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B-Type Natriuretic Peptide, Aldosterone, and Fluid Management in ARDS

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BACKGROUND: Conservative fluid management increases ventilator-free days without influencing overall mortality in acute respiratory distress syndrome. Plasma concentrations of B-type natriuretic peptide (a marker of ventricular filling) or aldosterone (a marker of effective circulating volume) may identify patients for whom fluid management impacts survival.

METHODS: This was a retrospective analysis of the Fluid and Catheter Treatment Trial (FACTT), a randomized trial comparing conservative with liberal fluid management in acute respiratory distress syndrome. Using plasma collected at study enrollment, we measured B-type natriuretic peptide and aldosterone by immunoassay. Multivariable analyses examined the interaction between B-type natriuretic peptide or aldosterone concentration and fluid strategy with regard to 60-day in-hospital mortality.

RESULTS: Among 625 patients with adequate plasma, median B-type natriuretic peptide concentration was 825 pg/mL (interquartile range, 144-1,574 pg/mL), and median aldosterone was 2.49 ng/dL (interquartile range, 1.1-4.3 ng/dL). B-type natriuretic peptide did not predict overall mortality, correlate with fluid balance, or modify the effect of conservative vs liberal fluid management on outcomes. In contrast, among patients with lower aldosterone concentrations, conservative fluid management increased ventilator-free days (17.1 ± 9.8 vs 12.5 ± 10.3, $P < .001$) and decreased mortality (19% vs 30%, $P = .03$) (P value for interaction = .01).

CONCLUSIONS: In acute respiratory distress syndrome, B-type natriuretic peptide does not modify the effect of fluid management on outcomes. Lower initial aldosterone appears to identify patients for whom conservative fluid management may improve mortality.

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KEY WORDS: acute lung injury; aldosterone; brain; natriuretic peptide; water-electrolyte balance

ABBREVIATIONS: APACHE = Acute Physiology and Chronic Health Evaluation; BNP = B-type natriuretic peptide; CVP = central venous pressure; FACTT = Fluid and Catheter Treatment Trial; IQR = interquartile range; VFD = ventilator-free day

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ARDS is characterized by increased pulmonary vascular permeability, pulmonary edema, and hypoxia.[1] However, most deaths result from nonpulmonary organ failure.[2] Fluid management strategies in ARDS may have conflicting effects on pulmonary and nonpulmonary organ function, with conservative fluid management prioritizing oxygenation and liberal fluid management prioritizing cardiac output and renal perfusion.[3] In the Fluid and Catheter Treatment Trial (FACTT),[4] a large, randomized comparison of conservative vs liberal fluid management in ARDS, a conservative fluid approach increased ventilator-free days (VFDs) without affecting the incidence of shock, renal failure, or death. The FACTT participants had a wide range of initial hemodynamic conditions, and the effects of fluid management on clinical outcomes may have differed in patients with different ventricular filling and effective circulating volume at baseline.

B-type natriuretic peptide (BNP), a polypeptide secreted by the cardiac ventricles in response to increased end-diastolic volume, has been proposed as a marker of intravascular volume,[5,6] right ventricular dysfunction,[7-9] and cardiopulmonary strain[10] in ARDS. Aldosterone, a mineralocorticoid hormone released from the zona glomerulosa after activation of the renin-angiotensin system by decreased renal perfusion, may serve as a marker of decreased effective circulating volume during acute illness.[11,12] We hypothesized that the FACTT patients with higher initial BNP concentration and lower initial aldosterone concentration would experience lower 60-day mortality when randomized to the conservative strategy.

Materials and Methods

Patient Population and Biologic Samples

Between June 8, 2000, and October 3, 2005, the FACTT randomized 1,000 ventilated patients within 48 h of ARDS diagnosis in a two-by-two factorial design to (1) hemodynamic monitoring via pulmonary artery catheter vs central venous catheter and (2) conservative vs liberal fluid management.[4] The original trial was approved by institutional review boards at participating hospitals, and the current analysis was approved by Vanderbilt's institutional review board (No. 070108). Plasma samples were obtained prior to randomization on the day of enrollment (day 0) and on the third calendar day after enrollment (day 3). Samples were stored at −80°C until the time of assay.

Laboratory Assays

BNP was measured using a commercially available peptide enzyme immunoassay (Peninsula Laboratories International). Aldosterone was measured by radioimmunoassay using ^{125}I-aldosterone (MP Biomedicals), a primary antibody to aldosterone (NIDDK National Hormone & Peptide Program), and a secondary antirabbit γ-globulin antibody (Linco Research).

End Points

The primary outcome was the proportion of patients who died before hospital discharge within 60 days after enrollment (60-day in-hospital mortality). Secondary outcomes included VFDs and ICU-free days within the first 28 days and duration of mechanical ventilation and ICU length of stay overall and among survivors.

Statistical Analyses

Continuous data are presented as mean ± SD or median and interquartile range (IQR) and compared using the Wilcoxon rank sum test. Categorical data are presented as frequency and proportion and compared using the Pearson χ^2 test.

We identified clinical characteristics associated with initial BNP or aldosterone (biomarker) concentration in univariate and multivariable analyses. We examined the ability of the biomarkers to predict mortality using receiver operating characteristic curves and multivariable logistic regression. We examined the ability of the biomarkers to predict VFDs and ICU-free days using multivariable linear regression.

To determine whether baseline biomarker concentration modified the effect of fluid management strategy on clinical outcomes, we performed multivariable logistic regression for 60-day in-hospital mortality with regard to baseline biomarker concentration and fluid group assignment as well as the interaction between them, with adjustment for age, sex, race, BMI, Acute Physiology and Chronic Health Evaluation (APACHE) III score, shock, and central venous pressure (CVP). The model was performed initially using only patients with complete data and then with all patients in which the biomarkers were measured using multiple imputations for missing BMI or CVP data (details provided in e-Appendix 1).

Finally, we examined predictors of change in biomarker concentration from day 0 to day 3 and the relationship between change in biomarker concentration and mortality using multivariable regression. All statistical analyses were performed using R version 3.2.0 (R Foundation for Statistical Computing).

Results

Study Population and Baseline Biomarker Concentration

Six hundred and twenty-five of the original 1,000 FACTT patients had adequate day 0 plasma for BNP and aldosterone measurement and were included in the analysis (Fig 1). Patients with available day 0 plasma

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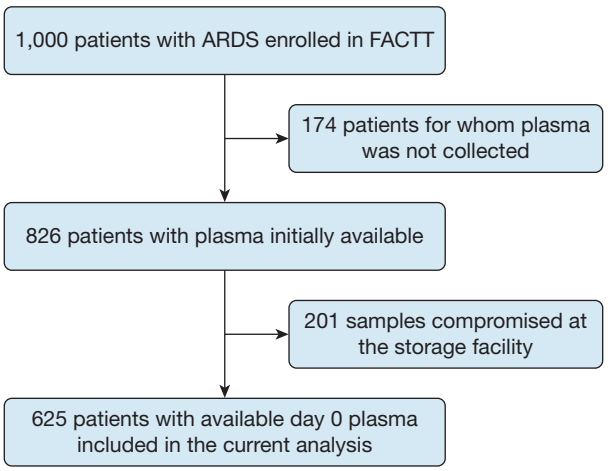

Figure 1 – *Derivation of the cohort for the primary analysis. The primary analysis was conducted using data from the 625 patients with adequate day 0 plasma for biomarker measurement. FACTT = Fluid and Catheter Treatment Trial.*

were representative of the overall study population and similar to those with missing samples except that they had higher cardiac index (4.4 ± 1.5 vs 4.0 ± 1.3 L/min/m^2, $P = .02$), lower creatinine (1.2 ± 0.8 vs 1.3 ± 0.9 mg/dL, $P = .03$), and lower mortality (22% vs 35%, $P < .001$) (e-Table 1).

Median BNP concentration at enrollment was 825 pg/mL (IQR, 144-1,574 pg/mL; normal range, <100 pg/mL), and median aldosterone concentration was 2.49 ng/dL (IQR, 1.1-4.3 ng/dL; normal range in supine adults, 2-9 ng/dL). Clinical characteristics of patients with higher vs lower BNP and aldosterone are summarized in Table 1. In multivariable analysis, older age ($P < .001$), female sex ($P < .001$), lower BMI ($P < .001$), higher creatinine ($P = .004$), and vasopressor use ($P = .046$) were independently associated with higher log-transformed BNP (e-Fig 1, e-Table 2). Younger age ($P = .002$), higher BMI ($P = .001$), and higher creatinine ($P < .001$) were independently associated with higher log-transformed aldosterone, whereas race ($P = .28$), sex ($P = .93$), CVP ($P = .05$), vasopressor use ($P = .98$), and APACHE III score ($P = .16$) were not (e-Fig 2, e-Table 2).

Baseline Biomarker Concentration and Outcomes

Overall, patients with higher vs lower baseline BNP and aldosterone concentration had similar VFDs, ICU-free days, and mortality (Table 1). Baseline BNP and aldosterone concentration did not predict mortality in the overall population (area under the receiver operating characteristic curve of 0.532 and 0.518, respectively) (e-Fig 3). Baseline BNP was not independently associated with VFDs (effect, 0.231; 95% CI, –0.354 to 0.816; $P = .62$) or mortality (OR, 0.927; 95% CI, 0.811-1.062; $P = .28$). Every increase in baseline aldosterone of 1 ng/dL was independently associated with almost a one-half day fewer VFDs (effect, –0.417; 95% CI, –0.796 to –0.038; $P = .02$) but no difference in mortality (OR, 1.029; 95% CI, 0.942-1.123; $P = .52$) (e-Fig 4).

Fluid Strategy and Outcomes by Baseline Biomarker Concentration

Table 2 shows clinical outcomes of conservative vs liberal fluid management for patients with higher and lower baseline BNP and aldosterone concentrations. Conservative fluid management increased VFDs without impacting mortality for both the higher and lower BNP groups. For those with higher baseline aldosterone concentrations, fluid management did not affect VFDs, ICU-free days, or mortality. Among patients with an initial aldosterone concentration below the median, however, conservative fluid management resulted in more VFDs (17.1 ± 9.8 vs 12.5 ± 10.3, $P < .001$), more ICU-free days (19.5 ± 9.5 vs 11.2 ± 9.9, $P < .001$), and lower 60-day mortality (19% vs 30%, $P = .03$).

In multivariable analysis, baseline BNP did not modify the effect of conservative vs liberal fluid management on mortality overall (Table 3) or among patients without renal failure, as defined by a serum creatinine cutoff of 2 mg/dL (P value for interaction = .74).[4] In contrast, patients' baseline aldosterone concentration significantly modified the effect of fluid management on mortality (P value for interaction = .01, P value for interaction = .01 in sensitivity analysis including baseline creatinine) (Table 3). Mortality was highest among patients with initially low aldosterone concentration treated with liberal fluid management (Fig 2). The effect on VFDs was similar (Fig 2, e-Table 3).

Change in Biomarker Concentration and Outcomes

In multivariable analysis examining change in biomarker concentration from day 0 to 3, increasing aldosterone concentration was associated with higher cumulative fluid balance (0.179 ng/dL increase with each 1 L increase in fluid balance; 95% CI, 0.067-0.291 ng/dL; $P < .001$), and none of the covariates tested were associated with a statistically significant change in BNP (e-Table 4). Increasing aldosterone was independently associated with increased overall mortality (OR, 1.037; 95% CI, 1.007-1.070; $P = .02$), whereas change in BNP was not (e-Fig 5, e-Table 5).

TABLE 1] Characteristics, Management, and Outcomes by Baseline Biomarker Concentration

Variable	Aldosterone			BNP		
	Above Median (n = 316)	Below Median (n = 316)	*P* Value	Above Median (n = 313)	Below Median (n = 313)	*P* Value
Baseline characteristic						
Age, y	48.2 ± 15.7	50.8 ± 15.6	.03	52.3 ± 16.4	46.6 ± 14.5	< .001
Men, No. (%)	160 (51)	165 (52)	.69	149 (48)	173 (55)	.06
White, No. (%)	221 (70)	203 (64)	.30	213 (68)	208 (66)	.48
BMI, kg/m^2	30.0 ± 8.0	27.9 ± 7.3	< .001	28.0 ± 7.1	30.0 ± 8.3	.004
Primary lung injury, No. (%)			.18			< .001
Pneumonia	139 (44)	160 (51)		157 (50)	139 (44)	
Sepsis	72 (23)	74 (23)		85 (27)	59 (19)	
Aspiration	51 (16)	43 (14)		41 (13)	51 (16)	
Other	44 (14)	26 (8)		33 (10)	67 (21)	
Coexisting conditions, No. (%)						
Diabetes	53 (17)	59 (19)	.51	55 (18)	55 (18)	.97
HIV infection or AIDS	15 (5)	19 (6)	.47	17 (6)	17 (6)	.98
Malignancy	13 (4)	20 (6)	.14	13 (4)	19 (6)	.35
APACHE III on enrollment	95.4 ± 31.7	91.1 ± 28.3	.12	95.9 ± 30.7	90.6 ± 29.5	.03
Hemodynamic variables						
Mean arterial pressure, mm Hg	76.7 ± 14.7	79.3 ± 15.1	.048	77.9 ± 15.1	78.3 ± 14.8	.44
Vasopressor, No. (%)	115 (36)	86 (27)	.01	114 (36)	85 (27)	.01
CVP, mm Hg	12.8 ± 4.7	11.2 ± 4.5	< .001	12.0 ± 4.8	12.1 ± 4.6	.66
PAOP, mm Hg	15.9 ± 4.6	16.0 ± 5.5	.85	15.9 ± 5.1	16.0 ± 5.0	.89
Cardiac index, L/min/m^2	4.3 ± 1.4	4.4 ± 1.6	.94	4.2 ± 1.5	4.6 ± 1.5	.03
Preenrollment fluid balance, L	2.8 ± 3.6	2.6 ± 3.6	.58	2.8 ± 3.4	2.6 ± 3.8	.18
Respiratory variables						
Tidal volume, mL/kg of PBW	7.4 ± 1.6	7.5 ± 1.8	.82	7.0 ± 1.7	7.5 ± 1.7	.23
PaO_2:FIO_2	143.7 ± 64.0	152.2 ± 70.5	.20	144.6 ± 61.9	150.9 ± 71.4	.53
Laboratory variables						
Creatinine, mg/dL	1.3 ± 1.0	1.1 ± 0.7	< .001	1.4 ± 1.0	1.2 ± 0.7	.11
Hemoglobin, g/dL	10.7 ± 2.0	10.2 ± 1.8	.003	10.3 ± 1.8	10.5 ± 2.0	.40
Time since ICU admission, h	40.2 ± 63.2	36.3 ± 31.4	.74	36.7 ± 60.6	39.9 ± 36.4	.42
On-study management						
Conservative study group	167 (53)	154 (49)	.30	167 (53)	150 (48)	.17
Cumulative fluid balance, L	3.5 ± 10.1	4.2 ± 10.5	.56	4.1 ± 11.1	3.6 ± 9.6	.89
Total furosemide dose, mg	311 ± 486	300 ± 448	.73	280 ± 411	333 ± 519	.29
Clinical outcomes						
Death by 60 d, No. (%)	62 (20)	77 (24)	.15	77 (25)	59 (19)	.08
Ventilator-free days	14.4 ± 10.1	14.8 ± 10.3	.57	14.4 ± 10.5	14.8 ± 9.9	.98
Duration of mechanical ventilation, overall, d	12.7 ± 12.4	12.7 ± 13.5	.50	12.4 ± 13.6	13.1 ± 12.4	.08
Duration of mechanical ventilation, among survivors, d	12.6 ± 12.7	11.7 ± 13.8	.09	12.2 ± 14.6	12.2 ± 12.0	.13

(Continued)

TABLE 1] *(Continued)*

Variable	Aldosterone			BNP		
	Above Median (n = 316)	Below Median (n = 316)	*P* Value	Above Median (n = 313)	Below Median (n = 313)	*P* Value
ICU-free days	13.0 ± 9.6	13.3 ± 9.9	.62	13.0 ± 10.1	13.3 ± 9.4	.81
ICU length of stay, overall, d	14.1 ± 11.7	14.5 ± 13.6	.74	13.9 ± 12.5	14.7 ± 12.7	.09
ICU length of stay, among survivors, d	13.9 ± 11.5	13.6 ± 13.8	.15	13.5 ± 12.8	14.0 ± 12.6	.12

Median BNP concentration was 825 pg/mL (interquartile range, 144-1,574 pg/mL), and median aldosterone concentration was 2.49 ng/dL (interquartile range, 1.1-4.3 ng/dL). Data are given as mean ± SD or as otherwise indicated. APACHE = Acute Physiology and Chronic Health Evaluation; BNP = B-type natriuretic peptide; CVP = central venous pressure; PaO_2:FIO_2 = ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen; PAOP = pulmonary artery occlusion pressure; PBW = predicted body weight.

Discussion

Our examination of BNP and aldosterone in the FACTT reveals two primary findings. In patients with ARDS, BNP is elevated but does not predict outcome, correlate with intracardiac pressures or fluid balance over time, or identify patients likely to benefit from a specific fluid management approach. In contrast, plasma aldosterone concentration appears to identify patients for whom conservative fluid management may improve not only VFDs but mortality.

The utility of plasma natriuretic peptide measurement in congestive heart failure to facilitate diagnosis,[13] provide a noninvasive surrogate of intravascular pressures,[14] and predict outcomes[15] has generated interest in BNP in noncardiogenic respiratory failure.[7,8,16] Early studies examined BNP's ability to discriminate cardiogenic from noncardiogenic pulmonary edema.[17-19] Diagnostic utility was limited by unexpectedly high levels of BNP in patients with ARDS,[17,19] the etiology of which remains incompletely understood. Although ARDS is classically characterized by normal or low left-sided intravascular pressures,[20] up to one-third of patients demonstrate elevated pulmonary capillary wedge pressure,[4] and whether BNP elevation arises from left ventricular dysfunction and pressure elevation,[21,22] right ventricular strain,[7,10,16] or an unrelated mechanism[23-27] remains unclear. Whether plasma BNP can be used to guide fluid management in ARDS, as it can in heart failure, has never to our knowledge been studied.

We examined plasma BNP levels measured within 48 h of ARDS onset for > 600 patients. BNP values correlated with characteristics such as age, sex, BMI, shock, and creatinine that have been previously shown to influence plasma BNP concentration.[21,28-30] The median BNP of 825 pg/mL was higher than the 400 to 650 pg/mL range seen at a similar time point in prior studies.[8,17,19]

Despite the high levels and wide range of concentrations in our study, baseline BNP was not predictive of any clinical outcome. This is consistent with the only prior examination of BNP in a pure ARDS cohort[8] and suggests that, unlike in undifferentiated shock[31,32] or mixed populations of cardiogenic and noncardiogenic pulmonary edema,[17-19] BNP does not predict survival in ARDS.

Our primary hypothesis was that elevated baseline BNP might identify patients with ARDS for whom conservative fluid management would result in better outcomes (whether because of higher left-sided filling pressure, lower cardiac output, or more right ventricular strain). Ultimately, we found that baseline BNP did not modify the effect of conservative vs liberal fluid management on any clinical outcome. Further, changes in BNP over time had no correlation with patients' cumulative fluid balance. The clinical implications of these findings are that, among patients with ARDS, plasma BNP concentration (1) may not reflect elevated cardiac filling pressures, (2) does not appear to identify patients more likely to benefit from conservative fluid management, and (3) may not be informative regarding fluid status over time. Further investigation into the pathophysiology of BNP in ARDS might well be directed away from traditional stretch-induced release of BNP by cardiomyocytes[7,16] toward (1) stimulation of BNP release by catecholamines, vasopressin, endothelin, angiotensin II, and hypoxia[23,24]; (2) direct pulmonary secretion of BNP[26]; or (3) impaired pulmonary BNP clearance.[25]

The lackluster performance of BNP contrasts with our findings regarding aldosterone. Plasma aldosterone concentration correlated appropriately with age, BMI, and kidney injury.[33,34] Observed values clustered in the normal range (2-9 ng/dL for supine adults)[35] but

TABLE 2] On-Study Management and Clinical Outcomes for Liberal vs Conservative Fluid Management by Baseline Biomarker Concentration

Variable	B-Type Natriuretic Peptide					
	Above Median			Below Median		
	Liberal (n = 146)	Conservative (n = 167)	*P* Value	Liberal (n = 163)	Conservative (n = 150)	*P* Value
On-study management						
Cumulative fluid balance, L	7.0 ± 10.5	1.2 ± 11.0	< .001	6.9 ± 8.9	−0.3 ± 9.0	< .001
Total furosemide dose, mg	132 ± 228	409 ± 485	< .001	130 ± 232	553 ± 642	< .001
Clinical outcomes						
Death by 60 d, No. (%)	41 (28)	36 (22)	.18	32 (20)	27 (18)	.71
Ventilator-free days	12.6 ± 10.4	15.9 ± 10.4	.001	13.9 ± 9.7	15.7 ± 10.1	.04
Duration of mechanical ventilation, overall, d	14.4 ± 14.8	10.7 ± 12.2	< .001	13.8 ± 12.0	12.3 ± 12.8	.04
Duration of mechanical ventilation, among survivors, d	14.4 ± 16.2	10.5 ± 12.9	.001	12.9 ± 11.2	11.4 ± 12.7	.02
ICU-free days	11.2 ± 9.9	14.7 ± 10.0	< .001	12.8 ± 9.2	13.8 ± 9.6	.24
ICU length of stay, overall, d	16.4 ± 14.4	11.7 ± 10.1	< .001	15.5 ± 13.7	13.8 ± 11.5	.19
ICU length of stay, among survivors, d	16.2 ± 15.2	11.4 ± 10.2	< .001	14.9 ± 13.7	13.1 ± 11.3	.16

Variable	Aldosterone					
	Above Median			Below Median		
	Liberal (n = 149)	Conservative (n = 167)	*P* Value	Liberal (n = 162)	Conservative (n = 154)	*P* Value
On-study management						
Cumulative fluid balance, L	6.0 ± 8.7	1.1 ± 10.9	< .001	7.9 ± 10.3	−0.3 ± 9.0	< .001
Total furosemide dose, mg	114 ± 186	487 ± 593	< .001	145 ± 262	463 ± 538	< .001
Clinical outcomes						
Death by 60 d, No. (%)	25 (17)	37 (22)	.23	48 (30)	29 (19)	.03
Ventilator-free days	14.3 ± 9.6	14.4 ± 10.6	.47	12.5 ± 10.3	17.1 ± 9.8	< .001
Duration of mechanical ventilation, overall, d	13.0 ± 10.9	12.5 ± 13.7	.06	15.0 ± 15.2	10.3 ± 11.0	< .001
Duration of mechanical ventilation, among survivors, d	12.9 ± 11.2	12.3 ± 14.1	.04	14.1 ± 15.83	9.5 ± 11.2	< .001
ICU-free days	12.9 ± 9.1	13.0 ± 10.1	.51	11.2 ± 9.9	19.5 ± 9.5	< .001
ICU length of stay, overall, d	14.4 ± 11.0	13.7 ± 12.2	.12	17.3 ± 16.2	11.6 ± 9.4	< .001
ICU length of stay, among survivors, d	14.3 ± 10.6	13.5 ± 12.3	.08	16.7 ± 17.4	10.8 ± 8.7	.002

Data are given as mean ± SD or as otherwise indicated.

spanned a wide spectrum from nearly 0 to > 60 ng/dL. To our knowledge, no prior studies have measured plasma aldosterone in patients with ARDS, but the values in our study were lower than reported in patients with congestive heart failure,[36] myocardial infarction,[12] sepsis,[37] and undifferentiated critical illness.[38,39] Fluid resuscitation in the 48 h between ARDS onset and aldosterone measurement may have contributed to the modestly lower aldosterone concentrations in our study. Nonetheless, baseline aldosterone concentration was independently associated with VFDs, and evidence of increasing aldosterone from day 0 to day 3 was associated with high risk for death. Moreover, the results confirmed our primary hypothesis that low initial aldosterone concentration would identify a subset of patients with ARDS for whom conservative fluid management appears to improve not only VFDs but also mortality.

Aldosterone is a mineralocorticoid hormone, and its synthesis in the zona glomerulosa of the adrenal cortex

TABLE 3] Multivariable Model for Mortality in Relation to Baseline BNP, Aldosterone, and Fluid Management Strategy

Characteristic	Complete Cases (n = 513)			Multiple Imputations (n = 625)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age, y	1.96	1.36-2.81	< .001	1.87	1.32-2.50	< .001
Female sex	0.60	0.37-0.99	.048	0.69	0.44-1.07	.10
Race (non-white to white)	1.23	0.73-2.06	.43	1.29	1.07-2.67	.03
BMI, kg/m^2	0.67	0.45-1.00	.03	0.78	0.55-1.20	.12
APACHE III score	3.28	2.15-4.99	< .001	3.33	2.26-4.84	< .001
Shock	1.94	1.16-3.23	.01	1.72	1.12-2.85	.02
Central venous pressure, mm Hg	0.86	0.59-1.25	.43	0.88	0.62-1.26	.35
Fluid strategy (liberal to conservative)	0.95	0.58-1.55	.82	1.148	0.74-1.78	.54
Conservative group						
BNP, log-transformed	0.78	0.42-1.43	.42	0.80	0.47-1.37	.42
Aldosterone, log-transformed	1.22	0.86-1.75	.26	1.22	0.88-1.67	.23
Liberal group						
BNP, log-transformed	0.71	0.38-1.33	.28	0.89	0.50-1.57	.69
Aldosterone, log-transformed	0.68	0.43-1.08	.10	0.64	0.43-0.96	.03
BNP × fluid strategy	…	…	.83	…	…	.79
Aldosterone × fluid strategy	…	…	.04	…	…	.01

Of the 625 patients with both biomarkers available on day 0, 112 were missing central venous pressure or BMI data and were either excluded (complete cases) or had these values imputed (multiple imputations). Sensitivity analysis adding baseline creatinine and blood urea nitrogen to the model did not change aldosterone's modification of the effect of fluid management on mortality (*P* value for interaction = .01). The odds of 60-d in-hospital mortality are given for the 75th percentile relative to the 25th percentile of age, BMI, APACHE III score, central venous pressure, log-transformed BNP, and log-transformed aldosterone. See Table 1 legend for expansion of abbreviations.

is tightly regulated through the influence of serum potassium, adrenocorticotropin, and the renin-angiotensin system.[40] In patients with decreased effective circulating volume, activation of the renin-angiotensin system increases levels of aldosterone, which interacts with mineralocorticoid receptors in the renal collecting duct to promote sodium and water retention and restore plasma volume. Prior work suggests that decreased effective circulating volume and renin activity, rather than potassium or adrenocorticotropin, are the primary regulators of the aldosterone level during critical illness.[41] Our results suggest that for the FACTT patients with higher initial aldosterone levels (lower effective circulating volume), the potential risks of fluid administration were balanced by the potential benefits in improving effective circulating volume. In contrast, for FACTT patients with lower initial aldosterone levels (higher effective circulating volume), diuresis and prevention of fluid administration appear to have improved mortality. Beyond the pulmonary consequences of volume overload that formed the rationale for the original FACTT, subsequent research has highlighted extrapulmonary mechanisms by which fluid accumulation may worsen outcomes.[42,43] Determining whether an individual patient will benefit from further fluid administration has been a focus of recent ICU research.[44] Our results suggest that, among patients with ARDS 1 to 2 days into their illness, measurement of plasma aldosterone may identify patients for whom fluid restriction and diuresis facilitate ventilator liberation and survival.

Our study has several strengths. With > 600 patients from 20 centers, it is the largest study of BNP in ARDS and the first to examine the relationship between BNP and fluid management. Moreover, it is the first report of aldosterone concentrations in ARDS and the only study to examine the relationship between aldosterone and outcomes of fluid management in any critical illness. The robust hemodynamic monitoring in the FACTT strengthens our evaluation of aldosterone, the generation of which is intrinsically linked to patient hemodynamics. Perhaps most importantly, unlike many observational studies linking fluid balance to outcomes, fluid management in the FACTT was driven by a tightly regulated study protocol that maximizes the likelihood

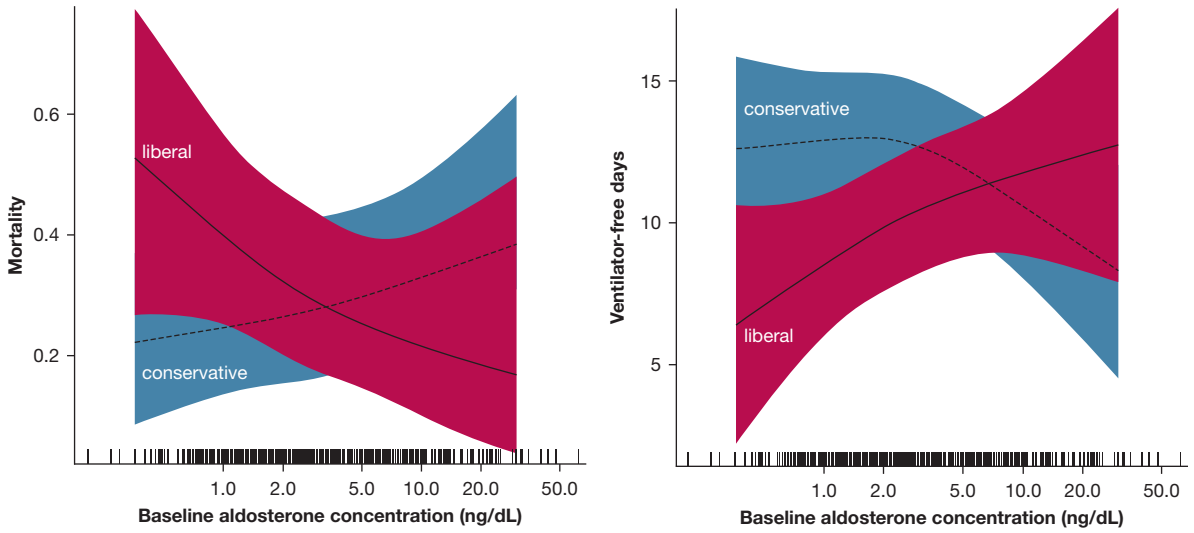

Figure 2 – *Clinical outcomes of conservative and liberal fluid management by baseline aldosterone concentration. The effect of conservative vs liberal fluid management on 60-d in-hospital mortality and ventilator-free days differed based on patients' initial serum aldosterone concentration. For patients with lower initial aldosterone concentration, liberal fluid management increased mortality and decreased ventilator-free days. The aldosterone values below which the point estimates for mortality and ventilator-free days appeared to favor conservative fluid management were 3.7 and 7.4 ng/dL, respectively. Display in the figure is standardized to an age of 70 y, male sex, non-white race, a BMI of 40 kg/m^2, a central venous pressure of 12 mm Hg, the absence of shock, and an Acute Physiology and Chronic Health Evaluation III score of 90.*

that differences observed between study groups were caused by the fluid intervention and not confounded by indication bias.

Our study also has weaknesses. Plasma for BNP and aldosterone measurement was available for only 625 of the original 1,000 FACTT patients. Although the 201 samples compromised at the storage facility may be missing at random, the 174 patients for whom samples were not originally collected[45] appear to have been more severely ill, and whether our findings apply to these patients is unknown. The timing of biomarker measurement around 48 h after ARDS onset, and then again 3 days later, may have influenced our findings. Measurement of BNP or aldosterone immediately on presentation might yield different results. Although it would be ideal to replicate in an independent cohort the finding that aldosterone modifies the effect of liberal vs conservative fluid management on clinical outcomes, the FACTT is the only large ARDS trial in which fluid management was controlled by study assignment. Our results may not generalize to other natriuretic peptides, such as atrial natriuretic peptide, which may better reflect intracardiac pressures in the acute setting.

These findings add to the growing evidence that fluid accumulation in the wrong context may be harmful to patients who are critically ill and suggest serum aldosterone concentration as a potential novel predictor of patients' response to fluid management.[44] Future research is needed to confirm these findings and explore the feasibility and utility of aldosterone as a guide to fluid management in the ICU.

Conclusions

Among patients with ARDS, BNP is elevated but does not predict outcome, correlate with fluid balance over time, or inform the approach to fluid management. In contrast, a low initial aldosterone level appears to identify patients with ARDS for whom conservative fluid management may improve not only VFDs but mortality.

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References

1. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1334-1349.
2. Montgomery AB, Stager MA, Carrico CJ, Hudson LD. Causes of mortality in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1985;132(3):485-489.
3. Humphrey H, Hall J, Sznajder I, Silverstein M, Wood L. Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure. *Chest*. 1990;97(5):1176-1180.
4. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564-2575.
5. Li G, Daniels CE, Kojicic M, et al. The accuracy of natriuretic peptides (brain natriuretic peptide and N-terminal pro-brain natriuretic) in the differentiation between transfusion-related acute lung injury and transfusion-related circulatory overload in the critically ill. *Transfusion (Paris)*. 2009;49(1):13-20.
6. Determann RM, Royakkers AA, Schaefers J, et al. Serum levels of N–terminal proB–type natriuretic peptide in mechanically ventilated critically ill patients – relation to tidal volume size and development of acute respiratory distress syndrome. *BMC Pulm Med*. 2013;13(1):42.
7. Phua J, Jason P, Lim TK, Keang LT, Lee KH, Hoe LK. B-type natriuretic peptide: issues for the intensivist and pulmonologist. *Crit Care Med*. 2005;33(9). 2094-2113.
8. Cepkova M, Kapur V, Ren X, et al. Clinical significance of elevated B-type natriuretic peptide in patients with acute lung injury with or without right ventricular dilatation: an observational cohort study. *Ann Intensive Care*. 2011;1(1):18.
9. Park BH, Kim YS, Chang J, et al. N-terminal pro–brain natriuretic peptide as a marker of right ventricular dysfunction after open-lung approach in patients with acute lung injury/acute respiratory distress syndrome. *J Crit Care*. 2011;26(3):241-248.
10. Bajwa EK, Januzzi JL, Gong MN, Thompson BT, Christiani DC. Prognostic value of plasma N-terminal probrain natriuretic peptide levels in the acute respiratory distress syndrome. *Crit Care Med*. 2008;36(8):2322-2327.
11. Fine D, Meiselas LE, Auerbach T. The effect of acute hypovolemia on the release of aldosterone and on the renal excretion of sodium. *J Clin Invest*. 1958;37(2):232-243.
12. Sigurdsson A, Held P, Swedberg K. Short- and long-term neurohormonal activation following acute myocardial infarction. *Am Heart J*. 1993;126(5):1068-1076.
13. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347(3):161-167.
14. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. *Am Heart J*. 1998;135(5 Pt 1):825-832.
15. Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. *BMJ*. 2005;330(7492):625.
16. Yap LB, Mukerjee D, Timms PM, Ashrafian H, Coghlan JG. NAtriuretic peptides, respiratory disease, and the right heart. *Chest*. 2004;126(4):1330-1336.
17. Jefic D, Lee JW, Jefic D, Savoy-Moore RT, Rosman HS. Utility of B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide in evaluation of respiratory failure in critically ill patients. *Chest*. 2005;128(1):288-295.
18. Karmpaliotis D, Kirtane AJ, Ruisi CP, et al. Diagnostic and prognostic utility of brain natriuretic peptide in subjects admitted to the ICU with hypoxic respiratory failure due to noncardiogenic and cardiogenic pulmonary edema. *Chest*. 2007;131(4):964-971.
19. Levitt JE, Vinayak AG, Gehlbach BK, et al. Diagnostic utility of B-type natriuretic peptide in critically ill patients with pulmonary edema: a prospective cohort study. *Crit Care Lond Engl*. 2008;12(1):R3.
20. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994;149(3 Pt 1):818-824.
21. Witthaut R, Busch C, Fraunberger P, et al. Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: impact of interleukin-6 and sepsis-associated left ventricular dysfunction. *Intensive Care Med*. 2003;29(10):1696-1702.
22. Charpentier J, Luyt CE, Fulla Y, et al. Brain natriuretic peptide: a marker of myocardial dysfunction and prognosis during severe sepsis. *Crit Care Med*. 2004;32(3):660-665.
23. Hill NS, Klinger JR, Warburton RR, Pietras L, Wrenn DS. Brain natriuretic peptide: possible role in the modulation of hypoxic pulmonary hypertension. *Am J Physiol*. 1994;266(3 Pt 1):L308-L315.
24. Nakanishi K, Tajima F, Itoh H, et al. Changes in atrial natriuretic peptide and brain natriuretic peptide associated with hypobaric hypoxia-induced pulmonary hypertension in rats. *Virchows Arch Int J Pathol*. 2001;439(6):808-817.
25. Klinger JR, Arnal F, Warburton RR, Ou LC, Hill NS. Downregulation of pulmonary atrial natriuretic peptide receptors in rats exposed to chronic hypoxia. *J Appl Physiol Bethesda Md 1985*. 1994;77(3):1309-1316.
26. Gerbes AL, Dagnino L, Nguyen T, Nemer M. Transcription of brain natriuretic peptide and atrial natriuretic peptide genes in human tissues. *J Clin Endocrinol Metab*. 1994;78(6):1307-1311.
27. Bayes-Genis A, Bellido-Casado J, Zapico E, et al. N-terminal pro-brain natriuretic peptide reflects pulmonary capillary leakage in patients with acute dyspnea. *Am J Cardiol*. 2004;94(5):669-670.
28. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol*. 2002;40(5):976-982.
29. Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. *Circulation*. 2004;109(5):594-600.
30. Tsutamoto T, Wada A, Sakai H, et al. Relationship between renal function and plasma brain natriuretic peptide in patients with heart failure. *J Am Coll Cardiol*. 2006;47(3):582-586.
31. Tung RH, Garcia C, Morss AM, et al. Utility of B-type natriuretic peptide for the evaluation of intensive care unit shock. *Crit Care Med*. 2004;32(8):1643-1647.

32. Januzzi JL, Morss A, Tung R, et al. Natriuretic peptide testing for the evaluation of critically ill patients with shock in the intensive care unit: a prospective cohort study. *Crit Care Lond Engl*. 2006;10(1):R37.

33. Hegstad R, Brown RD, Jiang NS, et al. Aging and aldosterone. *Am J Med*. 1983;74(3):442-448.

34. Briones AM, Nguyen Dinh Cat A, Callera GE, et al. Adipocytes produce aldosterone through calcineurin-dependent signaling pathways: implications in diabetes mellitus-associated obesity and vascular dysfunction. *Hypertension*. 2012;59(5):1069-1078.

35. Katz FH, Romfh P, Smith JA. Diurnal variation of plasma aldosterone, cortisol and renin activity in supine man. *J Clin Endocrinol Metab*. 1975;40(1):125-134.

36. Anand IS, Ferrari R, Kalra GS, Wahi PL, Poole-Wilson PA, Harris PC. Edema of cardiac origin. Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. *Circulation*. 1989;80(2):299-305.

37. du Cheyron D, Lesage A, Daubin C, Ramakers M, Charbonneau P. Hyperreninemic hypoaldosteronism: a possible etiological factor of septic shock-induced acute renal failure. *Intensive Care Med*. 2003;29(10):1703-1709.

38. Davenport MW, Zipser RD. Association of hypotension with hyperreninemic hypoaldosteronism in the critically ill patient. *Arch Intern Med*. 1983;143(4):735-737.

39. Raff H, Findling JW. Aldosterone control in critically ill patients: ACTH, metoclopramide, and atrial natriuretic peptide. *Crit Care Med*. 1990;18(9):915-920.

40. Longo D, Fauci A, Kasper D, Hauser S, Jamesone L, Loscalzo J. *Harrison's Principles of Internal Medicine*. 18th ed. New York, NY: McGraw-Hill; 2012.

41. Moraes RB, Friedman G, Viana MV, Tonietto T, Saltz H, Czepielewski MA. Aldosterone secretion in patients with septic shock: a prospective study. *Arq Bras Endocrinol Amp Metabol*. 2013;57(8):636-641.

42. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int*. 2009;76(4):422-427.

43. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA J Am Med Assoc*. 2012;308(15):1566-1572.

44. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med*. 2013;41(7):1774-1781.

45. Bajwa EK, Volk JA, Christiani DC, et al. Prognostic and diagnostic value of plasma soluble suppression of tumorigenicity-2 concentrations in acute respiratory distress syndrome. *Crit Care Med*. 2013;41(11):2521-2531.