Bolus intravenous 0.9% saline, but not 4% albumin or 5% glucose, causes interstitial pulmonary edema in healthy subjects

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Bihari S, Wiersema UF, Schembri D, De Pasquale CG, Dixon D-L, Prakash S, Lawrence MD, Bowden JJ, Bersten AD. Bolus intravenous 0.9% saline, but not 4% albumin or 5% glucose, causes interstitial pulmonary edema in healthy subjects. J Appl Physiol 119: 783–792, 2015. First published July 30, 2015; doi:10.1152/japplphysiol.00356.2015. —Rapid intravenous (iv) infusion of 0.9% saline alters respiratory mechanics in healthy subjects. However, the relative cardiovascular and respiratory effects of bolus iv crystalloids vs. colloid are unknown. Six healthy male volunteers were given 30 ml/kg iv 0.9% saline, 4% albumin, and 5% glucose at a rate of 100 ml/min on 3 separate days in a double-blinded, randomized crossover study. Impulse oscillometry, spirometry, lung volumes, diffusing capacity (DLCO), and blood samples were measured before and after fluid administration. Lung ultrasound B-line score (indicating interstitial pulmonary edema) and Doppler echocardiography indices of cardiac preload were measured before, midway, immediately after, and 1 h after fluid administration. Infusion of 0.9% saline increased small airway resistance at 5 Hz (P = 0.04) and lung ultrasound B-line score (P = 0.01) without changes in Doppler echocardiography measures of preload. In contrast, 4% albumin increased DLCO, decreased lung volumes, and increased the Doppler echocardiography mitral E velocity (P = 0.001) and E-to-lateral/septal e′ ratio, estimated blood volume, and N-terminal pro B-type natriuretic peptide (P = 0.01) but not lung ultrasound B-line score, consistent with increased pulmonary blood volume without interstitial pulmonary edema. There were no significant changes with 5% glucose. Plasma angiopoietin-2 concentration increased only after 0.9% saline (P = 0.001), suggesting an inflammatory mechanism associated with edema formation. In healthy subjects, 0.9% saline and 4% albumin have differential pulmonary effects not attributable to passive fluid filtration. This may reflect either different effects of these fluids on active signaling in the pulmonary circulation or a protective effect of albumin.

0.9% saline; 4% albumin; 5% glucose; pulmonary edema; cardiac output; ultrasound

THE ADMINISTRATION OF BOLUS intravenous (iv) fluid is a core component of resuscitation of the critically ill patient. Despite the widespread use of bolus fluid therapy, there is no consensus on the optimal choice of fluid that should be given (11, 18, 49). Both crystalloids and colloids have been advocated, and although some synthetic colloids have been associated with toxicity (43, 50), there is currently insufficient evidence to determine superiority of crystalloid or nonsynthetic colloid (11, 18, 49). The different types of fluid may, however, have inherently different effects on pulmonary function that would favor one type of fluid over another when given to certain patient groups, such as those susceptible to pulmonary edema. Historically, the volume of distribution and physiological sequelae of bolus iv fluid have been explained through the Starling equation. According to this, an iv bolus of isotonic crystalloid solution administered to a healthy subject should distribute within the extracellular space, a colloid solution should initially remain within the intravascular space (66), and free water should distribute throughout the extracellular and intracellular spaces. More recently, the revised Starling equation and glycocalyx model, in which the principal force opposing transcapillary filtration is the colloid osmotic pressure of the endovascular subglycocalyceal space instead of the colloid osmotic pressure of the interstitial space, challenge this interpretation (3, 21, 33, 72). The revised Starling equation predicts a much smaller difference in initial volume of distribution between isotonic crystalloid and colloid administration, with crystalloid initially distributing within the intravascular space and colloid within the plasma space (intravascular space minus the glycocalyx space). This has been supported by clinical studies of fluid resuscitation, demonstrating little difference between the amount of crystalloid and colloid required for resuscitation (9, 18, 28). The revised Starling principle also predicts a minimal effect of intravascular colloid osmotic pressure on transcapillary filtration.

Volume kinetic studies have demonstrated that with isotonic crystalloid infusion, intravascular volume expansion is followed by redistribution of fluid to the interstitial space (21). On the other hand, the initial plasma volume expansion (similar in magnitude to that obtained with isotonic crystalloid solutions) with rapid infusion of 5% glucose (similar osmolarity but a hypotonic solution) is rapidly followed by fluid redistribution to the intracellular space, without significant interstitial space expansion (21). The cardiorespiratory implications of this improved understanding of fluid physiology remain unclear. In previous studies of healthy subjects, rapid iv infusion of 0.9% saline reduced forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) through small airway compression and premature closure—findings attributed to the development of interstitial pulmonary edema (15, 42, 48, 55). However, to our knowledge, these effects in healthy subjects have not previously been

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compared with the pulmonary effects of rapid infusion of a colloid solution or of free water (5% glucose).

In the current study, we compared the cardiopulmonary effects of identical volumes of bolus iv isotonic crystalloid (0.9% saline), colloid (4% albumin), and free water (5% glucose) in healthy human subjects. Lung mechanics, lung ultrasound, echocardiography, and plasma angiotensin (Ang) levels were measured before and after fluid loading to detect the development and mechanism of pulmonary edema. We hypothesized that both 0.9% saline and 4% albumin would cause interstitial pulmonary edema, the former predominantly through redistribution of fluid into the interstitial space and the latter through an increase in hydrostatic pressure, due to greater intravascular volume expansion. Based on the volume kinetic studies, we hypothesized that a 5% glucose bolus would have minimal pulmonary sequelae and not result in interstitial pulmonary edema (21).

METHODS

Subjects and design. The study was approved by the Southern Adelaide Clinical Human Research Ethics Committee. Written, informed consent was obtained from all subjects. Six healthy, male volunteers, aged <40 yr, who were nonsmokers and had a body mass index <30 and no history of cardiac, pulmonary, or other chronic disease, were enrolled. Each subject was administered an iv infusion of 30 ml/kg (divided into two successive doses of 15 ml/kg) of 0.9% saline (Baxter IV; Baxter, Deerfield, IL), 4% albumin (CSL Biopharmacies, Victoria, Australia), or 5% glucose (Baxter IV; Baxter), at a rate of 100 ml/min on three separate, nonconsecutive mornings in a double-blind, randomized crossover design. Measurements were taken at baseline [time point 1 (T1)], after 15 ml/kg fluid had been given (T2), after a total of 30 ml/kg fluid had been given (T3), and 1 h after fluid therapy was completed (T4). The study protocol is shown in Fig. 1.

Heart rate, noninvasive blood pressure (BP), and oxygen saturation by pulse oximeter (SpO2) were measured during each measurement period (CASMED 740 Vital Sign Monitor; CAS Medical Systems, Branford, CT). The mean of three measures of each variable is reported. A self-administered, modified Borg dyspnea scale score was recorded at the start of each measurement period (30).

Respiratory mechanics. All respiratory measurements were taken according to American Thoracic Society/European Respiratory Society guidelines (39) by a laboratory scientific staff with at least 10 yr of experience and holding up-to-date certification for respiratory function scientists by the Australian and New Zealand Society of Respiratory Science. All subjects underwent lung function test training in the respiratory function laboratory before their first study day.

Respiratory measurements were taken in the same sequence during each measurement period (Fig. 1) as follows: impulse oscillometry for respiratory resistance and reactance, slow spirometry, forced spirometry, body plethysmography lung volumes, and single breath gas analysis (CareFusion Jaeger MasterScreen) were taken in duplicate with vital capacity (VC), repeatable within 150 ml. For forced spirometry measurements, the highest value of FEV1 and FVC from each measurement session is reported. Total lung capacity (TLC) was measured by body plethysmography on the same system. Functional residual capacity (FRC) was estimated with support connected at a breathing frequency of 15-20 breaths/min. At least three measurements were obtained within 5% variability and TLC calculated from FRC plus inspiratory capacity. Residual volume was calculated as TLC minus VC. Transfer coefficient (Kco; mathematically equal to DLco/unit alveolar volume) was measured using the single-breath method (CareFusion Jaeger MasterScreen pulmonary function testing) and was corrected for hemoglobin (37, 39, 69). In each case, at least two measurements were made, repeatable to within 1.0 ml/min $^{-1}$mmHg.

Lung ultrasound and echocardiography. A single experienced operator blinded to the type of study fluid performed all of the lung ultrasound and echocardiography studies. An M-Turbo ultrasound machine (Sonosite, Bothell, WA) with a phased array (1–5 MHz) transducer was used for all ultrasound imaging. Subjects were imaged in the supine position for lung ultrasound and examination of the inferior vena cava (IVC) and in the left lateral decubitus position for the remainder of the echocardiography study. A screening echocardiogram was performed on each subject to exclude any cardiac structural abnormality.

During each measurement period (Fig. 1), lung ultrasound images were examined for the presence of sonographic B-lines (considered to represent the presence of interstitial pulmonary edema) (2, 5, 27). Ultrasound images were taken at each intercostal space, from the second to fifth space along the midclavicular line; the parasternal line; and the anterior, middle, and posterior axillary lines, bilaterally (27). The total number of B-lines was summed to provide a B-line score (27). Echocardiography measurements were taken, according to the guidelines of the American Society of Echocardiography (45, 53, 57). During each measurement period (Fig. 1), measurements were taken immediately after fluid bolus, 15 min postbolus, and 1 h after fluid therapy was completed (T4). The study protocol is shown in Fig. 1.

Cardiac output was calculated as LVOT VTI $\times$ LVOT cross-sectional area $\times$ heart rate.

Blood samples. Venous blood samples were collected before and after fluid administration. Serum electrolytes were measured with an indirect ion-selective electrode technique (Roche/Hitachi Modular Analyzer; Hitachi High-Technologies, Tokyo, Japan). Serum albumin was measured with a standard colorimetric method (Bromocresol purple; Roche/Hitachi Modular Analyzer). Hemoglobin was measured spectrophotometrically (Cyan-Met Hemoglobin, UniCel DxC800; Beckman Coulter, Brea, CA) and hematocrit calculated from red blood cell count and mean cell volume.

Plasma Ang-1 and Ang-2 were measured using commercially available kits, as per the manufacturer’s instructions (R&D Systems, Minneapolis, MN). Plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) was measured with an electrochemiluminescence immunoassay (Cobas e immunoassay analyzer, Elecsys 2010; Roche, Basel, Switzerland).

Blood volume at baseline was estimated according to the method described by Nadler et al. (44). Calculations for changes in blood volume and extravascular fluid volume were based on changes in hematocrit and body weight and were made using a formula described
previously (12, 35). Participants passed urine as needed. The time to each micturition from the start of fluid administration was noted.

Statistical analysis. Data are reported as means with SD or median with interquartile range (IQR), as appropriate. Analysis was performed using SPSS version 22.0 (IBM, Armonk, NY). Differences between variables over time were analyzed by repeated-measures ANOVA. The effect of type of fluid was analyzed as an interaction effect between fluid type and time. The relationships between change in blood volume and change in cardiac output are described using regression analysis, which took into account the repeated measurements within the same subjects (61). The effect of each individual fluid in each subject was analyzed with a two-tailed paired t-test. The conventional two-tailed alpha level of <0.05 was chosen for discussion of potential effects.

RESULTS

Six subjects were enrolled, all of whom completed the study. The median (IQR) age was 35 (32–37) yr, weight was 80 (64–82) kg, and height was 179 (171–181.8) cm. None of the subjects reported dyspnea (modified Borg scale score of 0) after infusion of 15 ml/kg of any of the fluids. One subject reported slight breathlessness immediately after infusion of 30 ml/kg of 0.9% saline (modified Borg scale score of 2), but this

![Fig. 1. Protocol used in the study. T, Time points examined in the study; HR, heart rate; BP, blood pressure; SPO2, oxygen saturation by pulse oximeter.](http://jap.physiology.org/Downloadedfrom)
resolved during the recovery period (modified Borg scale score of 0). There was no significant change in BP or Spo2 with any fluid during the study period. The heart rate was unchanged after infusion of 4% albumin (P = 0.38) or 5% glucose (P = 0.11) but decreased significantly after infusion of 0.9% saline (P = 0.02) (Table 1).

Respiratory mechanics. The administration of 4% albumin resulted in an increase in KCO (DLCO/unit alveolar volume; P = 0.003) and a fall in FVC (P = 0.005), FEV1 (P = 0.002), and FRC (P = 0.04), consistent with an increase in pulmonary blood volume, whereas 0.9% saline administration led to an increase in arterial oxygen saturation at 5 Hz (P = 0.04) and decrease in inductance (dX/dflow; P = 0.01; Table 2). There was a decrease in peak expiratory flow rate (PEFR) with both 4% albumin (P = 0.03) and 0.9% saline (P = 0.04). There were no changes in lung function with administration of 5% glucose.

Lung ultrasound. Administration of 0.9% saline led to an increase in lung B-line score (P = 0.01), which persisted through to the recovery period. There was not statistically significant difference in B-line score with administration of 4% albumin (P = 0.36) or 5% glucose (P = 0.18; Table 2).

Echocardiography. None of the three fluids caused a significant change in cardiac output, stroke volume, or IVC variability (Table 1). There was also no difference between fluids in their effect on cardiac output (P = 0.22), LVOT VTI (P = 0.29), stroke volume (P = 0.25), or IVC variability (P = 0.77). Administration of 4% albumin led to an increase in mitral inflow E-wave velocity (P = 0.001), E-to-lateral e’ velocity ratio (P = 0.002), and E-to-septal e’ velocity ratio (P = 0.01), consistent with an increase in pulmonary venous pressure (Table 3) (19, 45). The IVCmax diameter also increased with 4% albumin (P = 0.02), suggestive of an increase in right atrial pressure (57).

There was a positive relationship between the change in blood volume and change in cardiac output (R² = 0.57); unstandardized B coefficient 1.09, SE 0.23, P < 0.01; Fig. 2). However, cardiac output was only increased significantly (0.19 l/min, 95% confidence interval 0.02–0.35) when the increase in blood volume exceeded 0.7 liters.

Table 1. Hemodynamic parameters and lung ultrasound “B-lines” before (T1), half-way (T2), at the end (T3), and at recovery (T4) after the fluid bolus

<table>
<thead>
<tr>
<th>Hemodynamic Parameters and USG B-Lines</th>
<th>P</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output (l/min)</td>
<td></td>
<td>4.73 (0.9)</td>
<td>4.27 (0.8)</td>
<td>4.37 (0.9)</td>
<td>4.29 (1.2)</td>
</tr>
<tr>
<td>SV (ml/min)</td>
<td></td>
<td>60.6 (11.6)</td>
<td>66.3 (12.9)</td>
<td>68.8 (12.4)</td>
<td>67.2 (17.7)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td></td>
<td>96 (5)</td>
<td>100 (5)</td>
<td>100 (5)</td>
<td>96 (7)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td></td>
<td>79 (15)</td>
<td>65 (12)</td>
<td>64 (12)</td>
<td>65 (13)</td>
</tr>
<tr>
<td>Lung USG B-line (total no.)</td>
<td></td>
<td>0 (0)</td>
<td>5.7 (7)</td>
<td>8.9 (9)</td>
<td>7.6 (13)</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td></td>
<td>4.54 (0.7)</td>
<td>4.73 (1.0)</td>
<td>4.93 (1.1)</td>
<td>4.98 (1.0)</td>
</tr>
<tr>
<td>SV (ml/min)</td>
<td></td>
<td>61.1 (10.4)</td>
<td>64.7 (5.1)</td>
<td>69.0 (10.1)</td>
<td>69.7 (9.4)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td></td>
<td>93 (10)</td>
<td>95 (7)</td>
<td>92 (9)</td>
<td>95 (7)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td></td>
<td>76 (18)</td>
<td>75 (20)</td>
<td>74 (20)</td>
<td>72 (17)</td>
</tr>
<tr>
<td>Lung USG B-line (total no.)</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.2 (0.4)</td>
<td>0.2 (0.4)</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td></td>
<td>4.54 (0.6)</td>
<td>4.23 (0.8)</td>
<td>4.34 (0.8)</td>
<td>4.73 (1.3)</td>
</tr>
<tr>
<td>SV (ml/min)</td>
<td></td>
<td>64.5 (13.4)</td>
<td>66.9 (10.0)</td>
<td>65.4 (8.1)</td>
<td>64.6 (9.4)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td></td>
<td>93 (6)</td>
<td>94 (6)</td>
<td>100 (5)</td>
<td>98 (3)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td></td>
<td>71 (13)</td>
<td>64 (11)</td>
<td>67 (15)</td>
<td>73 (13)</td>
</tr>
<tr>
<td>Lung USG B-line (total no.)</td>
<td></td>
<td>0.1 (0.2)</td>
<td>1.6 (1.5)</td>
<td>3.2 (3.6)</td>
<td>2.2 (4.8)</td>
</tr>
</tbody>
</table>

T: timepoints examined in the study; SV: stroke volume; MAP: mean arterial pressure; HR: heart rate; USG: ultrasonography. Data presented as means ± SD. Analyzed with repeated-measures ANOVA individually for each fluid type.

Table 2. Respiratory measures

<table>
<thead>
<tr>
<th>Respiratory measures</th>
<th>0.9% Saline, 30 ml/kg</th>
<th>5% Glucose, 30 ml/kg</th>
<th>4% Albumin, 30 ml/kg</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung B-lines, ultrasound</td>
<td>0 ± 0</td>
<td>8.9 ± 9</td>
<td>0.01</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>Airway resistance 5 Hz, kPa/l/s</td>
<td>0.29 ± 0.1</td>
<td>0.40 ± 0.1</td>
<td>0.04</td>
<td>0.30 ± 0.1</td>
</tr>
<tr>
<td>KCO, ml · min⁻¹ · mmHg⁻¹ · l⁻¹</td>
<td>4.9 ± 0.2</td>
<td>5.1 ± 0.3</td>
<td>0.07</td>
<td>4.9 ± 0.3</td>
</tr>
<tr>
<td>FVC, liter</td>
<td>5.08 ± 1.3</td>
<td>4.95 ± 1.3</td>
<td>0.12</td>
<td>5.12 ± 1.3</td>
</tr>
<tr>
<td>FRC, liter</td>
<td>3.6 ± 1.1</td>
<td>3.4 ± 1.2</td>
<td>0.15</td>
<td>3.6 ± 1.1</td>
</tr>
<tr>
<td>FEV1, liter</td>
<td>3.95 ± 1.2</td>
<td>3.83 ± 1.2</td>
<td>0.13</td>
<td>3.93 ± 1.1</td>
</tr>
<tr>
<td>PEFR, l/s</td>
<td>9.80 ± 1.8</td>
<td>9.14 ± 1.9</td>
<td>0.04</td>
<td>9.85 ± 2.1</td>
</tr>
<tr>
<td>dX/dflow 5 Hz, kPa/l/s</td>
<td>0.04 ± 0.03</td>
<td>-0.04 ± 0.03</td>
<td>0.01</td>
<td>-0.02 ± 0.05</td>
</tr>
</tbody>
</table>

KCO, diffusion capacity for carbon monoxide corrected for alveolar volume; FVC, forced vital capacity; FRC, functional residual capacity; FEV1, forced expiratory volume in 1 s; PEFR, forced expiratory flow rate; dX/dflow, delta reactance/delta flow rates. T1, before fluid bolus; T3, end of 30 ml/kg fluid bolus. Data presented as means ± SD. *Paired t-test; † repeated-measures ANOVA with fluid interaction.
Blood samples. Administration of 4% albumin led to an increase in plasma NT-proBNP concentration ($P = 0.01$), as well as the greatest observed decrease in hematocrit ($P < 0.001$; greatest rise in estimated blood volume), with a simultaneous increase in serum albumin ($P = 0.01$) and decrease in serum-ionized calcium (corrected for pH; $P = 0.001$; Table 4). Administration of 0.9% saline led to a decrease in hematocrit and serum albumin ($P < 0.001$) and an increase in serum chloride ($P < 0.001$). Infusion of 0.9% saline also led to an increase in plasma Ang-2 (corrected for blood volume; $P = 0.001$) and a decrease in the Ang-1/Ang-2 ratio ($P = 0.05$), suggesting a proinflammatory effect. Time to micturition was also longest with 0.9% saline ($P = 0.001$; Table 4). Administration of 5% glucose led to a decrease in serum albumin ($P < 0.001$), sodium ($P = 0.001$), and chloride ($P = 0.001$), with no change in NT-proBNP ($P = 0.9$) and a decrease in Ang-2 ($P = 0.02$).

**DISCUSSION**

The major finding of our study is that in healthy subjects, rapid iv infusion of 30 ml/kg of 0.9% saline and 4% albumin had very different cardiorespiratory effects. Infusion of 0.9% saline led to development of interstitial pulmonary edema, as evidenced by lung ultrasound B-lines and an increase in small airway resistance, without evidence for increased pulmonary capillary pressure or pulmonary blood flow on echocardiography. An increase in plasma Ang-2 concentration and a resultant decrease in the Ang-1/Ang-2 ratio suggest a possible inflammatory association with edema formation. In contrast, there was no evidence for interstitial pulmonary edema after infusion of the same volume of 4% albumin, even though there was an increase in DL$_{CO}$, a fall in lung volumes (FEV$_1$, FVC, and FRC), an increase in Doppler echocardiographic indices of preload, and elevated plasma NT-proBNP, all of which are consistent with an increase in pulmonary blood volume and capillary pressure. The differences between the effects of 0.9% saline and 4% albumin may have direct clinical consequences for patient resuscitation, such as development of pulmonary edema with 0.9% saline and a decrease in lung volume with 4% albumin.

**Choice of fluid bolus volume used in this study.** Previously, the rapid iv infusion of 20 ml/kg of 0.9% saline did not impair resting pulmonary gas exchange in a study of healthy human subjects, as measured by the multiple inert gas elimination technique (51), nor did it alter lung density when analyzed by MRI (22). We chose 30 ml/kg, as rapid infusion of this dose of 0.9% saline has previously been shown to reduce lung volumes (42, 55) and cause mild airflow obstruction and enhanced airway responsiveness (48). Furthermore, this volume was sufficient to alter Doppler echocardiography indices of preload and pulmonary artery occlusion pressure in normal subjects (19) and is frequently used in clinical medicine for fluid resuscitation (18, 38, 50, 71).

**Table 3. Cardiac ultrasound parameters**

<table>
<thead>
<tr>
<th></th>
<th>0.9% Saline, 30 ml/kg</th>
<th>5% Glucose, 30 ml/kg</th>
<th>4% Albumin, 30 ml/kg</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T3</td>
<td>$P^*$</td>
<td>T1</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>4.53 ± 0.9</td>
<td>4.47 ± 0.9</td>
<td>0.20</td>
<td>4.46 ± 0.7</td>
</tr>
<tr>
<td>LVOT VTI, cm</td>
<td>16.04 ± 2.6</td>
<td>17.9 ± 2.8</td>
<td>0.09</td>
<td>17.0 ± 3.2</td>
</tr>
<tr>
<td>Stroke volume, ml/min</td>
<td>60.6 ± 11.6</td>
<td>68.8 ± 12.4</td>
<td>0.06</td>
<td>64.5 ± 13.4</td>
</tr>
<tr>
<td>IVCmax diameter, cm</td>
<td>1.6 ± 0.6</td>
<td>1.6 ± 0.5</td>
<td>0.69</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>Mitral E, cm/s</td>
<td>61.7 ± 10.7</td>
<td>71.7 ± 11.3</td>
<td>0.07</td>
<td>65.8 ± 9.4</td>
</tr>
<tr>
<td>E/e', lateral</td>
<td>4.5 ± 1.0</td>
<td>5.3 ± 1.2</td>
<td>0.09</td>
<td>4.6 ± 0.9</td>
</tr>
<tr>
<td>e', septal, lateral</td>
<td>4.2 ± 2.3</td>
<td>5.0 ± 2.5</td>
<td>0.15</td>
<td>5.2 ± 0.8</td>
</tr>
<tr>
<td>e', lateral, cm/s</td>
<td>13.9 ± 1.5</td>
<td>14.9 ± 2.7</td>
<td>0.26</td>
<td>14.4 ± 1.2</td>
</tr>
<tr>
<td>IVCTmax diameter, cm</td>
<td>12.2 ± 0.8</td>
<td>12.7 ± 1.5</td>
<td>0.50</td>
<td>12.2 ± 2.0</td>
</tr>
<tr>
<td>DT</td>
<td>213 ± 19</td>
<td>204 ± 26</td>
<td>0.28</td>
<td>227 ± 48</td>
</tr>
<tr>
<td>E/A</td>
<td>1.4 ± 0.2</td>
<td>1.8 ± 0.6</td>
<td>0.08</td>
<td>1.4 ± 0.1</td>
</tr>
</tbody>
</table>

LVOT, left ventricular outflow tract; VTI, velocity time integral; IVCmax, maximum inferior vena cava; DT, deceleration time. T1, before fluid bolus; T3, end of 30 ml/kg fluid bolus. Data presented as means ± SD. *Paired t-test; †repeated-measures ANOVA with fluid interaction.

**Fig. 2. Change in cardiac output with increase in blood volume ($R^2 = 0.57$, $P < 0.01$).**
Effects of 0.9% saline. Rapid iv infusion of an isosmotic solution, such as 0.9% saline, is expected to result in fluid filtration and leakage from pulmonary vessels (67, 68, 70). We found that administration of 0.9% saline led to development of interstitial pulmonary edema, as demonstrated by lung ultrasound B-lines. Similar findings have been described using chest radiography (15) and computed tomography, where an increase in airway wall thickness was attributed to peribronchial edema formation (31).

We measured small (distal) airway resistance at a low frequency (5 Hz) by impedance oscillometry, which has proven reproducible and correlates well with spirometry and plethysmographic values (47). We found an increase in distal airway resistance, which has previously been attributed to increased small airway wall edema encroaching on the bronchial lumen (48). Other authors have argued that the initial increase in airway resistance observed in experimentally induced pulmonary edema is secondary to distension of the pulmonary arteries within bronchovascular sheaths, with subsequent compression of the smaller peripheral airways (23, 40, 63).

A narrowing of airways with large caliber from peribronchial edema should manifest as a reduction in FEVs (FEV1 and FVC) and flow rate (PEFR). Such changes in lung function have been shown to occur with 0.9% saline infusion in several previous studies (15, 42, 48) and except for PEFR did not occur in our study. Our study protocol involved lung ultrasound and echocardiography measurements immediately after fluid administration, causing a slight delay in the respiratory measurements. Therefore, it is possible that different results would have been obtained had the test been performed sooner. However, in contradiction to this, ultrasound B-lines were still present 1 h after of 0.9% saline infusion, suggesting a slow reabsorption of the interstitial edema. This is consistent with previous reports of slow (up to 2 days) resolution after 0.9% saline infusion (14). We also found that the time to first micturition was longest with 0.9% saline, a finding similar to that reported by Chowdhury et al. (12) and consistent with extravascular fluid redistribution.

An important finding of our study is an increase in plasma Ang-2 and decrease in the Ang-1/Ang-2 ratio after 0.9% saline infusion. Plasma Ang-1 is secreted from pericytes and is required for blood vessel maturation and stabilization, whereas Ang-2 is endothelial derived and sensitizes the endothelial cell to the inflammatory actions of TNF-α, further perpetuating inflammation (17); its regulation is flow dependent (20). Ang-2 is stored in the Weibel-Palade bodies (endothelial cell storage vesicles), which also contain von Willebrand factor and P-selectin, necessary for the inflammatory sequestration of leukocytes into tissues (56). Ang-2 predicts development of lung injury in at-risk patients and mortality in patients with established acute respiratory distress syndrome (1, 65). The elevated plasma Ang-2 concentration and decrease in the Ang-1/Ang-2 ratio after administration of 0.9% saline suggest active exocytosis of Weibel-Palade bodies and a proinflammatory effect of bolus 0.9% saline. Interestingly, in a study of patients with acute lung injury, conservative fluid therapy was associated with decreased plasma Ang-2 concentration over time and better outcome compared with a nonconservative fluid strategy (10).

In our study, 0.9% saline also led to an increase in serum chloride, similar to previous reports in healthy volunteers (12, 54) and critically ill patients (7, 73). Chloride transport-driven alveolar fluid secretion is considered a major contributor to pulmonary edema formation (62), and a transient rise in serum chloride levels after 0.9% saline administration may exacerbate this process.

Effects of 4% albumin. As far as we are aware, there are no previously published studies that describe the effect of rapid iv infusion of 4% albumin in healthy subjects. In our study, infusion of 4% albumin led to an increase in estimated blood volume and a simultaneous increase in Doppler echocardiographic indices of preload (left atrial pressure) and IVCmax diameter. In addition, there was an increase in plasma NT-proBNP, consistent with increased cardiac chamber wall tension. A concurrent decrease in measured lung volumes can be explained by a rise in intrathoracic blood volume, leading to compression of the lungs. This explanation is supported by the rise in DLCO (corrected for blood volume), as described previously (34). Despite these findings, there was no evidence for the development of interstitial pulmonary edema after infusion of 4% albumin.

There are several potential counter-regulatory effects of 4% albumin that may protect against the development of pulmo-
nary edema. Although 4% albumin led to an increase in pulmonary capillary pressure and hence, should have increased the net microvascular filtration rate into the interstitium, it also led to a simultaneous increase in serum albumin concentration, increasing the colloidal osmotic pressure and counteracting the effect of the rise in capillary pressure. Application of the revised Starling equation requires consideration of the effect of the endothelial glycocalyx on fluid dynamics (3, 33, 72). Under this revised paradigm, the colloidal osmotic effect of albumin would not promote absorption of interstitial edema, and the hypervolemia caused by 4% albumin administration should lead to disruption of the endothelial glycocalyx and enhanced vascular permeability (8, 26). However, the increased permeability is likely to be distributed systemically, with only a small proportion contributed by the pulmonary vasculature (74). Furthermore, albumin is protective to the glycocalyx structure, improves endothelial integrity (25, 64), is a specific inhibitor of endothelial apoptosis (75), and leads to the release of an endothelial-derived relaxation factor (29), with vasodilation and a decrease in shear forces.

Some of the risk of lung injury from increased pulmonary capillary pressure may be mediated through an increase in endothelial calcium ion concentration from external calcium ions (24, 32). In our study, administration of 4% albumin led to a decrease in the serum-ionized calcium, likely due to binding of free calcium by the albumin solution, which does not contain calcium. A transient drop in serum-ionized calcium thus may have impeded the adverse effects of elevated pulmonary capillary pressures on the development of interstitial pulmonary edema. This decrease in calcium has been seen in patients with septic shock treated with 4% albumin solution (7), and in hypovolemic trauma patients who received multiple blood transfusions. It is of note that calcium-free perfusate is often used in isolated, perfused lung-injury models as a negative control (32).

Effects of 5% glucose. Administration of 5% glucose (similar osmolality but a hypotonic solution) did not cause any major cardiorespiratory changes. These results were as anticipated, given the capacity for distribution of a large volume of free water in the body, principally to the intracellular space (21). However, there was a significant decrease in serum sodium, chloride, and albumin concentrations. The decrease in serum sodium and chloride concentrations was due to the similar osmolality but hypotonic nature of 5% glucose and its rapid rate of administration, according to the study protocol, to provide consistency of administration between each of the study fluids. Even though we observed an acute decrease in serum sodium concentration—some of this may have been due to pseudohyponatremia from elevated blood glucose concentrations—there were no adverse effects observed in our monitored subjects, except for a faster time to micturition. Adverse effects of a rapid fall in serum sodium concentration have been reported, particularly in female subjects (4); hence, we only included male volunteers in our study. Previous investigators have administered between 10 and 25 ml/kg iv 2.5% glucose over 30–60 min in both healthy subjects and patients undergoing elective surgery with either a similar fall in serum sodium (36) or no measurement of serum sodium, with no reported adverse effects (58–60). However, we would caution future investigators with regard to the risk of a significant decrease in serum sodium concentration with rapid iv infusion of 5% glucose if our protocol is replicated.

Changes in hemodynamic and echocardiographic variables. We found no significant increase in cardiac output with fluid loading, a trend toward an increase in stroke volume with 0.9% saline and 4% albumin, and only a weakly positive correlation between change in cardiac output and change in blood volume; a significant increase in cardiac output was only seen when the increase in estimated blood volume was >0.7 liters. Our measure of cardiac output was based on the Doppler echocardiographic measurement of LVOT VTI and was not continuous. We measured the LVOT diameter (to calculate LVOT cross-sectional area) only at the first measurement period with each fluid. It is possible that the LVOT cross-sectional area increased with fluid loading; thus there may have been a relative underestimation of the increase in stroke volume after fluid administration. However, previous studies have also shown only a small, or no, increase in cardiac output in response to rapid infusion of fluid (0.9% saline) (13, 42). We did not observe an increase in heart rate (Bainbridge reflex), as reported previously (13), likely due to multiple factors. Of interest, the relative change in estimated blood volume between equivalent volumes of 0.9% saline infusion and 4% albumin infusion in our study is consistent with the revised Starling equation and glycocalyx model (72), although these findings should be interpreted with caution, as they were not direct measures.

In our study, with infusion of 4% albumin, Doppler echocardiography demonstrated a significant increase in mitral E velocity but not in tissue Doppler septal or lateral e’ velocities. There was a nonsignificant increase in mitral E velocity with 0.9% saline infusion. In a previous study of healthy volunteers, infusion of the same volume of 0.9% saline at the same rate resulted in an increase in pulmonary artery occlusion pressure and a significant increase in E, septal e’, but not lateral e’ velocity (19), suggesting that in normal subjects, both E and septal e’ velocities are sensitive to changes in preload (left atrial pressure). However, in the setting of impaired relaxation, e’ becomes insensitive to alterations in preload, and the ratio of E to e’ is a guide to preload (45). Although our subjects had structurally normal hearts and had similar baseline Doppler echocardiographic values for E velocities, e’ velocities, and E/e’ ratios to those in the study by Firstenberg et al. (19), the slightly prolonged E wave DT (>200 ms) suggests that our subjects may have had mild impairment of myocardial relaxation. In taking these facts into consideration, our results are consistent with a significant increase in preload (pulmonary capillary pressure and pulmonary venous pressure) with infusion of 4% albumin. This is also consistent with the increased total blood volume (decrease in hematocrit) and increased pulmonary blood volume (increase in KCO) seen with 4% albumin. Although the change in total blood volume with infusion of 0.9% saline suggests that there was also a small increase in preload with 0.9% saline (19), the Doppler echocardiography indices were not sensitive enough to detect this. The slight (statistically insignificant) increase in KCO after 0.9% saline infusion may represent the opposing effects of a minor increase in pulmonary blood volume and the presence of interstitial lung edema. Previous studies have reported no change in DLCO with 0.9% saline (51, 52, 55).
We found no changes in the IVC variability, which has only a weak correlation with simulated hypovolemia in healthy volunteers (41), and despite its validation in ventilated patients (6, 16), it has not been validated with fluid administration in healthy human subjects.

Validation of lung ultrasound B-lines to detect interstitial pulmonary edema. The number of lung ultrasound B-lines (B-line score) correlates with lung weight and density, determined by computerized tomography (5), and with pulmonary artery occlusion pressure and extravascular lung water, determined by the indicator dilution method (2). The B-line score has satisfactory intra- and interobserver variability, ∼5% and 7%, respectively (27). Dynamic changes in the B-line score have been demonstrated by the disappearance of B-lines after fluid removal during hemodialysis (46). These data support the use of lung ultrasound to evaluate real-time changes in extravascular lung water and the physiological response to fluid administration.

Study limitations. Our study should be viewed in light of several limitations, most notably, the number of subjects examined. However, the crossover design of the study meant that each subject served as his own control, adding strength to our results. We did not examine the effect of fluid administration on other organs, such as the kidney, as this was not the focus of our study. This study did not use a chloride-balanced fluid; therefore, the cardiorespiratory effects of chloride balance were not examined.

Conclusion. In healthy subjects, the rapid iv infusion of 0.9% saline and 4% albumin had different pulmonary effects not directly attributable to a passive, hydrostatic mechanism for the development of pulmonary edema. Infusion of 0.9% saline resulted in the development of interstitial pulmonary edema, whereas 4% albumin caused hypervolemia without interstitial pulmonary edema. The different effects of these two resuscitation fluids may be due to differences in active signaling in the pulmonary vasculature or a protective effect of albumin. The processes and mechanisms that underlie these differential responses to fluid bolus administration should be explored in future studies.

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