92 (60%)	121 (64%)	190 (65%)	
Asian	42 (27%)	36 (19%)	32 (11%)	
Black	6 (4%)	12 (6%)	50 (17%)	
Other/Unknown	14 (9%)	21 (11%)	19 (7%)	
BMI	26 (5)	27 (6)	26 (5)	.29
Alcohol misuse ^a				< .001
Yes	21 (14%)	57 (30%)	124 (43%)	
No	80 (52%)	80 (42%)	96 (33%)	
Unknown	53 (34%)	53 (28%)	71 (24%)	
Drug Use ^b				
Opiates	1 (1%)	7 (4%)	29 (11%)	< .001
Cocaine	3 (2%)	11 (7%)	61 (23%)	< .001
Methamphetamine	1 (1%)	5 (3%)	39 (15%)	< .001
Marijuana	7 (6%)	18 (11%)	58 (22%)	< .001
Malignancy	10 (7%)	15 (8%)	5 (2%)	.002
Diabetes	31 (20%)	21 (11%)	12 (4%)	< .001
Injury severity score	26 (12-33)	25 (10-30)	22 (10-30)	.36
Chest Abbreviated Injury Scale	0 (0-3)	0 (0-3)	0 (0-3)	.78
Traumatic Brain Injury ^c	111 (72%)	129 (68%)	173 (59%)	.02
Shock (SBP < 90)	11 (7%)	14 (7%)	17 (6%)	.77

Cotinine < 0.02 ng/mL = nonsmokers. Cotinine $\geq$ 0.02 ng/mL & < 3.08 ng/mL = passive smokers. Cotinine $\geq$ 3.08 ng/mL = active smokers. Normally distributed variables are presented as mean (SD). Non-normally distributed variables are presented as median (IQR). SBP = systolic BP.

^aBy chart review or alcohol use disorders identification test (AUDIT), when completed by patient or surrogate.

^bBy chart review, drug use status unknown for 31 nonsmokers, 32 passive smokers, 31 active smokers.

^cAny of the following conditions: epidural hematoma, subdural hematoma, subarachnoid hemorrhage, brain contusion, intraventricular hemorrhage, midline shift, diffuse axonal injury, intraventricular hemorrhage.

TABLE 2] Odds of Developing ARDS After Trauma by Plasma Cotinine Smoking Status

Smoking Status ^a	Univariate		Multivariate ^b	
	OR (95% CI)	P	OR (95% CI)	P
2005-2015 (n = 635)				
Passive smokers (n = 190)	2.1 (1.2-3.5)	.007	2.6 (1.4-4.8)	.002
Active smokers (n = 291)	1.5 (0.9-2.5)	.11	1.9 (1.0-3.5)	.046
2009-2015 (n = 491)				
Passive smokers (n = 148)	2.2 (1.2-4.0)	.02	3.4 (1.6-7.1)	.001
Active smokers (n = 215)	1.1 (0.6-2.1)	.67	1.6 (0.8-3.5)	.21

^aCotinine < 0.02 ng/mL = nonsmokers. Cotinine ≥ 0.02 ng/mL & < 3.08 ng/mL = passive smokers. Cotinine ≥ 3.08 ng/mL = active smokers. All analyses were performed with nonsmokers as the reference group.

^bAge, sex, race, diabetes, traumatic brain injury, injury severity score, and alcohol misuse.

We found that ARDS incidence in our cohort declined over time, from 42% in 2005 to 2008 to 18% from 2009 to 2015 ($P < .0001$), independent of ISS ([e-Fig 2](#)). We then studied whether changes in processes of care may have also occurred over time. First, we compared the administration of IV crystalloid and blood products between smoking groups. Active and passive smokers received fewer platelet transfusions (13% vs 15% vs 23%; $P = .02$) and higher amounts of IV crystalloid (4.6 vs 4.7 vs 3.9 L; $P = .03$) compared with nonsmokers, with no differences in packed RBC (pRBC), fresh frozen plasma (FFP), or cryoprecipitate transfusions in the first 24 hours of admission ([e-Table 2](#)). Next, we compared key demographic variables and resuscitation practices between our two time periods. In more recent years, patients had lower rates of TBI and ISS, although the chest abbreviated injury scale was unchanged ([Table 3](#)). In addition, recently enrolled patients had significantly decreased levels of crystalloid administered and decreased transfusion of pRBCs, platelets, FFP, and cryoprecipitate in the first 24 hours after trauma, although no difference was found in the pRBC:FFP ratio. No differences were seen in day 1 tidal volumes or positive end-expiratory pressure ([Table 3](#)).

Next, we examined whether the relationship between cigarette smoke exposure and ARDS changed over time. In the subgroup of patients comprising those enrolled since our prior analyses (2009-2015), a statistically significantly increased risk of ARDS was seen in passive (OR, 3.3; 95% CI, 1.6-6.8; $P = .002$) but not active smokers (OR, 1.6; 95% CI, 0.8-3.4, $P = .22$) compared with nonsmokers in multivariate analyses ([Table 2](#)). Compared with active smokers, passive smokers had increased odds of developing ARDS (OR, 2.0; 95% CI, 1.1-3.8; $P = .03$). In our prior work including patients from 2005 through February 2009, we reported that

active smokers and patients with heavy passive exposure had an increased risk of developing ARDS compared with nonsmokers and those with low levels of passive cigarette smoke exposure.¹ However, in patients enrolled between 2009 and 2015, those with low levels of passive cigarette smoke exposure had the highest rate of ARDS ([Fig 1](#)), with increased odds of developing ARDS compared with nonsmokers (OR, 3.8; 95% CI, 1.7-8.9; $P = .002$) in a multivariate model. These findings suggest that over time a shift occurred in the relationship between cigarette smoke exposure and ARDS, with a relatively increasing risk in patients with low levels of exposure.

We next studied whether key processes of care impacted patients with cigarette smoke exposure differently from those without exposure. In multivariate logistic regression with ARDS as the outcome, we found a statistically significant interaction between cigarette smoke exposure and pRBC transfusion ($P = .04$) and FFP ($P = .03$), but not IV crystalloid or other blood products. For every SD increase in pRBCs transfused, the odds of developing ARDS was higher in active smokers (OR, 5.6; 95% CI, 2.6-11.8; $P < .001$) than in passive smokers (OR, 1.8; 95% CI, 1.1-3.0; $P = .02$) or nonsmokers (OR, 1.9; 95% CI, 1.2-2.9; $P = .004$) ([Fig 2](#)). Similarly, for every SD increase in FFP transfused, the odds of developing ARDS were higher in active smokers (OR, 4.5; 95% CI, 2.2-9.0; $P < .001$) than in passive smokers (OR, 2.1; 95% CI, 1.2-3.8; $P = .01$) or nonsmokers (OR, 1.9; 95% CI, 1.2-2.8; $P = .005$) ([Fig 2](#)). Inclusion of prehospital IV crystalloid did not change our findings (data not shown). These findings suggest that pRBC and FFP transfusion in the first 24 hours are associated with an increased risk of developing ARDS in patients with cigarette smoke exposure to a greater extent than in those without exposure.

TABLE 3] Demographics and Processes of Care in Patients Enrolled Before and After 2009

Characteristic/Variable	Cohort 2005-2008 ^a (n = 144)	Cohort 2009-2015 (n = 491)	P
Age, y	48 (20)	46 (20)	.32
Male	105 (73%)	368 (75%)	.62
Race			.01
White	87 (60%)	316 (64%)	
Asian	34 (24%)	76 (15%)	
Black	18 (12%)	50 (10%)	
Other/unknown	5 (3%)	49 (10%)	
Smoking status ^b			.07
Nonsmokers	27 (19%)	127 (26%)	
Passive smokers	53 (37%)	137 (28%)	
Active smokers	64 (44%)	227 (46%)	
Alcohol misuse ^c			< .001
Yes	37 (26%)	165 (34%)	
No	39 (27%)	217 (44%)	
Unknown	68 (47%)	109 (22%)	
Injury Severity Score	26 (17-35)	22 (10-30)	< .0001
Chest Abbreviated Injury Scale	0 (0-3)	0 (0-3)	.62
Traumatic Brain Injury ^d	104 (72%)	309 (63%)	.04
Shock (SBP < 90)	11 (8%)	31 (6%)	.59
Any pRBC transfused, 24 h	76 (53%)	188 (38%)	.001
pRBC transfused, units, 24 h	1 (0-5)	0 (0-2)	.0001
Any platelets transfused, 24 h	30 (21%)	71 (14%)	.05
Platelets transfused, units, 24 h	0 (0-0)	0 (0-0)	.05
Any fresh frozen plasma transfused, 24 h	55 (38%)	132 (27%)	.005
Fresh frozen plasma transfused, units, 24 h	0 (0-4)	0 (0-1)	.001
Any cryoprecipitate transfused, 24 h	13 (9%)	17 (3%)	.003
Cryoprecipitate transfused, units, 24 h	0 (0-0)	0 (0-0)	.003
pRBC: Fresh frozen plasma, 24 h	1.3 (0.9-2.0)	1.2 (1.0-1.8)	.44
Crystalloid, L, 24 h	6.0 (4.3-10)	4.1 (2.7-5.9)	< .0001
Colloid, L, 24 h	0 (0-0)	0 (0-0)	.14
Tidal volume, cc/kg	7.9 (1.3)	8.0 (4.3)	.89
PEEP (cm H ₂ O)	6 (2)	6 (2)	.33

pRBC = packed RBC.

^aTwo patients in this timeframe were enrolled in January-February 2009.^bCotinine < 0.02 ng/mL = nonsmokers. Cotinine ≥ 0.02 ng/mL & < 3.08 ng/mL = passive smokers. Cotinine ≥ 3.08 ng/mL = active smokers. Normally distributed variables are presented as mean (SD). Non-normally distributed variables are presented as median (IQR).^cBy chart review or alcohol use disorders identification test (AUDIT), when completed by patient or surrogate.^dAny of the following conditions: epidural hematoma, subdural hematoma, subarachnoid hemorrhage, brain contusion, intraventricular hemorrhage, midline shift, diffuse axonal injury, intraventricular hemorrhage.

Discussion

In this study, we report that despite changes in trauma resuscitation and declining ARDS incidence, cigarette smoking remains associated with an increased risk of developing ARDS. However, we observed a changing pattern over time, with passive smokers particularly vulnerable to developing ARDS in more recent years. Even patients with low levels of

passive cigarette smoke exposure were at increased risk of developing ARDS, independent of demographics and injury severity. Notably, we found that pRBC and FFP transfusion in the first 24 hours after trauma were associated with an increased risk of ARDS to a greater extent in patients with higher levels of cigarette smoke exposure and that transfusion of these products decreased over time.

Figure 1 – Changes in the proportion of severe blunt trauma patients with ARDS by smoking status by study time period.

In the early years of this cohort, increasing cigarette smoke exposure was associated with an increased risk of developing ARDS, with the highest risk in patients with the highest exposure. However, this pattern changed over time. Although ARDS incidence dropped across all groups over time, in recent years, passive smokers had the highest risk of developing ARDS, largely driven by a decrease in the risk of ARDS in patients with the highest exposure, suggesting a threshold effect. The potential threshold effect in the relationship between cigarette smoke and ARDS that we found is supported by recent

cell- and animal-based studies.^{19,20} The change in the relationship between cigarette smoke exposure and ARDS may be in part due to changing demographics amongst smokers. Stricter smoking bans, including a local ban in multi-unit dwelling common areas and local secondhand smoking ordinances, took effect in the second half of this study, potentially decreasing secondhand smoke exposure. This hypothesis is supported by the reduction in passive smokers we observed from 38% in 2005 to 2008 to 30% in 2009 to 2015, with a concomitant increase in nonsmokers. In

Figure 2 – Forest plot depicting the odds of developing ARDS in the overall population, nonsmokers, passive smokers, and active smokers for each SD increase in pRBC transfusion and fresh frozen plasma transfusion (n = 635, 2005-2015). FFP = fresh frozen plasma; pRBC = packed RBC.

addition, there may have been a change in the type of smoke exposure in patients with cotinine levels in the passive range. The prevalence of nondaily smoking,²¹ which may lead to cotinine levels in the passive range,²² is increasing. Coupled with decreases in secondhand smoke exposure, this change in use pattern may have resulted in some misclassification, with larger numbers of “passive smokers” being intermittent active users rather than nonsmokers with secondhand smoke exposure, and who may be at greater risk of developing ARDS. Furthermore, some of these patients may have used increasingly popular alternative tobacco products, such as e-cigarettes, which contain nicotine and result in detectable levels of plasma cotinine.²³ We cannot exclude the possibility that polytobacco or alternative tobacco product use may impact the risk of developing ARDS. Further epidemiologic and mechanistic studies are needed to understand emerging patterns of tobacco product use and their effects on lung health.

Another possible explanation for our observations is a shift in pro/antiinflammatory imbalance with lower levels of smoking. Although cigarette smoke has numerous pro-inflammatory properties, cigarettes also possess antiinflammatory properties, which are mediated through activation of alpha-7 nicotinic receptors by nicotine.²⁴ Activation of this pathway is associated with decreased inflammation and improved survival in animal models of sepsis^{24,25} but less is known about its effects in the setting of ARDS, although some evidence suggests that it may decrease inflammation.²⁶ Thus, patients with lower levels of cotinine, a nicotine metabolite, may have less activation of nicotine-related antiinflammatory pathways while still having activation of pro-inflammatory pathways associated with other components of cigarette smoke.

Our findings are consistent with prior studies that have indicated that early blood product transfusions are associated with an increased risk of ARDS.²⁷⁻³⁰ In our study, we also noted that patients with cigarette smoke exposure responded differently to early transfusion of pRBCs or FFP compared with patients without smoke exposure. In patients with higher levels of cigarette smoke exposure, transfusion of these products was associated with increased odds of developing ARDS, compared with in patients without cigarette smoke exposure. We did not detect similar differences associated with IV crystalloid, suggesting that this effect was not simply due to the volume of products instilled in patients. Our findings that cigarette smokers may respond differently to pRBC and FFP transfusion are

consistent with prior studies that have shown cigarette smoking to be a risk factor for transfusion-related acute lung injury.² Prior studies have suggested that pRBCs and FFP may increase the risk of developing ARDS via several mechanisms, such as alloimmunization of recipient WBCs by donor antibodies, recipient response to active lipids in donor plasma, or via pro-inflammatory cytokines intrinsic to blood products,³¹⁻³³ all of which may promote inflammation and oxidative stress, particularly in susceptible individuals. Given our report that cigarette smokers develop an exaggerated response to inflammatory stimuli, specifically inhaled lipopolysaccharide,³⁴ smokers also may be more prone to develop inflammation in the setting of transfusion, thereby increasing the risk of developing ARDS. The decreases in transfusions we observed over time may possibly have impacted the epidemiologic relationship between cigarette smoke and ARDS, contributing to the decrease in ARDS incidence among heavy passive and active smokers. Notably, studies in trauma populations have reported a similar decline in the incidence of ARDS.^{35,36} Studies including nontrauma patients also found a decrease in the incidence of ARDS over time,³⁷ suggesting that changes in critical care delivery, such as improved adherence to low-tidal volume ventilation strategies, may have contributed to this reduction. In our study, we did not identify any differences in tidal volumes between time periods; however, we cannot exclude the possibility that other changes in critical care delivery may have contributed to the reduction in ARDS incidence.

This study has several strengths. First, our cohort was large, allowing us to adjust for a number of key confounders. Second, we used a well-validated biomarker to quantify cigarette smoke exposure in our cohort. Prior studies suggest that biomarkers of cigarette smoke exposure provide a more accurate assessment of true exposure in critically ill populations.¹⁵ Third, we used a standardized protocol with a two-physician review to assess all patients in our study for ARDS, which has been shown to be superior to simply relying on chest radiograph reports.³⁸

Our study also has limitations. First, our findings were limited to trauma patients. Although this population is ideal for studying cigarette smoking given the high usage rates, additional studies are needed in other cohorts to increase generalizability. Second, we cannot exclude the possibility of novel tobacco product use in this cohort. Although much of the cohort was enrolled before the recent rise in alternative tobacco product use, it is

possible that a small amount of polytobacco use cannot be differentiated from exclusive cigarette smoking by cotinine levels alone. Similarly, we cannot completely exclude the use of blunts, which can result in low-level nicotine exposure but are associated with substantial cannabis smoke exposure, in our findings. However, additional adjustments in our findings for marijuana use did not alter our findings (data not shown). Third, we cannot fully exclude the possibility that changes in research coordinator hours, from primarily daytime coverage earlier in the study period to 24-hour coverage later in the study, or some other population-level change impacted patient enrollment in the two different periods. However, a sensitivity analysis between 2009 and 2015 found no significant difference in ISS or rate of ARDS between patients enrolled in the daytime vs nighttime (data not shown), suggesting that research coordinator availability should not have substantially impacted our results. Fourth, a relatively large number of patients had unknown alcohol misuse status, particularly early in the cohort, which could confound our data. However, we performed multiple imputation for the variable of alcohol misuse and conducted sensitivity analyses with these imputed data, which did not differ significantly from our findings (e-Tables 3 and 4), suggesting that these missing data did not significantly impact our results. Finally, because of the imprecise nature of ARDS onset time, possibly some

patients may have had ARDS during the first 24 hours of admission, confounding the time ordering of resuscitation and ARDS onset. However, a sensitivity analysis excluding patients who developed ARDS before 48 hours did not change our results (data not shown).

In conclusion, we noted that despite changes in trauma resuscitation and the incidence of ARDS over time, cigarette smoke exposure remained associated with an increased risk of developing ARDS after blunt trauma. However, the relationship between cigarette smoke exposure and ARDS changed over time. Whereas we previously detected a dose-response relationship, in the more recent subset of our cohort, we noted a particularly elevated risk of ARDS in passive smokers, including those with low levels of passive smoke exposure, suggesting a threshold effect. In addition, we observed that active smokers were at particularly increased risk of ARDS after pRBC and FFP transfusion and that the reduction in blood product transfusion may have contributed to the decreased risk of ARDS in active smokers over time. These studies lay the groundwork for future studies assessing the benefits of tailoring processes of care to specific subpopulations at risk for ARDS. In addition, these findings highlight the need for additional mechanistic and epidemiologic studies of the effects of low levels of cigarette smoke exposure on lung health.

Acknowledgments

Author contributions: Study concept and design: F. M., M. J. C., C. S. C. Acquisition of data: F. M., C. H., A. C., L. K., M. J. C., C. S. C.; analysis and interpretation of data: All; drafting of the manuscript: F. M., C. S. C.; critical revision of the manuscript for important intellectual content: All; statistical analysis: F. M., K. D., C. S. C.; guarantor: F. M.; approval of final manuscript: All.

Financial/nonfinancial disclosures: None declared.

Other contributions: The authors thank Polly Cheung, BS, and Trisha Mao, BS, for performing analytical chemistry as well as Mary Nelson, RN, for her assistance managing this cohort.

Additional information: The e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

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