

Research

Effects of contrast material on computed tomographic measurements of lung volumes in patients with acute lung injuryBélaid Bouhemad¹, Jack Richecoeur², Qin Lu³, Luiz M Malbouisson⁴, Philippe Cluzel⁵, Jean-Jacques Rouby⁶ and the ARDS CT Scan Study Group⁷¹Chef de Clinique en Réanimation Chirurgicale Pierre Viars (Department of Anaesthesiology), Hospital Pitié-Salpêtrière, University of Paris VI, Paris, France²Praticien Hospitalier en Réanimation Médicale Polyvalente de Pontoise, Pontoise, France³Praticien Assistant Contractuel en Réanimation Chirurgicale Pierre Viars (Department of Anaesthesiology), Hospital Pitié-Salpêtrière, University of Paris VI, Paris, France⁴Research fellow, Department of Anaesthesiology, Hospital das Clinicas, São Paulo, Brazil⁵Professor of Radiology, Department of Radiology, Hospital Pitié-Salpêtrière, University of Paris VI, Paris, France⁶Professor of Anaesthesia and Critical Care, Réanimation Chirurgicale Pierre Viars, and Director of Research, Hospital Pitié-Salpêtrière, University of Paris VI, Paris, France⁷See acknowledgementCorrespondence: Pr J. J. Rouby, jjrouby.pitie@invivo.edu

Received: 2 February 2002

Revisions requested: 18 April 2002

Revisions received: 24 July 2002

Accepted: 4 November 2002

Published: 16 December 2002

Critical Care 2003, **7**:63-71 (DOI 10.1186/cc1852)This article is online at <http://ccforum.com/content/7/1/63>© 2003 Bouhemad *et al.*, licensee BioMed Central Ltd (Print ISSN 1364-8535; Online ISSN 1466-609X). This is an Open Access article: verbatim copying and redistribution of this article are permitted in all media for any non-commercial purpose, provided this notice is preserved along with the article's original URL.**Abstract****Background** Intravenous injection of contrast material is routinely performed in order to differentiate nonaerated lung parenchyma from pleural effusion in critically ill patients undergoing thoracic computed tomography (CT). The aim of the present study was to evaluate the effects of contrast material on CT measurement of lung volumes in 14 patients with acute lung injury.**Method** A spiral thoracic CT scan, consisting of contiguous axial sections of 10 mm thickness, was performed from the apex to the diaphragm at end-expiration both before and 30 s (group 1; $n = 7$) or 15 min (group 2; $n = 7$) after injection of 80 ml contrast material. Volumes of gas and tissue, and volumic distribution of CT attenuations were measured before and after injection using specially designed software (Lungview®; Institut National des Télécommunications, Evry, France). The maximal artifactual increase in lung tissue resulting from a hypothetical leakage within the lung of the 80 ml contrast material was calculated.**Results** Injection of contrast material significantly increased the apparent volume of lung tissue by 83 ± 57 ml in group 1 and 102 ± 80 ml in group 2, whereas the corresponding maximal artifactual increases in lung tissue were 42 ± 52 ml and 31 ± 18 ml.**Conclusion** Because systematic injection of contrast material increases the amount of extravascular lung water in patients with acute lung injury, it seems prudent to avoid this procedure in critically ill patients undergoing a thoracic CT scan and to reserve its use for specific indications.**Keywords** acute lung injury, contrast material, lung volumes, thoracic computed tomography scan**Introduction**

Since the early 1990s, spiral computed tomography (CT) scanners have permitted assessment of the entire pulmonary

parenchyma in a very short period of time [1–3]. In patients with acute lung injury (ALI) injection of contrast material is considered useful for differentiating consolidated lung parenchyma from pleural effusion and for diagnosing lung

abscess. It is also required for diagnosis of pulmonary embolism. As a consequence, injection of contrast material is routinely performed in critically ill patients undergoing a thoracic CT scan [4,5].

In the presence of alterations in the blood–brain barrier, injection of contrast material increases brain oedema [6–9]. This is due to the direct toxic effects of the contrast material on nerve cells [10], which result from its osmotic effect after intracellular penetration. Similarly, in ALI breakdown of the constituents of the alveolar–capillary barrier (pulmonary epithelium or capillary endothelium) causes an increase in lung permeability, which is accompanied by interstitial and alveolar accumulation of water and proteins [11]. Alteration in the alveolar–capillary barrier could also promote leakage of contrast material into the interstitial and alveolar spaces, with a consequent increase in extravascular lung water. Using CT, the latter may be measured as an increase in lung tissue. However, administration of contrast material creates a density artifact that may lead to an overestimation of lung tissue. The aim of the present study was to evaluate the effects of intravenous injection of contrast material on CT measurement of volumes of gas and lung tissue in patients with ALI, and to test the hypothesis that administration of contrast material increases extravascular lung water. In addition, in order to estimate the range of error in determining lung tissue that results from administration of contrast material, a 'lung phantom' was filled with known volumes of water containing increasing concentrations of contrast material and was scanned to compare the calculated increases in volume of water with the actual instilled volume.

Materials and method

Patients

Fourteen patients hospitalized in the Surgical Intensive Care Unit of La Pitié-Salpêtrière for ALI were prospectively studied [12]. Inclusion criteria were as follows: a ratio of arterial oxygen tension to fractional inspired oxygen of less than 300 mmHg at zero end-expiratory pressure; bilateral hyperdensities on a bedside chest radiogram; and pulmonary capillary wedge pressure below 18 mmHg and/or left ventricular ejection fraction greater than 50%, as estimated by transoesophageal echocardiography. Informed consent was obtained from the patients' next of kin. In each patient, a thoracic CT scan with injection of contrast material was indicated clinically for diagnosing lung abscess, pulmonary embolism or pleural effusion.

Spiral thoracic computed tomography scan: technical characteristics

Each patient was transported to the Department of Radiology (Thoracic Division) by two experienced physicians. Patients were sedated and paralyzed with a continuous intravenous infusion of 5 µg/kg per hour fentanyl, 0.1 mg/kg per hour midazolam and 0.05 mg/kg per hour vecuronium. Mechanical ventilation was provided using an Osiris ventilator (Taema,

Antony, France), which was specifically designed for delivering 100% oxygen during transportation of critically ill patients. Electrocardiography, pulse oxymetry and systemic arterial pressure were monitored continuously using a Propaq 104 EL monitor (Protocol System, North Chicago, IL, USA).

Spiral lung scanning was performed at end-expiration from the apex to the diaphragm using a Tomoscan SR 7000 (Philips, Eindhoven, The Netherlands). Disconnection from the ventilator and 15 s apnoea were necessary to obtain the CT sections, which resulted in a transient desaturation in most patients, the lowest oxygen saturation measured being 87%. All images were observed and photographed at a window width of 1600 Hounsfield units (HU) and a level of –700 HU. The exposures were taken at 120 kV and 250 mA. The value of the pitch was 1. In the present study, each voxel had a volume of 1.7 mm³. As previously described [2,3,13,14], we evaluated contiguous axial CT sections 10 mm thick, which were reconstructed from the volumetric data. On each CT section, right and left lung parenchyma were delineated using the roller ball of the computer. The reproducibility of manual delineation was excellent, with determinations of the overall lung volume by three different operators showing a maximal difference of 25 ml. The respective volumes of gas and lung tissue, and the distribution of lung aeration were compared before and after injection of contrast material using the Lungview[®] (Institut National des Télécommunications, Evry, France), as was previously described [2–4,15].

Two groups of patients were studied; in group 1 ($n = 7$) CT sections were acquired before and 30 s after injection of contrast material, and in group 2 ($n = 7$) the CT sections were obtained before and 15 min after injection of contrast material. In both groups, a volume of 80 ml of contrast material (iobitridol; Xenetix 350, Guerbet, Roissy, France) was automatically injected into the superior vena cava at a constant flow of 4 ml/s. In one patient, CT sections acquired 30 s after the injection of contrast material were repeated 15 min later.

Computed tomography measurement of lung volumes and blood density

Apparent lung volumes of gas and tissue

CT scans obtained before and after injection of contrast material were analyzed using specially designed software (Lungview[®]), which is based on the tight correlations that exist between radiological and physical densities [16].

Before and after injection of contrast material, the analysis was performed according to the following principles. The CT number characterizing each individual voxel is expressed in HU and is defined as the attenuation coefficient of the radiogram by the material being studied minus the attenuation coefficient of water divided by the attenuation coefficient of water. By convention, the CT number of water is 0 (HU). The CT number is scaled by a factor 1000, the CT number of gas

being -1000 HU. A lung area characterized by a mean CT number of -500 HU is considered to be composed of 50% gas and 50% tissue. A lung area characterized by a mean CT number of -200 HU is considered to be composed of 20% gas and 80% tissue. Using this analysis, it was possible to compute the volume of gas and tissue present in the lungs.

In the first step, the distribution of CT numbers was measured on each CT section for 256 compartments between -1200 HU and +200 HU, examining an interval of 5.47 HU per compartment. For each compartment of a known number of voxels, the total volume and the volume of gas and lung tissue were computed using the following equations (in which 'CT' is the mean CT number of the compartment analyzed):

$$\text{Volume of the voxel} = (\text{size of the pixel})^2 \times \text{section thickness} \quad (1)$$

$$\text{Total volume} = \text{number of voxels} \times \text{volume of the voxel} \quad (2)$$

$$\begin{aligned} \text{Apparent volume of gas} &= (-\text{CT}/1000) \times \text{total volume,} \\ \text{if the compartment considered has a CT number} \\ \text{below 0 (volume of gas} &= 0 \text{ if the compartment} \\ \text{considered has a CT number above 0)} \end{aligned} \quad (3)$$

$$\begin{aligned} \text{Apparent volume of tissue} &= ([1 + \text{CT}]/1000) \times \\ \text{total volume, if the compartment considered has a} \\ \text{CT number below 0} \end{aligned} \quad (4)$$

$$\begin{aligned} \text{or, volume of tissue} &= \text{number of voxels} \times \text{volume of the} \\ \text{voxel, if the compartment considered has a CT number} \\ \text{above 0} \end{aligned} \quad (4')$$

In a second step, the volumes of gas and lung tissue of each region of interest were calculated by adding the values of all of the compartments present within the region of interest considered. In a third step, the volumes of gas and lung tissue of both lungs were calculated by adding the volumes of all lung regions (right lung + left lung). The total lung volume at end-expiration was defined as the sum of gas and tissue volumes. The overall volume of gas present at end-expiration in both lungs was defined as functional residual capacity.

The distribution of lung tissue along the cephalocaudal axis was determined in patients by taking into consideration all 10 mm thick CT sections between the apex and the lung base. The distribution of gas and lung tissue along the anteroposterior axis was determined on five contiguous 10 mm thick CT sections located around the tracheal carina (one located at the carina level, and two above and two below the carina level) by taking into consideration 10 contiguous compartments of similar height between the sternum and the vertebrae [17].

Maximal artifactual increase in lung tissue

In each patient, blood density was measured in the pulmonary artery before and after injection of contrast material in order

to determine the concentration of contrast material present in the pulmonary circulation 30 s and 15 min after injection.

The maximal artifactual increase in lung tissue was calculated as follows. First, it was hypothesized that the 80 ml contrast material had penetrated into the alveolar-interstitial compartment and had created a gas-contrast material interface. It was assumed that the alveolar-interstitial contrast material concentration was equal to the concentration measured within pulmonary arteries, a positive concentration gradient between extravascular and vascular spaces being very unlikely. The new CT number of the lung parenchyma (CT_{new}) was then calculated as follows:

$$\text{CT}_{\text{new}} = \frac{(\text{CT}_{\text{control}} \times \text{volume}_{\text{tot control}}) + (80 \times \text{CT}_{\text{blood inj}})}{\text{volume}_{\text{tot control}} + 80} \quad (5)$$

Where $\text{CT}_{\text{control}}$ = mean CT number of the lung parenchyma before injection, $\text{volume}_{\text{tot control}}$ = total lung volume before injection, and $\text{CT}_{\text{blood inj}}$ = CT number of the pulmonary artery following injection. The apparent volume of lung tissue following injection ($V_{\text{tissue } 1}$) would have been calculated as follows:

$$V_{\text{tissue } 1} = ([1 + \text{CT}_{\text{new}}]/1000) \times \text{volume}_{\text{tot inj}} \quad (6)$$

Where $\text{volume}_{\text{tot inj}}$ = total lung volume following injection. If the 80 ml contrast material had been replaced by 80 ml plasma, then the new CT number (CT_{80}) and the calculated volume of lung tissue ($V_{\text{tissue } 2}$) would have been:

$$\text{CT}_{80} = \frac{(\text{CT}_{\text{control}} \times \text{volume}_{\text{tot control}}) + (80 \times \text{CT}_{\text{blood control}})}{\text{volume}_{\text{tot control}} + 80} \quad (7)$$

$$V_{\text{tissue } 2} = ([1 + \text{CT}_{80}]/1000) \times \text{volume}_{\text{tot inj}}$$

Where $\text{CT}_{\text{blood control}}$ = CT number of the pulmonary artery before injection. The maximal artifactual increase in lung tissue following the injection of contrast material was then calculated as $V_{\text{tissue } 1} - V_{\text{tissue } 2}$, and the minimal actual increase in lung tissue as the apparent increase in lung tissue minus the maximal artifactual increase in lung tissue.

Preparation of the human lung phantom

The error resulting from the presence of contrast material in the determination of gas and lung tissue volumes was assessed on a lung phantom that was prepared according to a technique proposed by Markarian and Dailey in 1975 [18,19]. This simple and easily implemented method is aimed at producing a lung specimen that can be stored for over 10 years without damage [20] and is suitable for histopathology, radiography and CT examinations.

In 1993, a postmortem left pneumonectomy was performed in a 65-year-old man who died from acute respiratory distress

syndrome complicating postoperative bronchopneumonia 5 days after surgical resection of a thoracoabdominal aortic aneurysm. The pneumonectomy was performed according to the French legislation (law no 781181, December 22, 1976, followed by the statutory order no 78501 of March 31, 1978 and the implementation order of April 3, 1978) and after obtaining informed consent from the patient's relatives. A thoracotomy was performed in the fifth left intercostal space at the bedside under surgical conditions within 20 min after death. After cessation of mechanical ventilation, both lungs were then removed from the thorax, with the trachea being sectioned immediately beneath the larynx. After dissection (carefully avoiding lung laceration), both lungs were separated by a tracheal section at the carina level, leaving a long portion of the left main stem bronchus; the pulmonary vessels were tied with strings; and the left main stem bronchus was cannulated with an endotracheal tube no 7.5. The left lung was then inflated via the endotracheal tube by a fixative composed of polyethylene glycol 400 (25%), ethyl alcohol 95% (10%), formaldehyde 37% (10%) and water (55%). The fixative was instilled by gravity at a pressure of 30 cmH₂O until the lung surface was firmly distended and small amounts of fixative were weeping through the pleural surface. The endotracheal tube was clamped in order to prevent loss of fluid, and the lung specimen was floated in a container filled with the same fixative for 7 days.

The lung was then suspended from a ring stand over a drip basin and the endotracheal tube was connected to a source of air equipped with a continuous positive airway pressure system set at a pressure of 30 cmH₂O. The air pressure causing the fixative to weep from the pleural surface was maintained over 3 days, and a dry left lung with spongy texture was obtained. The lung was stored in a hermetically sealed bag between 1993 and 1999 without detectable deterioration.

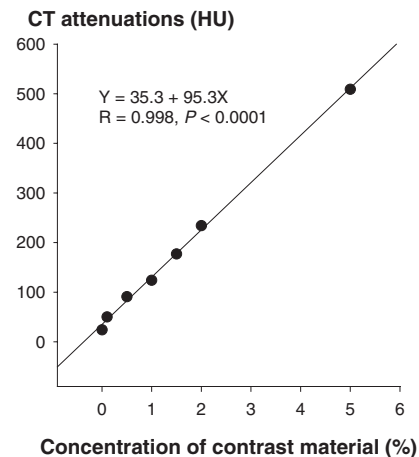
Effects of contrast material on computed tomography determination of lung volumes

The effect of contrast material on CT determination of gas and lung tissue volumes was assessed according to a technique recently described [15].

In a first step, the contrast material was diluted with water to obtain solutions of increasing concentrations: 0%, 0.1%, 0.5%, 1%, 1.5%, 2% and 5%. The mean CT attenuation corresponding to each concentration of contrast material was measured by scanning one reservoir filled with water and six reservoirs filled with the solutions of increasing concentrations. The CT attenuation of pure contrast material was 3918 HU. As shown in Fig. 1, CT attenuation increased linearly with the concentration of contrast material in the solution.

In a second step, assessment of the artifactual changes in gas and tissue volume in the presence of contrast material

Figure 1



Changes in computed tomography (CT) attenuation with increasing concentrations of contrast material in the solution. HU, Hounsfield units.

was performed on the lung phantom. The volumes of the different aliquots instilled in the phantom were compared with the volumes computed using Lungview[®] on the corresponding CT scans. Equation 4 above (which does not take into consideration the presence of contrast material) was used for this calculation. Eight CT scans of the human lung phantom were performed following successive bronchial instillations of water or solution containing 5% iobitridol. The phantom was first filled with three aliquots of water (50, 100 and 150 ml) administered into the left mainstem bronchus. After each aliquot, the phantom was weighed using an electronic scale (Teraillon BE 201, Paris, France). The phantom was then dried with a hair drier until its weight returned to the initial dry weight. One week later, the phantom was filled with three aliquots of a solution containing 5% of iobitridol and weighed after each aliquot.

The volume of each aliquot of water was equivalent to its weight (physical density = 1 mg/ml). The volume of each aliquot (W_{aliquot}) containing 5% contrast material was lower than its weight (physical density = 1.2 g/ml). As a consequence, the volume of the aliquot (V_{aliquot}) was calculated as $V_{\text{aliquot}} = 0.943 \cdot W_{\text{aliquot}}$. The volume of each aliquot measured from its weight was then compared with the volume of the aliquot calculated using Lungview[®].

Statistical analysis

Results are expressed as mean $\pm$ SD. Lung volumes before and after injection of contrast material were compared using a Wilcoxon test. The measured and Lungview[®]-derived volumes of aliquots were compared by linear regression analysis and using the Bland–Altman method [21]. Statistical analysis was performed using Statview 5.0 (SAS Institute Inc., Cary, NC, USA), and $P < 0.05$ was considered statistically significant.

Table 1**Clinical and respiratory characteristics of the 14 patients with acute lung injury**

Patient no	Age/sex	Cause of ALI	Lung morphology*	Outcome	SAPS II	LISS	PaO ₂ : FiO ₂ (mmHg)
Group 1							
1	67/M	BPN	LA	D	42	1.7	176
2	34/M	PC	PA	S	55	3.5	262
3	81/M	BPN	LA	D	44	1.7	292
4	54/M	BPN	PA	S	16	2.0	205
5	68/M	BPN	LA	S	27	1.7	132
6	67/M	BPN	LA	S	46	1.5	238
7	74/M	BPN	LA	D	64	1.66	164
Mean ± SD	64 ± 15				42 ± 16	2.0 ± 0.7	210 ± 57
Group 2							
8	72/M	BPN	LA	S	79	1.5	250
9	49/M	PC	PA	S	22	2.3	250
10	22/M	BPN	LA	S	24	2	136
11	48/M	BPN	LA	D	49	2	139
12	41/M	BPN	LA	S	29	1.66	182
13	35/M	BPN	PA	D	74	2.75	150
14	69/M	BPN	LA	D	27	2.33	160
Mean ± SD	42 ± 18				43 ± 24	2.1 ± 0.4	181 ± 49

In group 1 computed tomography (CT) sections were acquired before and 30 s after injection of contrast material, and in group 2 the CT sections were obtained before and 15 min after injection of contrast material. *The morphological CT pattern is classified into lobar (LA) and patchy (PA) CT attenuations, according to the definitions reported by Puybasset and coworkers [4]. BPN, ventilator associated bronchopneumonia; D, died; F, female; FiO₂, fractional inspired oxygen; LISS, Lung Injury Severity Score; M, male; PaO₂, arterial oxygen tension; S, survived; SAPS II, Simplified Acute Physiological Score.

Results

Patients

The clinical and respiratory characteristics of the 14 patients are summarized in Table 1. No statistically significant differences were found between the two groups. Patients were admitted for ALI complicating major vascular surgery ($n = 7$), oesophageal surgery ($n = 1$) and multiple trauma ($n = 6$). All patients except one were receiving norepinephrine (noradrenaline) for septic shock. Eight patients met criteria for acute respiratory distress syndrome [22].

Effects of injection of contrast material on volumes of gas and lung tissue

Table 2 shows the CT number of pulmonary arteries before and after injection of contrast material. The pulmonary arterial concentration of contrast material ranged between 0.3% and 2% at 30 s after the injection, and between 0% and 0.07% at 15 min after the injection. Fig. 2 shows three representative CT sections acquired in one patient at baseline, and 30 s and 15 min following injection of contrast material. Pulmonary vessels were opacified by contrast material only on the CT

sections taken 30 s after injection, whereas lung parenchyma was opacified on CT sections taken 30 s and 15 min after injection. The corresponding apparent volumes of lung tissue were 1445 ml (baseline), 1555 ml (30 s) and 1553 ml (15 min).

As shown in Table 3, injection of contrast material increased the apparent volume of lung tissue by 83 ± 57 ml in group 1 ($P = 0.02$) and 102 ± 80 ml in group 2 ($P = 0.01$), whereas the apparent volume of gas decreased by 86 ± 102 ml in group 1 ($P = 0.03$) and 90 ± 48 ml in group 2 ($P = 0.02$). Total lung volume remained unchanged in both groups. The changes in apparent lung tissue volumes between the two groups did not reach statistical significance ($P = 0.06$).

As shown in Fig. 3, the individual increase in lung tissue volume was variable from one patient to another, ranging from 2% to 20% and with mean changes of $8 \pm 6\%$ in group 1 and $7 \pm 5\%$ in group 2. Thirty seconds after the injection, the maximal artifactual increase in lung tissue represented $39 \pm 35\%$ of the apparent increase in lung tissue (extremes 0

Table 2**Pulmonary arterial computed tomography attenuations before and after injection of contrast material in the two groups of patients**

Patient no	Mean CT attenuation before injection (HU)	Mean CT attenuation after injection (HU)	Pulmonary concentration of contrast material (%)
Group 1 (30 s after injection)			
1	31	245	1.9
2	45	218	1.8
3	49	110	0.3
4	49	169	1.2
5	36	265	2
6	43	146	0.7
7	46	219	1.4
Mean $\pm$ SD	43 $\pm$ 7	196 $\pm$ 56	1.3 $\pm$ 0.8
Group 2 (15 min after injection)			
8	43	83	0.005
9	62	67	0
10	25	60	0
11	21	60	0
12	39	55	0
13	65	75	0
14	30	72	0.07
Mean $\pm$ SD	41 $\pm$ 17	67 $\pm$ 10	0.02 $\pm$ 0.002

CT, computed tomography; HU, Hounsfield units.

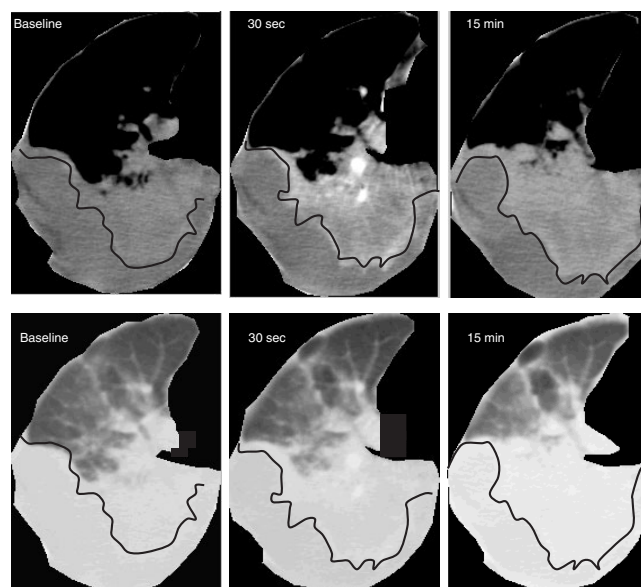
and 85%). Fifteen minutes after the injection, the maximal artifactual increase in lung tissue represented $45 \pm 43\%$ of the apparent increase in lung tissue (extremes 6 and 100%).

Effects of contrast material on computed tomography lung volume determination

As shown in Fig. 4, a close correlation was found between the measured volumes of aliquots and the volumes of aliquots calculated using Lungview[®]. The mean bias and precision were -0.7 and 9 ml when the fixed lung model was instilled with water, and -8.8 and 3.8 ml when a solution containing 5% of contrast material was instilled, respectively. The presence of contrast material in the aliquots was associated with an 8% overestimation of the liquid volume by Lungview[®].

Discussion

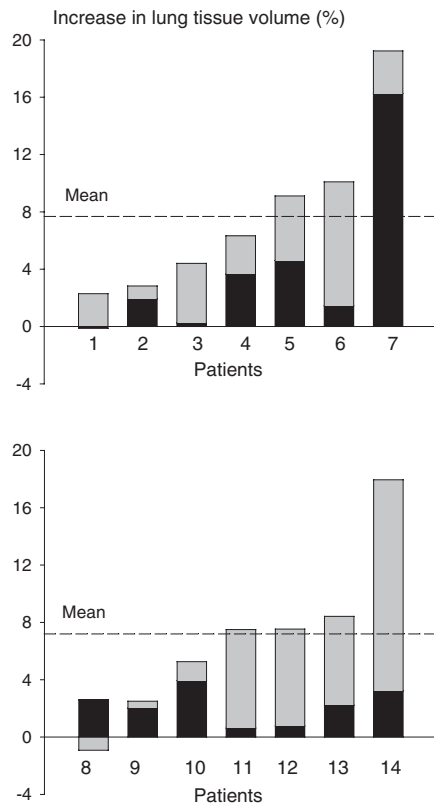
The present study shows an increase in the volume of lung tissue at 30 s and at 15 min after injection of contrast material in patients with ALI. This finding probably results from a true increase in extravascular lung water and from an artifactual

Figure 2

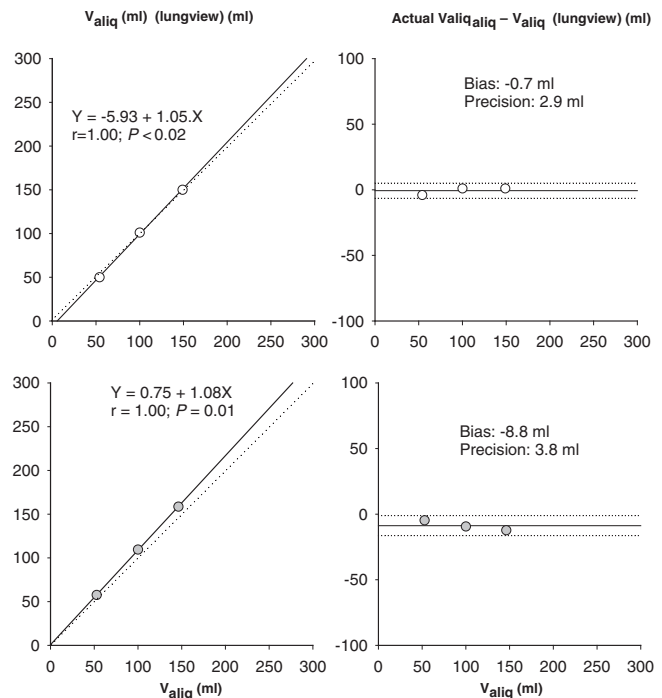
Three representative mediastinal (upper panels) and parenchymal (lower panels) windows of computed tomography sections obtained before (baseline), and 30 s and 15 min after injection of contrast material in one patient. At 30 s, both lung parenchyma and pulmonary vessels are opacified. At 15 min, contrast material can be observed only in the lung parenchyma. The black line delineates lung parenchyma (accentuated contrast after injection of contrast material) from pleural effusion (same contrast after injection of contrast material).

increase in lung density caused by the intrapulmonary diffusion of contrast material. The former effect, which is not observed when the lungs are healthy [2], probably depends on alteration in the alveolar–capillary barrier that promotes extravascular leakage of contrast material.

The accuracy of Lungview[®] for measuring lung tissue volume was recently assessed by instilling known volumes of water and albumin into a fixed spongy textured human lung phantom [15]. In the present study, using the same model, we found that the administration of solutions containing 5% of contrast material resulted in an 8% artifactual overestimation of lung tissue volume. A 5% concentration was chosen to mimic clinical conditions; as shown in Fig. 2, pulmonary vessels and lung parenchyma were opacified 30 s after injection of contrast material, and CT attenuations measured in pulmonary arteries corresponded to low concentrations of contrast material ranging between 0.3% and 2%. In six patients the apparent increase in lung tissue was either below or slightly greater than 8% of the preinjection lung tissue volume, and could therefore be artifactual. However, the concentration of contrast material was less than 2% in all patients, and we calculated the maximal artifactual increase in lung tissue that would have resulted from a total leakage of the contrast material into the lung parenchyma. As shown in Table 4 and Fig. 3, after eliminating the maximal artifactual

Figure 3

Individual percentage of changes in the apparent volume of lung tissue 30 s and 15 min after injection of 80 ml contrast material in patients in group 1 (upper panel) and group 2 (lower panel). The horizontal line indicates the mean value of the apparent volume of lung tissue. Black bars represent individual percentage of maximum artifactual increase in lung tissue calculated according to the hypothesis that the 80 ml of contrast material penetrated into the alveolar-interstitial space and formed an interface with the alveolar gas.

Figure 4

Correlation (left panels) and agreement (right panels) between volumes of aliquots (V_{aliquot}) calculated using Lungview® and measured from lung weight after instillation of lung water (upper panels) and a solution containing 5% of contrast material (lower panels) into the human lung phantom. In the left panels, the dotted line represents the identity line and the solid line represents the linear regression line. In the right panels, the solid line represents the difference between calculated (using Lungview®) and measured (actual) aliquots (bias), and the dotted lines represents 2 SD (precision of the bias, according to the Bland-Altman method).

Table 3

Apparent lung volumes before and after injection of contrast material in the two groups of patients

Patients	Before injection	After injection	P value
Group 1 (30 s after injection)			
Total volume (ml)	2546 ± 914	2542 ± 909	NS
Volume of gas (ml)	1444 ± 849	1358 ± 794	0.03
Volume of tissue (ml)	1105 ± 235	1193 ± 245	0.02
Group 2 (15 min after injection)			
Total volume (ml)	2801 ± 882	2826 ± 833	NS
Volume of gas (ml)	1415 ± 853	1337 ± 838	0.02
Volume of tissue (ml)	1386 ± 109	1488 ± 157	0.01

The two-way analysis of variance for one within factor (before and after injection of contrast material) and one grouping factor (group 1 and group 2) showed an absence of interaction between the two groups.

Table 4**Individual increases in lung tissue volumes following injection of contrast material in the two groups of patients**

Patient no	Apparent increase in lung tissue (ml)	Maximum artifactual increase in lung tissue (ml)	Minimum actual increase in lung tissue (ml)
Group 1 (30 s after injection)			
1	27	0	27
2	31	21	10
3	38	2	36
4	74	43	31
5	139	70	69
6	96	14	82
7	173	146	27
Mean $\pm$ SD	83 $\pm$ 57	42 $\pm$ 52	40 $\pm$ 26
Group 2 (15 min after injection)			
8	24	37	0
9	32	26	6
10	77	57	19
11	108	9	99
12	107	11	96
13	100	26	74
14	266	48	218
Mean $\pm$ SD	102 $\pm$ 80	31 $\pm$ 18	73 $\pm$ 76

increase in lung tissue, a true increase in the volume of lung tissue was observed in each individual. It must be pointed out that the assumption that 100% of the contrast material had penetrated into the lung parenchyma 30 s after the injection is unlikely to be valid. As a consequence, the actual increase in lung tissue was in fact much greater, depending on the amount of contrast material that penetrated into the lungs. In healthy volunteers, injection of contrast material did not produce any detectable modification in the lung tissue volume calculated using Lungview®, probably because the contrast material remained strictly intravascular in the presence of an intact alveolar–capillary barrier and was rapidly eliminated in the urine [2].

Fifteen minutes after injection pulmonary vessels were no longer opacified, and CT attenuations measured in pulmonary arteries corresponded to concentrations of contrast material of 0.1% or less. In the patients with an apparent increase in lung tissue of greater than 8% of the preinjection lung tissue volume, the artifact created by the presence of contrast material within the lung parenchyma contributed far less than

25%. In other words, a significant and clinically relevant increase in lung tissue was observed 15 min after injection of contrast material in four patients. This increase in lung tissue volume is probably due to an increase in extravascular lung water.

The injured lung is characterized by an excessive amount of extravascular lung water that accumulates in interstitial and alveolar compartments and by an infiltration of lung structures by inflammatory cells. Excessive oedema and lung inflammation are measured as 'tissue in excess' by the CT method [4]. In patients ventilated for ALI, variations in lung tissue volumes and aeration have been observed following changes of position or administration of positive end-expiratory pressure [5,23–25]. In patients with chronic renal failure, haemodialysis-induced decrease in intravascular and extravascular water is associated with a decrease in lung CT attenuation [26]. In the present study, injection of contrast material shifted the volumic distribution of CT attenuation toward higher values, suggesting an increase in extravascular lung water. A number of elements support a true increase in the volume of extravascular lung water rather than a simple density artifact resulting from the presence of contrast material in the vascular space. First, the increase in volume of lung tissue that was observed 30 s after injection of contrast material persisted 15 min later, although the concentrations of contrast material decreased below 0.1%, thereby creating a negligible density artifact that is unable to account for the persisting increase in lung tissue. Second, the mean increase in the volume of lung tissue was 10-fold greater than the expected increase in pulmonary blood volume resulting from injection of 80 ml contrast material. Third, the majority of patients had an ALI characterized by a lobar CT attenuation pattern with a large predominance of nonaerated lung tissue. Accordingly, the increase in lung tissue was computed for a good part as the additional number of voxels with a CT attenuation greater than 0. Consequently, the increase in CT attenuation resulting from the intraparenchymal diffusion of contrast material could not be the cause of a major artifactual increase in lung tissue in nonaerated lung regions. Indeed, counting a voxel with a CT attenuation equal to 0 or +500 HU has the same significance as a lung area with a mean CT attenuation close to 0.

The amplitude of the increase in lung tissue was variable from one patient to another, depending on the relative importance of the artifactual increase in lung density and the true increase in extravascular lung water. In fact, our findings partly invalidate a statement that we made in a previous study [2] that the injection of contrast material does not influence the distribution of CT numbers in ALI; this statement is true in healthy volunteers but it does not apply to patients with ALI. Although we did not assess the clinical relevance of the measured increase in lung tissue, it appears prudent to restrict the indication of CT scans with contrast to specific indications such as diagnosis of pulmonary embolism. Based on the potential of contrast material to worsen the respiratory

Key messages

- In patients with ALI, administration of contrast material induces an apparent increase in lung tissue
- This apparent increase in lung tissue results from a true increase in extravascular lung water and from an artifactual increase in lung density resulting from leakage of contrast material into the lung parenchyma
- The increase in extravascular lung water persists 15 min after injection
- Because injection of contrast material may worsen lung injury, it appears prudent to limit this procedure to specific indications in patients with ALI undergoing a thoracic CT scan

condition of patients with ALI, its administration to assist in differentiating between lung consolidation and pleural effusion does not appear justified.

Competing interests

None declared.

Acknowledgement

The following members of the CT scan ARDS Study Group participated in the present study: P Gusman, MD, Department of Anesthesiology, UNESP, Botucatu, Brazil; S Vieira, MD, Hospital De Clinicas de Porto Alegre, UFRGS, Brazil; M Elman, MD, Department of Anesthesiology Faculdade de Ciências Médicas de Santa Casa, São Paulo, Brazil; L Puybasset, PhD, MD, P Coriat, PhD, MD, MO Roussat, MD, I Goldstein, MD, A Nieszkowska, MD, Unité de Réanimation Chirurgicale Pierre Viars, Hôpital de La Pitié-Salpêtrière, Paris, France.

LMM is the recipient of a scholarship provided by the Ministères des Affaires Étrangères Français (ref 2334471).

References

1. Umamaheswara Rao GS, Gallart L, Law-koune J-D, Lu Q, Puybasset L, Coriat P, Rouby JJ: **Factors influencing the uptake of inhaled nitric oxide in patients on mechanical ventilation.** *Anesthesiology* 1997, **87**:823-834.
2. Vieira S, Puybasset L, Richecoeur J, Lu Q, Cluzel P, Gusman P, Coriat P, Rouby JJ: **A lung computed tomographic assessment of positive end-expiratory pressure-induced lung overdistension.** *Am J Respir Crit Care Med* 1998, **158**:1571-1577.
3. Vieira S, Puybasset L, Lu Q, Richecoeur J, Cluzel P, Coriat P, Rouby JJ: **A scanographic assessment of pulmonary morphology in acute lung injury: signification of the lower inflection point detected on lung pressure-volume.** *Am J Respir Crit Care Med* 1999, **159**:1612-1623.
4. Puybasset L, Cluzel P, Gusman P, Grenier P, Preteux F, Rouby JJ: **Regional distribution of gas and tissue in acute respiratory distress syndrome. I. Consequences for lung morphology.** *CT Scan ARDS Study Group.* *Intensive Care Med* 2000, **26**:857-869.
5. Puybasset L, Gusman P, Muller J-C, Cluzel P, Coriat P, Rouby J-J, CT scan ARDS study group: **Regional distribution of gas and tissue in acute respiratory distress syndrome – part 3: consequences for the effects of positive end expiratory pressure.** *Intensive Care Med* 2000, **26**:1215-1227.
6. Junck L, Marshall WH: **Neurotoxicity of radiological contrast agents.** *Ann Neurol* 1983, **13**:469-484.
7. Junck L, Marshall WH: **Fatal brain edema after contrast-agent overdose.** *Am J Neuroradiol* 1986, **7**:522-525.
8. Knof J, Pommer W, Kern D: **Permeability disorders of the blood-brain barrier following intravascular contrast medium administration in kidney failure [in German].** *Rofo Fortschr Geb Rontgenstr Neuen Bildged Verfahr* 1992, **156**:103-105.
9. Sage MR: **Blood-brain barrier: phenomenon of increasing importance to the imaging clinician.** *AJR Am J Roentgenol* 1982, **138**:887-898.
10. Waldron RLD, Bridenbaugh R, Purkenson M, Dempsey EW: **The effect of angiographic contrast media at the cellular level in the brain.** *Radiology* 1973, **108**:187-189.
11. Ware LB, Matthay MA: **The acute respiratory distress syndrome.** *N Engl J Med* 2000, **342**:1334-1349.
12. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R: **Report of the American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination.** *The Consensus Committee.* *Intensive Care Med* 1994, **20**:225-232.
13. Puybasset L, Rouby JJ, Mourgeon E, Cluzel P, Law-Koune JD, Stewart T, Devilliers C, Lu Q, Roche S, Kalfon P, Vicaut E, Viars P: **Factors influencing cardiopulmonary effects of inhaled nitric oxide in acute respiratory failure.** *Am J Respir Crit Care Med* 1995, **152**:318-328.
14. Puybasset L, Cluzel P, Chao N, Slutsky A, Coriat P, Rouby JJ, CT Scan ARDS Study group: **A computed tomography assessment of regional lung volume in acute lung injury.** *Am J Respir Crit Care Med* 1998, **158**:1644-1655.
15. Malbouissin LM, Preteux F, Puybasset L, Grenier P, Coriat P, Rouby JJ: **Validation of a software designed for computed tomographic (CT) measurement of lung water.** *Intensive Care Med* 2001, **27**:602-608.
16. Mull RT: **Mass estimates by computed tomography: physical density from CT numbers.** *AJR Am J Roentgenol* 1984, **143**:1101-1104.
17. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M: **Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study.** *Am Rev Respir Dis* 1987, **136**:730-736.
18. Markarian B: **A simple method of inflation-fixation and air drying of lungs.** *Am J Clin Pathol* 1975, **63**:20-24.
19. Markarian B, Dailey ET: **Preparation of inflated lung specimens.** In *The Lung. Radiologic Pathologic Correlations*. Edited by Heitzman ER. St Louis, Princeton, Toronto: C.V. Mosby Company; 1984:4-12.
20. Bessis L, Callard P, Gotheil C, Biaggi, Grenier P: **High-resolution CT of parenchymal lung disease: precise correlation with histologic findings.** *Radiographics* 1992, **12**:45-58.
21. Bland JM, Altman DG: **Statistical methods for assessing agreement between two methods of clinical measurement.** *Lancet* 1986, **1(8476)**:307-310.
22. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R: **Report of the American-European Consensus conference on acute respiratory distress syndrome: definitions, mechanisms, relevant outcomes, and clinical trial coordination.** *Consensus Committee.* *J Crit Care* 1994, **9**:72-81.
23. Gattinoni L, Mascheroni D, Torresin A, Marcolin R, Fumagalli R, Vesconi S, Rossi G, Rossi F, Baglioni S, Bassi F, Nastro F, Pesenti A: **Morphological response to positive end expiratory pressure in acute respiratory failure. Computerized tomography study.** *Intensive Care Med* 1986, **12**:137-142.
24. Gattinoni L, Pesenti A, Baglioni S, Vitale G, Rivolta M, Pelosi P: **Inflammatory pulmonary edema and positive end-expiratory pressure: correlations between imaging and physiologic studies.** *J Thorac Imag* 1988, **3**:59-64.
25. Dambrosio M, Roupie E, Mollet JJ, Angalade MC, Vasile N, Lemaire F, Brochard L: **Effects of positive end-expiratory pressure and different tidal volumes on alveolar recruitment and hyperinflation.** *Anesthesiology* 1997, **87**:495-503.
26. Metry G, Wegenius G, Hedenström H, Wikström B, Danielson BG: **Computed tomographic measurement of lung density changes in lung water with hemodialysis.** *Nephron* 1997, **75**:394-401.