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[Original Research **Critical Care**]

CHEST

Distinct Molecular Phenotypes of Direct vs Indirect ARDS in Single-Center and Multicenter Studies

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Background

ARDS is by definition heterogenous, encompassing lung injury in the setting of underlying illnesses that may cause either direct injury to the lung (eg, pneumonia, aspiration of gastric contents) or indirect injury to the lung (eg, nonpulmonary sepsis, massive transfusion, pancreatitis).

Animal models suggest that direct lung injury begins with an insult to the lung epithelium and consequently leads to more severe lung epithelial injury compared with indirect lung injury. Whether these differences are relevant to human ARDS remains unknown.

Background

Although some human studies demonstrated differences in clinical phenotype between respiratory diseases, however, ARDS have not drawn significant distinctions based on direct or indirect lung injury.

If significant differences in pathogenesis are present in human direct vs. indirect ARDS, this heterogeneity may obscure treatment effects evident only in subgroups and may contribute to the many negative pharmaceutical trials in ARDS.

Background

We tested this hypothesis in two cohorts of patients with ARDS: (1) a single-center observational cohort study in 100 patients with ARDS and severe sepsis and (2) a multicenter sample of 853 patients with ARDS enrolled in a randomized controlled trial of fluid management strategies.

We measured lung epithelial and endothelial injury and inflammation using a panel of plasma biomarkers with an established value for pathogenesis and prognosis in ARDS.

We determined whether the prognostic value of these biomarkers differed based on direct vs. indirect lung injury.

Materials and Methods

Single-Center Study

We used 100 patients who met criteria for ARDS and had severe pulmonary or nonpulmonary sepsis at enrollment.

Patients with sepsis due to pneumonia or aspiration were categorized as having direct lung injury (n=44). Patients with nonpulmonary sepsis were categorized as having indirect lung injury(n=56).

Materials and Methods

multicenter Study

We included patients with a primary ARDS risk factor of pneumonia or aspiration (direct lung injury; n=620) or nonpulmonary sepsis (indirect lung injury; n=233); patients with other primary ARDS risk factors were excluded.

Materials and Methods

Biosamples

markers of lung epithelial injury
Surfactant protein D (SP-D)
soluble receptor for advanced glycation end products (RAGE)

marker of endothelial injury
Angiopoietin-2 (Ang-2)
von Willebrand Factor antigen (vWF),

markers of inflammation
IL-6 and IL-8

Statistical Analysis

To test whether associations between biomarker levels and direct vs. indirect ARDS were confounded by severity of illness or lung injury, we carried out logistic regression using direct vs. indirect ARDS as the outcome and biomarker level as the predictor.

To test whether the prognostic value of biomarkers for mortality differed based on type of lung injury, we conducted logistic regressions stratified by direct vs. indirect ARDS.

Results

In the single-center study, 32 of the 44 patients with direct ARDS were given a primary diagnosis of pneumonia; all 56 patients with indirect ARDS had nonpulmonary sepsis as their primary ARDS risk factor.

In the multicenter study, 471 of the patients with direct ARDS had pneumonia, and 149 had aspiration as their primary ARDS risk factor; all 233 patients with indirect ARDS had nonpulmonary sepsis as their primary ARDS risk factor.

Results

TABLE 1] Patient Characteristics in the Single-Center and Multicenter Studies

Characteristic	Single Center			Multicenter		
	Direct (n = 44)	Indirect (n = 56)	*P* Value	Direct (n = 620)	Indirect (n = 233)	*P* Value
Age, y	55 ± 14	58 ± 11	.32	51 ± 15	51 ± 17	.49
Male sex	25 (57)	27 (48)	.39	324 (52)	120 (52)	.84
Race			.18			.01
White	42 (95)	47 (84)		403 (65)	146 (63)	
Black	2 (5)	8 (14)		145 (23)	43 (19)	
Other	0 (0)	1 (2)		72 (12)	44 (19)	
On vasopressors on study day 1	14 (32)	30 (54)	.03	186 (30)	114 (49)	< .001
AIDS	0 (0)	0 (0)	...	60 (10)	8 (4)	.002
Chronic liver disease	3 (7)	10 (18)	.10	26 (4)	5 (2)	.15
Diabetes	10 (23)	14 (25)	.79	104 (17)	52 (23)	.07
APACHE II score	27 ± 7	29 ± 6	.12	...	...	...
APACHE III score	...	...	...	94 ± 31	103 ± 31	.0002
Pao_2/Fio_2 ratio	128 ± 82	158 ± 77	.11	128 ± 60	136 ± 64	.08
Died[a]	14 (32)	17 (30)	.88	177 (29)	82 (35)	.06
Ventilator-free days	21 (1-24)	17 (4-25)	.95	17 (0-23)	13.5 (0-22)	.007

Data are presented as mean ± SD, No. (%), or median (interquartile range) unless otherwise indicated. APACHE = Acute Physiology and Chronic Health Evaluation.

[a]Mortality at hospital discharge in the single-center cohort, 90 d in multicenter cohort.

Results

Single-Center Study

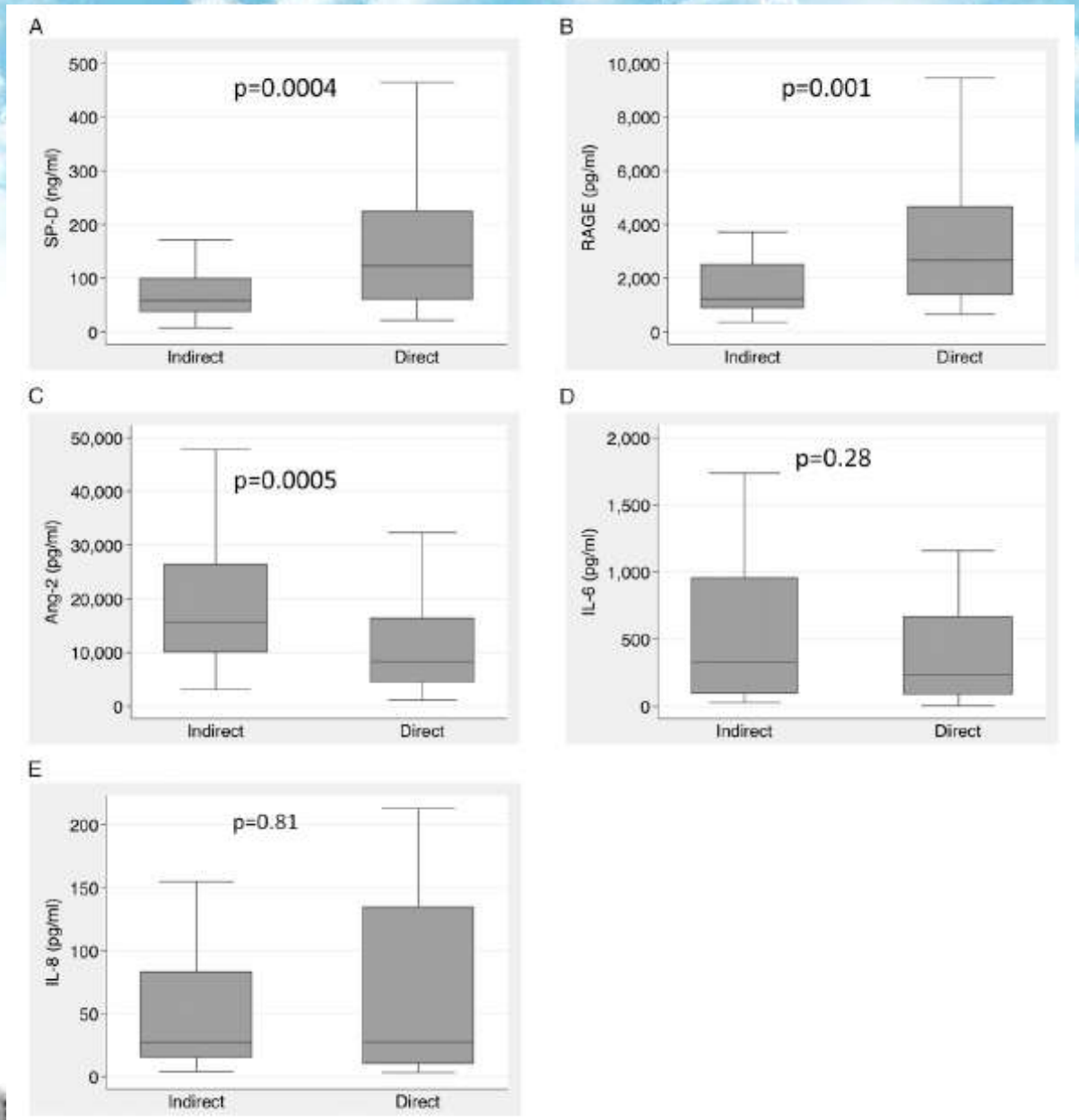

Figure 1 – A-E, Biomarker levels in the single-center study (n = 100). Box plots showing median, interquartile range (box), and upper and lower adjacent values (bars) for biomarker levels stratified by direct (n = 44) vs indirect (n = 56) lung injury. Biomarkers depicted are SP-D (A), RAGE (B), Ang-2 (C), IL-6 (D), and IL-8 (E). Ang-2 = angiopoietin-2; RAGE = receptor for advanced glycation end products; SP-D = surfactant protein D.

Results

Multicenter Study

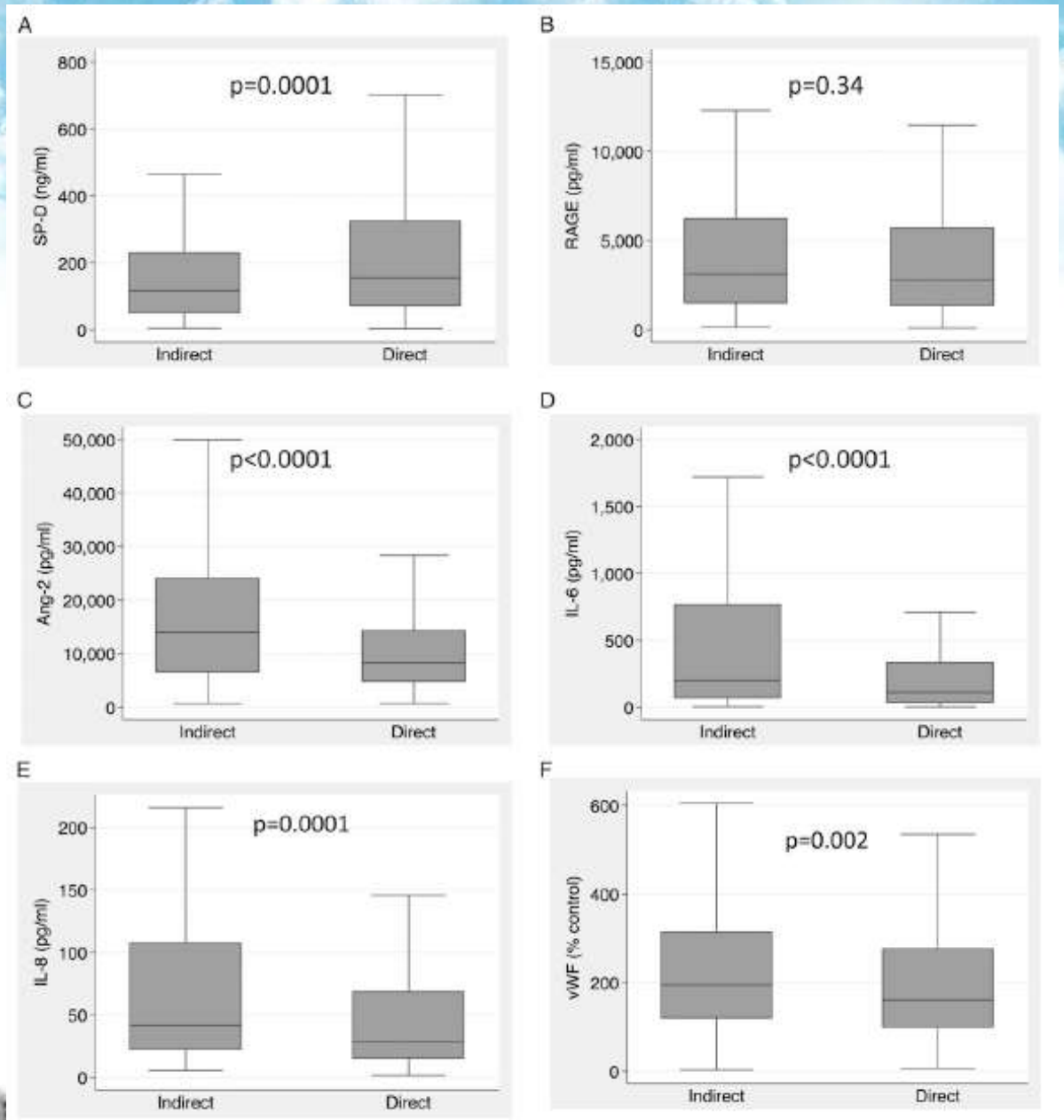

Figure 2 – *A-F, Biomarker levels in the multicenter study (n = 853). Box plots showing median, interquartile range (box), and upper and lower adjacent values (bars) for biomarker levels stratified by direct (n = 620) vs indirect (n = 233) lung injury. Biomarkers depicted are SP-D (A), RAGE (B), Ang-2 (C), IL-6 (D), IL-8 (E), and vWF (F). vWF = von Willebrand factor antigen. See Figure 1 legend for expansion of other abbreviations.*

Results *Multivariable Models*

TABLE 2] Associations Between Plasma Biomarkers and Direct Etiology of ARDS in Single-Center and Multicenter Studies

Biomarker, per 1-Log Increment	Direct ARDS,[a] Unadjusted	*P* Value	Direct ARDS, Adjusted for APACHE Score[a]	*P* Value	Direct ARDS, Adjusted for PF Ratio[a]	*P* Value
Single center						
IL-8	1.01 (0.82-1.26)	.91	1.06 (0.84-1.33)	.61	1.00 (0.76-1.31)	.99
IL-6	0.88 (0.71-1.09)	.24	0.92 (0.73-1.16)	.48	0.98 (0.75-1.28)	.87
SP-D	2.45 (1.45-4.14)	.001	2.38 (1.41-4.02)	.001	2.46 (1.34-4.53)	.004
RAGE	2.11 (1.27-3.48)	.004	2.40 (1.40-4.12)	.002	2.24 (1.22-4.11)	.009
Ang-2	0.37 (0.21-0.67)	.001	0.36 (0.19-0.70)	.003	0.50 (0.27-0.95)	.04
Multicenter						
IL-8	0.87 (0.78-0.96)	.005	0.92 (0.83-1.03)	.15	0.86 (0.78-0.95)	.004
IL-6	0.81 (0.75-0.89)	<.001	0.84 (0.77-0.92)	<.001	0.80 (0.74-0.88)	<.001
SP-D	1.33 (1.16-1.52)	<.001	1.33 (1.15-1.52)	<.001	1.32 (1.15-1.51)	<.001
RAGE	0.92 (0.79-1.07)	.26	0.96 (0.83-1.12)	.62	0.89 (0.77-1.04)	.14
Ang-2	0.55 (0.45-0.68)	<.001	0.62 (0.50-0.77)	<.001	0.55 (0.45-0.67)	<.001
vWF	0.72 (0.58-0.90)	.003	0.81 (0.64-1.02)	.07	0.72 (0.58-0.90)	.004

Data are presented as OR (95% CI) unless otherwise indicated. Ang-2 = angiopoietin-2; PF = Pao_2/Fio_2; RAGE = receptor for advanced glycation end products; SP-D = surfactant protein D; vWF = von Willebrand factor antigen. See Table 1 legend for expansion of other abbreviation.

[a]Referent group in logistic regressions is indirect ARDS.

Results

Prognostic Value of Biomarkers

TABLE 3] Prognostic Value of Plasma Biomarkers in Single-Center and Multicenter Studies

Biomarker, per 1-Log Increment	Death	*P* Value
Single center		
IL-8	1.65 (1.25-2.17)	<.001
IL-6	1.81 (1.34-2.45)	<.001
SP-D[a]	1.33 (0.82-2.14)	.25
RAGE	1.98 (1.18-3.33)	.01
Ang-2	2.54 (1.38-4.68)	.003
Multicenter		
IL-8	1.41 (1.27-1.57)	<.001
IL-6	1.24 (1.14-1.35)	<.001
SP-D	1.09 (0.95-1.24)	.23
RAGE	1.16 (1.003-1.34)	.045
Ang-2[b]	1.43 (1.19-1.73)	<.001
vWF	1.83 (1.46-2.30)	<.001

Data are presented as OR (95% CI). See Table 2 legend for expansion of abbreviations.

[a]OR for mortality in indirect ARDS, 0.99 (95% CI, 0.52-1.91; $P = .98$); OR for mortality in direct ARDS, 2.26 (95% CI, 0.94-5.45; $P = .07$). Test of interaction $P = .14$. There was no evidence for interaction for any other biomarker in the single-center data.

[b]OR for mortality in indirect ARDS, 1.17 (95% CI, 0.85-1.62; $P = .33$); OR for mortality in direct ARDS, 1.51 (95% CI, 1.19-1.91; $P = .001$). Test of interaction $P = .22$. There was no evidence for interaction for any other biomarker in the multicenter data.

Conclusion

Direct lung injury in humans is characterized by a molecular phenotype consistent with more severe lung epithelial injury and less severe endothelial injury. The opposite pattern was identified in indirect lung injury.

Clinical trials of novel therapies targeted specifically at the lung epithelium or endothelium may benefit from preferentially enrolling patients with direct and indirect ARDS, respectively.

Thank You!

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