The Recruitability Paradox

Bedside assessment of lung recruitability is no longer a topic for curious physiologists. It is now a central concept for intensivists to assess the severity of acute respiratory distress syndrome (1), to individualize positive end-expiratory pressure (PEEP) and protective lung strategies, to decide for a lung-recruitment maneuver (2), or even to balance how much we should challenge the hemodynamic system, coping with higher intrathoracic pressures.

Using computed tomography (CT), recruitability is measured as the amount of not-inflated tissue at a given pressure that reinflates at higher pressure. The method is based on voxel-by-voxel analysis, with each voxel classified as either "recruited" or "not recruited," depending on a density threshold defined with good rationale (but always including some arbitrariness). Each voxel may include a few collapsed pulmonary acini; thus, minor estimation errors are possible when heterogeneities among neighbor units are present.

On the basis of previous research, investigators have used a threshold of −100 (3) or −200 Hounsfield units (HU) (4) to define an open, functional voxel (keeping >10–20% of aeration during end expiration). Above this aeration threshold, the unit(s) are assumed to not recollapse at end expiration and to fully participate in tidal ventilation and in gas exchange. After calculating how much tissue is present in each voxel, the recruitment measured by CT scan quantifies tissue recruitment as grams of tissue reinflating, or as reinflating fractions of total lung weight. Although precise, CT-based methods are demanding and cumbersome and expose patients to multiple risks, such as radiation and intrahospital transportation.

Luckily, alternative methods based on lung mechanics have been proposed. They comprise variants, depending on how we measure lung volumes and the predicted increment in lung volume at higher pressures (inflation of previously aerated units), differentiating it from the "beyond predicted" increment in lung volume (gas entering newly recruited units).

In older studies, a prolonged exhalation against atmosphere was proposed as a method to estimate all lung volume gained by PEEP (inflation plus recruitment). After discounting the exhaled tidal volume, the whole volume collected during prolonged exhalation should be subtracted from the inflation volume caused by PEEP (calculated as ΔPEEP, multiplied by compliance of respiratory system). Any residual difference should be considered as recruited volume (5, 6). Variants of this method based on multiple breaths, calculating accumulated volumes (7), were proposed. Later on, it became clear that this method underestimates the recruitment promoted by PEEP, because a prolonged exhalation is not enough to fully empty newly recruited units (for instance, because of some gas trapping behind unstable airways) (8). Thus, more recently, differences in end-expiratory lung volume (EELV) promoted by PEEP were directly measured, either by helium dilution methods (8, 9), by nitrogen washout techniques (10), or by electrical impedance tomography (EIT) (11). After computing the difference in EELV between two PEEP levels, we subtract the inflation volume caused by PEEP (ΔPEEP × tidal compliance), and the residual difference is then a better estimate of recruited volume.

The inflation volume promoted by PEEP can also be estimated by the P–V method, in which two P–V curves are superposed in the same graph, with a common reference for absolute lung volumes on the *y*-axis. One curve starts from a lower PEEP/EELV point, and another starts from a higher PEEP/EELV point. If no recruitment occurred, the two curves should superpose for overlapping alveolar pressures. In contrast, if a vertical distance between the curves appears, with more gas in the curve starting at higher PEEP, this is considered recruitment (7, 11). This phenomenon is essentially equivalent to the hysteresis observed between inspiratory and expiratory P–V loops, frequently associated with lung recruitment (12). This recruitment measured by mechanics is essentially gas recruitment, expressed as the absolute amount of gas or as fractions of the total gas content of the lung (6, 13). As expected (10), and further corroborated in this issue of the *Journal* by Chiumello and colleagues (pp. 1254–1263), both methods based on mechanics are closely related (9).

A refined, more laborious version of this method has been proposed by Malbouisson and colleagues, in which the measured variable is also the extra volume entering previously collapsed areas at lower PEEPs, but with the refinement of computing only the fraction of air entering nonaerated or poorly aerated areas (i.e., voxels with densities between +100 HU and −500 HU) (14). This method requires extensive CT analysis but essentially measures gas recruitment as in the mechanics-based methods. Essentially, thus, it differs from the traditional method of estimating tissue recruitment in CT studies.

For the first time, in a well-designed study, Chiumello and colleagues compared the CT-based against the mechanics-based methods to assess to what degree they are interchangeable (9). Interestingly, they found that they do not correlate, and, in fact, they seemed to measure different phenomena. Some patients not presenting any tissue recruitment on CT scan presented a clear vertical displacement between P–V curves, suggesting an evident gas recruitment. Challenging further the gas-recruitment method, Stahl and colleagues demonstrated the paradox in which patients with healthier lungs presented higher recruitability (15). Also, by using EIT, they observed that most of this recruited volume was entering nondependent lung regions where tissue collapse was unlikely.

How to reconcile those findings, assuming that good correlations, reported in the past (13, 14), between gas recruitment and other physiological parameters like oxygenation were not misleading coincidences?

By physical intuition, we have to assume that the recruitment of a new lung unit at a higher PEEP must cause the entrance of some extra gas inside the lung. This extra gas is needed for the reaeration of the unit, causing some displacement in this new PEEP curve, or causing the new EELV to stay above the predicted inflation volume. It is impossible to imagine some recruitment without a vertical displacement (i.e., without any extra volume). But is it possible to observe the contrary (i.e., some vertical displacement without any tissue recruitment, as measured by CT voxels)? The work of Chiumello and colleagues suggests that this possibility is

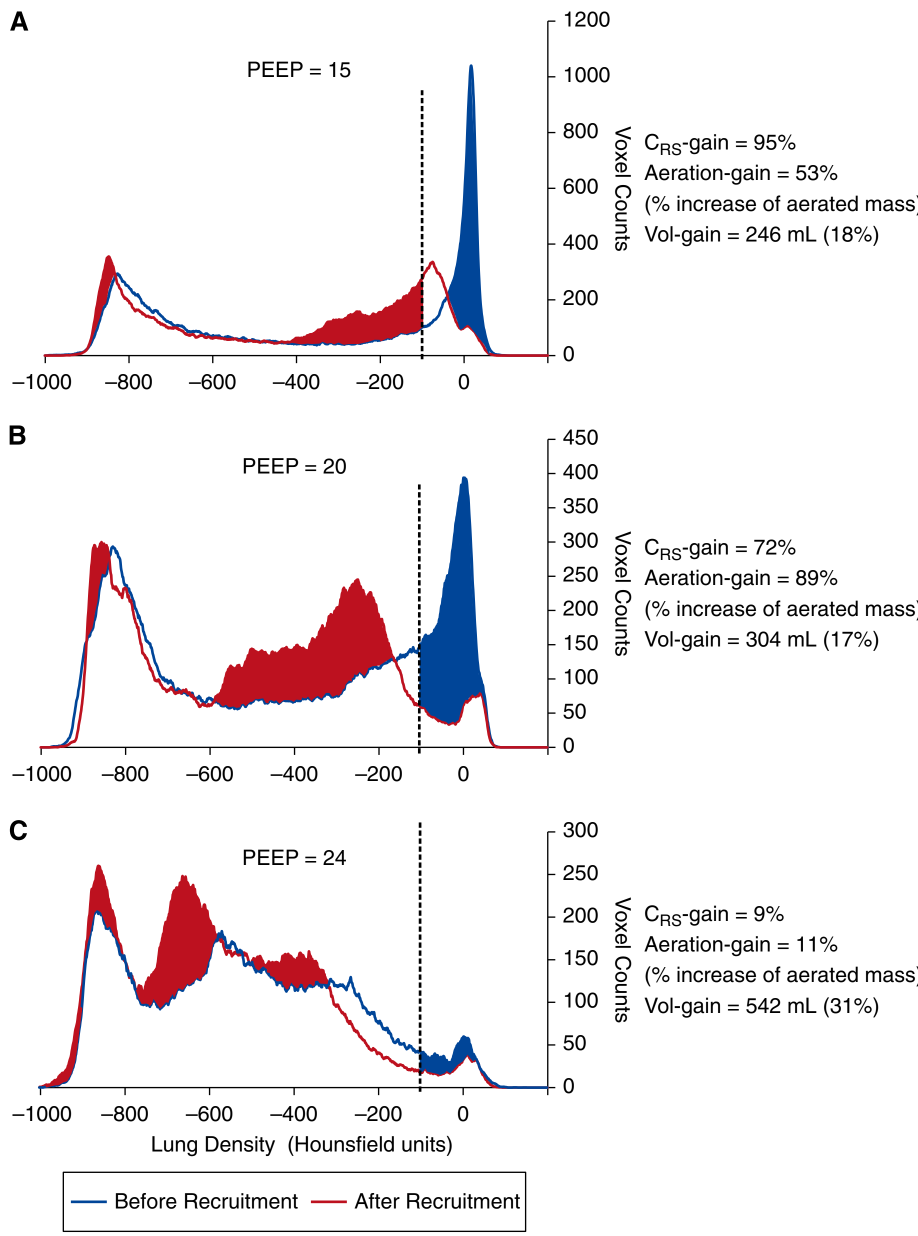

Figure 1. Density histograms of whole-lung computed tomography (CT) images (animal preparation in which a pig had acute respiratory distress syndrome induced by repeated lung lavage plus 3 h ventilation at driving pressures of 40 cm H_2O). Great vessels, cardiac, and diaphragm artifacts were manually excluded. Two CT scans were performed at fixed positive end-expiratory pressure (PEEP) levels before (*blue*) and after (*red*) a recruiting maneuver, which transiently elevated airway pressures to 55 cm H_2O. The fixed PEEP levels used in *A*, *B*, and *C* were, respectively, 15, 20, and 24 cm H_2O. Tidal compliance (C_{RS}) was measured during small tidal volume ventilation (5 ml/kg [predicted body weight]), thus minimizing tidal recruitment during the six conditions shown. Depending on the PEEP level, the voxels presented three different patterns of migration within the histograms, after the recruiting maneuver, respectively observed in *A*–*C*. Observe that the number of units suffering reaeration was very large in *A* (large tissue recruitment, *shaded blue area*) but with the migrating voxels just reaerating up to 30% gas–tissue ratio (*shaded red area*). In contrast, the number of units suffering reaeration was modest in *C* (small tissue recruitment), but each unit was now reaerated up to 90% gas–tissue ratio. As a consequence, the improvement in lung tidal compliance was very large in *A* (many new units sharing tidal volume) but associated with modest volume gain (small gas recruitment). In opposition, the improvement in tidal compliance was small in *C* (few reopened units quickly becoming fully stretched) but accompanied by a large volume gain (large gas recruitment). *B* represents an intermediate possibility, in which the gains in tidal compliance and gas volume are better balanced. Those figures explain why gas recruitment may reflect (or not) tissue recruitment measured by CT. Depending on lung condition, and also on airway pressures applied, the amount of gas recruitment may be quite large, out of proportion if compared with tissue recruitment (as in *C*).

likely and, more than this, that the two measurements (tissue vs. gas recruitment) can be, sometimes, uncorrelated (9).

To understand this paradox, it is helpful to consider the common pattern observed in the density histograms derived from two CT images (Figs 1A–1C), obtained before and after a recruiting maneuver. These histograms are equivalent to those used in calculations by Chiumello and colleagues, except that Chiumello and colleagues collected them before and after a PEEP raise (9). But here, to facilitate comprehension, we selected images obtained at the same PEEP, when the difference between two images is only related to volume history (i.e., the previous application of recruiting maneuvers). Thus, differences caused by gradual inflation of previously aerated lung units are minimized, and the remaining differences reflect (mostly) the "quantum" migration of some previously nonaerated lung units (typically located rightward on the *x*-axis) to a lower density window (leftward on the *x*-axis). These migrations reflect a quality change in alveoli condition.

Three different migrations were observed, respectively, from Figures 1A to 1C. The figures explain why gas recruitment may reflect (or not) tissue recruitment measured by CT. Depending on lung condition, and also on airway pressures applied, the amount of gas recruitment may be quite large, out of proportion if compared with tissue recruitment (as in Fig 1C). It is even possible that recruitment of some units within the −100 HU to −300 HU density window (units that might be hidden by some partial volume effects) cause a large gas recruitment, thus explaining some of the paradoxical patients from Chiumello and colleagues, in whom zero tissue recruitment (using the traditional −100 HU threshold) was observed, side by side with large gas recruitment (9).

After considering the work of Chiumello and colleagues in the context above (9), we have to consider that substantial air recruitment is informative only when followed by improvements in other functional indexes, like improvements in tidal compliance or pulmonary shunt (4). Only then can we confirm some tissue recruitment. Alternatively, the absence of any air recruitment excludes the possibility of tissue recruitment, which is also informative. To make things harder, however, the use of different PEEP levels during subsequent compliance measurements creates difficulties in deciding whether the drop in compliance at a higher PEEP was just expected, or lower than expected (in this case suggesting an increased number of newly recruited lung units).

Thus, much work has to be done in the next years. The bedside methods to calculate air recruitment are welcome, providing useful information for clinicians, but they still require the conjunct analysis of other physiological parameters to confirm and quantify lung tissue recruitment at the bedside. We are still waiting for some promising news arising from bedside ultrasound and EIT methods. ■

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ORIGINAL ARTICLE

Lung Recruitment Assessed by Respiratory Mechanics and Computed Tomography in Patients with Acute Respiratory Distress Syndrome
What Is the Relationship?

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Abstract

Rationale: The assessment of lung recruitability in patients with acute respiratory distress syndrome (ARDS) may be important for planning recruitment maneuvers and setting positive end-expiratory pressure (PEEP).

Objectives: To determine whether lung recruitment measured by respiratory mechanics is comparable with lung recruitment measured by computed tomography (CT).

Methods: In 22 patients with ARDS, lung recruitment was assessed at 5 and 15 cm H_2O PEEP by using respiratory mechanics–based methods: (*1*) increase in gas volume between two pressure–volume curves (P–Vrs curve); (*2*) increase in gas volume measured and predicted on the basis of expected end-expiratory lung volume and static compliance of the respiratory system (EELV-Cst,rs); as well as by CT scan: (*3*) decrease in noninflated lung tissue (CT [not inflated]); and (*4*) decrease in noninflated and poorly inflated tissue (CT [not + poorly inflated]).

Measurements and Main Results: The P–Vrs curve recruitment was significantly higher than EELV-Cst,rs recruitment (423 ± 223 ml vs. 315 ± 201 ml; $P < 0.001$), but these measures were significantly related to each other ($R^2 = 0.93$; $P < 0.001$). CT (not inflated) recruitment was 77 ± 86 g and CT (not + poorly inflated) was 80 ± 67 g ($P = 0.856$), and these measures were also significantly related to each other ($R^2 = 0.20$; $P = 0.04$). Recruitment measured by respiratory mechanics was 54 ± 28% (P–Vrs curve) and 39 ± 25% (EELV-Cst,rs) of the gas volume at 5 cm H_2O PEEP. Recruitment measured by CT scan was 5 ± 5% (CT [not inflated]) and 6 ± 6% (CT [not + poorly inflated]) of lung tissue.

Conclusions: Respiratory mechanics and CT measure—under the same term, "recruitment"—two different entities. The respiratory mechanics–based methods include gas entering in already open pulmonary units that improve their mechanical properties at higher PEEP. Consequently, they can be used to assess the overall improvement of inflation. The CT scan measures the amount of collapsed tissue that regains inflation.

Clinical trial registered with www.clinicaltrials.gov (NCT00759590).

Keywords: acute respiratory distress syndrome; lung computed tomographic scan; lung recruitment; pressure–volume curve; respiratory system compliance

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At a Glance Commentary

Scientific Knowledge on the Subject: Recruitability is highly variable in the lungs of patients with acute respiratory distress syndrome. Its assessment may be a rational strategy for setting positive end-expiratory pressure. Computed tomography (CT) can indicate how much lung tissue is recruited at two pressure levels. CT-based methods are demanding and impractical, however. The assumption behind bedside respiratory mechanics methods is that changes in respiratory system compliance are due to recruitment, and therefore they are measured accordingly.

What This Study Adds to the Field: Respiratory mechanics–based methods are used to measure not only gas entering previously empty pulmonary units but also gas entering already open units. Consequently, they provide information on overall improvement of inflation but do not measure the collapsed and/or recruitable lung tissue, as CT can (threshold, −100 Hounsfield units).

"Recruitment" can be defined as the enrollment of pulmonary units in a new status of inflation. Using computed tomography (CT), recruitment at two pressure levels has been defined either as the amount of noninflated tissue at a given pressure that reinflates at higher pressure (1) or as the difference in noninflated plus poorly inflated tissue at the two pressures (2). The recruitment measured using a CT scan usually refers to tissue recruitment and is expressed as grams of tissue reinflating or as a fraction of the total lung weight. Its routine use in clinical practice, however, is problematic, on account of the X-ray exposure, the risks of transferring patients to the CT scan facilities, and the time-consuming work needed to complete the necessary computations (3).

Therefore, other measurement methods have been suggested (4, 5). The most popular are based on changes in respiratory mechanics. As an example, to estimate recruitment between 5 and 15 cm H_2O positive end-expiratory pressure (PEEP), it has been suggested that the expected end-expiratory lung volume (EELV) at 15 cm H_2O airway pressure, as computed from respiratory system compliance, should be compared with the measured EELV, and the difference is the recruitment (5, 6). Another approach is to trace two pressure–volume (P–V) curves, starting at different EELV and pressures (5 and 15 cm H_2O), and compare the gas differences between the two curves at 20 cm H_2O (4, 7). More gas at this pressure in the P–V curve starting at higher volume is considered recruitment. The recruitment measured by respiratory mechanics is gas recruitment and is expressed as the absolute amount of gas or as a fraction of the total gas content.

In this study, we compared CT scan–based and respiratory mechanics–based methods to assess to what degree they are interchangeable. Recruitability may be important in clinical practice for assessing the severity of acute respiratory distress syndrome (ARDS), planning recruitment maneuvers, and setting adequate PEEP levels during mechanical ventilation (8, 9).

Methods

The study protocol is summarized in the online supplement.

Study Population

This study was approved by the institutional review board of our hospital, and informed consent was obtained according to Italian regulations. We enrolled 22 patients with ARDS, classified according to tertiles of Pa_{O_2}/FI_{O_2} (at 5 cm H_2O PEEP) to obtain balanced groups. We used the tertiles because classification according to the Berlin Definition at standard PEEP (10) would have produced unbalanced groups (5 mild, 15 moderate, and 2 severe ARDS).

Lung Recruitment Assessment

CT scan. The voxels in the whole lungs were grouped in 11 CT compartments at 100–Hounsfield unit (HU) steps, from greater than 0 (totally not inflated) to −1,000 HU (only gas). According to the CT distribution of normal lung, we defined four lung inflation status groups: not inflated (greater than −100 HU), poorly inflated (−100 to −500 HU), well inflated (−500 to −900 HU), and overinflated (less than −900 HU) (11).

Lung recruitment measured by CT. Lung recruitment was computed as the amount of lung tissue (not inflated or not + poorly inflated) in which the inflation changed upon raising PEEP from 5 to 15 cm H_2O. Recruitment was expressed as grams of tissue or as a percentage of total lung tissue weight, as follows:

$$\text{Method A}: \ \text{recruitment (g)} = NI_5 - NI_{15}$$

$$\text{Method B}: \ \text{recruitment (g)} = (NI_5 + PI_5) - (NI_{15} + PI_{15}),$$

where NI_5 and NI_{15} are grams of noninflated tissue at 5 and 15 cm H_2O PEEP and PI_5 and PI_{15} are grams of poorly inflated tissue at 5 and 15 cm H_2O PEEP.

Gas volume entering newly recruited tissue. To estimate how much gas was recruited per gram of tissue recruited upon raising PEEP from 5 to 15 cm H_2O, we assumed that recruited units at 15 cm H_2O PEEP had the same gas-to-tissue ratio as the units already open at the same pressure. Therefore, we estimated the CT scan recruited gas as follows:

$$\text{Method A gas rec}_{5-15} = (NI_5 - NI_{15}) \times g/t_{15}$$

$$\text{Method B gas rec}_{5-15} = [(PI_5 + NI_5) - (PI_{15} + NI_{15})] \times g/t_{15},$$

where gas rec_{5-15} is the gas in the tissue recruited from 5 to 15 cm H_2O PEEP and g/t_{15} is the total gas/(over + well + poorly) inflated tissue CT (g) at 15 cm H_2O PEEP. The gas in recruited tissue was expressed in absolute terms (in milliliters) and as percentages of the total gas at 5 cm H_2O PEEP.

Estimation of lung recruitment with a P–V curve. The pressure–volume curves of the respiratory system (P–Vrs) were traced starting from 5 and 15 cm H_2O PEEP and from the corresponding EELVs measured using the helium dilution technique (12, 13). The P–V curves were fitted to a sigmoid model as proposed by Venegas and colleagues (14), and the lung recruitment was computed as the gas difference measured on the two P–V curves at 15 cm H_2O PEEP (4, 7). Lung recruitment was expressed in absolute terms (in milliliters) and as a percentage of EELV at 5 cm H_2O PEEP.

Calculation of lung recruitment by EELV and static compliance of the respiratory system. Lung recruitment was calculated as the difference between the EELV at 15 cm H_2O PEEP and the volume expected after raising the pressure from 5 to 15 cm H_2O PEEP (5, 6, 12), according to this equation:

$$\begin{aligned}\text{Gas recruited} &= \text{EELV}_{\text{PEEP }15\,\text{cmH}_2\text{O}} - \big(\text{EELV}_{\text{PEEP }5\,\text{cmH}_2\text{O}} \\ &\quad + \big(\text{Cst, rs}_{\text{PEEP }5\,\text{cmH}_2\text{O}} \times 10\ \text{cm}\ \ \text{H}_2\text{O}\big)\big),\end{aligned}$$

where the static respiratory system compliance was measured as

$$\begin{aligned}\text{Cst, rs}_{\text{PEEP }5\,\text{cmH}_2\text{O}} &= \text{tidal volume(ml)}/ \\ &\big(\text{plateau pressure}_{\text{starting from PEEP }5\,\text{cmH}_2\text{O}} \\ &- \text{end-expiratory pressure at PEEP }5\,\text{cm}\ \ \text{H}_2\text{O}\big).\end{aligned}$$

Lung recruitment was expressed in absolute terms (in milliliters) and as a percentage of EELV at 5 cm H_2O PEEP.

Statistical Analysis

Data are expressed as mean ± SD or median (interquartile range). For comparisons, we used one-way analysis of variance (ANOVA) or one-way ANOVA on ranks when variables did not appear to be normally distributed. Two-way repeated measures ANOVA (one-factor repetition) or two-way repeated measures ANOVA (one-factor repetition) on ranks (when variables did not appear normally distributed) were used to compare tertiles of $Pa_{O_2}/F_{I_{O_2}}$ ratios and PEEP levels. The χ^2 test was used to compare categorical variables. Agreement between the different methods for measuring recruitment was checked by linear regression and Bland–Altman analysis (15). Two-way repeated measures ANOVA was used to compare the 11 compartments of tissue and gas distribution. Correlations between recruitment at 5 and 15 cm H_2O PEEP and the baseline physiological and CT scan variables were established with linear regression. $P < 0.05$ was considered significant. All statistical tests were done with SAS 9.2 (SAS Institute, Cary, NC) or SigmaPlot 11.0 (Systat Software, San Jose, CA) software.

Results

Patients

We studied 22 patients 4.2 ± 3.2 days after the onset of ARDS. Table 1 shows their baseline characteristics according to tertiles of $Pa_{O_2}/F_{I_{O_2}}$ at 5 cm H_2O PEEP. The first tertile (median [interquartile range] $Pa_{O_2}/F_{I_{O_2}}$, 216 [193–273]) comprised five patients with mild ARDS and two patients with moderate ARDS as per the Berlin Definition. The second tertile ($Pa_{O_2}/F_{I_{O_2}}$, 161 [152–169]) comprised eight patients with moderate ARDS. The third tertile ($Pa_{O_2}/F_{I_{O_2}}$, 126 [86–140]) comprised five patients with moderate ARDS and two with severe ARDS. Their main physiological and CT variables at 5 and 15 cm H_2O PEEP are reported in Table 2. Most of the variables improved with the higher PEEP. The results according to the Berlin classification of ARDS (unbalanced groups) are reported in the online supplement.

Recruitment

CT gas and tissue distribution at 5 and 15 cm H_2O. Figure 1 depicts the tissue (*left panel*) and gas distribution (*right panel*) in the different CT compartments. Upon raising the PEEP from 5 to 15 cm H_2O, there was significantly less tissue in the completely degassed (>0 HU) and almost completely degassed CT compartments (0 to −100 HU) (i.e., the noninflated lung compartment). The amounts of tissue in the compartments from −100 to −600 HU did not change with 5 or 15 cm H_2O PEEP, while the tissue between −700 and −900 HU significantly increased.

The gas distribution (Figure 1, *right panel*) was similar in CT compartments between 0 and −700 HU at 5 and 15 cm H_2O PEEP. In contrast, the gas in the CT compartments already inflated between

Table 1. Baseline Characteristics of the Study Population

Characteristics	Overall Population (*n* = 22)	First Tertile	Second Tertile	Third Tertile	*P* Value*
$Pa_{O_2}/F_{I_{O_2}}$ at 5 cm H_2O PEEP	161 (140–193)	216 (193–273)	161 (152–169)	126 (86–140)	
Age, yr	67.5 ± 11.7	65.6 ± 16.4	71.8 ± 10.9	64.4 ± 6.0	0.445
Male sex, n (%)	15 (68%)	4 (57%)	4 (50%)	7 (100%)	0.087
Body mass index, kg/m^2	27.4 ± 7.1	24.8 ± 5.6	29.4 ± 9.3	27.6 ± 5.6	0.485
Tidal volume/actual body weight, ml/kg	8.1 (7.0–9.8)	8.3 (7.5–9.8)	8.9 (8.0–9.8)	7.0 (6.3–7.9)	0.153
Respiratory rate, breaths/min	12.5 (12.0–15.0)	12.0 (10.0–17.0)	13.5 (12.0–16.0)	13.0 (12.0–15.0)	0.708
Minute ventilation, L/min	7.1 ± 1.4	7.3 ± 2.0	7.1 ± 1.3	6.9 ± 1.1	0.881
PEEP, cm H_2O	10.0 (10.0–12.0)	10.0 (5.0–10.0)	10.0 (10.0–10.5)	12.0 (10.0–15.0)	0.058
Static compliance of respiratory system, ml/cm H_2O	43.8 ± 17.9	53.1 ± 26.0	36.1 ± 10.3	43.3 ± 11.6	0.185
Intensive care mortality, n (%)	13 (59%)	4 (57%)	6 (75%)	3 (43%)	0.447
Causes of ARDS					
Pneumonia	13	3	5	5	0.210
Sepsis	4	2	0	2	
Aspiration	3	2	1	0	
Other	2	0	2	0	
$Pa_{O_2}/F_{I_{O_2}}$ ratio at clinical PEEP	195 ± 37	222 ± 12	198 ± 38	165 ± 34†	0.010
Pa_{CO_2}, mm Hg	40.2 (36.1–44.5)	35.7 (32.3–41.0)	42.7 (38.5–48.4)	42.4 (39.0–44.5)	0.043

Definition of abbreviations: ARDS = acute respiratory distress syndrome; PEEP = positive end-expiratory pressure.
Patients were classified according to tertiles of $Pa_{O_2}/F_{I_{O_2}}$ at 5 cm H_2O PEEP.
Data are expressed as mean ± SD or median (interquartile range) as appropriate unless otherwise indicated.
**P* values were determined using one-way analysis of variance or Kruskal–Wallis one-way analysis of variance on ranks.
$^{\dagger}P < 0.05$ versus first tertile.

Table 2. Gas Exchange, Partitioned Respiratory Mechanics, and Computed Tomographic Scan Variables

Characteristics	PEEP (*cm H_2O*)	Overall Population (*n = 22*)	First Tertile (*n = 7*)	Second Tertile (*n = 8*)	Third Tertile (*n = 7*)	*P* Value for Group	*P* Value for PEEP
$Pa_{O_2}/F_{I_{O_2}}$ at 5 cm H_2O PEEP		161 (140–193)	216 (193–273)	161 (152–169)	126 (86–140)		
Pa_{O_2}, mm Hg							
	5	81 ± 17	97 ± 16	80 ± 11	66 ± 7	0.094	<0.001
	15	112 ± 28	120 ± 24	109 ± 32	107 ± 28		
Sv_{O_2}, %							
	5	77.6 (69.4–79.4)	78.6 (63.3–79.6)	77.6 (73.7–81.7)	74.6 (69.4–79.1)	0.685	0.046
	15	79.5 (72.9–83.6)	76.1 (69.8–80.2)	80.8 (72.6–83.5)	80.0 (72.9–86.5)		
Venous admixture, % (*P* value for interaction = 0.005)							
	5	37.3 ± 14.7	24.7 ± 6.3	37.0 ± 15.5*†	50.3 ± 7.0†‡§	<0.001	<0.001
	15	27.2 ± 7.8	20.1 ± 3.7	28.3 ± 8.9	33.1 ± 2.7*		
Dav_{O_2}, ml/100 ml							
	5	2.7 (2.1–3.3)	2.9 (2.6–4.1)	2.4 (2.1–3.4)	2.3 (1.7–2.9)	0.080	0.050
	15	2.4 (2.0–3.1)	3.1 (2.2–4.2)	2.4 (2.0–3.0)	2.2 (1.6–2.6)		
Pa_{CO_2} (mm Hg)							
	5	46 ± 10	40 ± 6	46 ± 9	51 ± 12	0.196	0.002
	15	48 ± 11	43 ± 9	49 ± 11	52 ± 12		
Dead space, V_D/V_T, % (*P* value for interaction = 0.014)							
	5	60 ± 11	55 ± 10†	62 ± 9†	63 ± 14	0.553	<0.001
	15	63 ± 11	60 ± 11	65 ± 10	63 ± 14		
Static compliance of respiratory system, ml/cm H_2O							
	5	43.7 ± 13.7	50.5 ± 16.1	39.8 ± 9.9	41.2 ± 14.1	0.446	0.035
	15	38.9 ± 15	42.3 ± 16.7	34.8 ± 11.9	40.3 ± 17.4		
Static compliance of the lung, ml/cm H_2O							
	5	57.8 ± 20.6	65.5 ± 24.3	52.3 ± 15.2	56.2 ± 22.5	0.397	0.065
	15	50.0 ± 19.9	56.9 ± 24.0	44.0 ± 16.5	50.1 ± 19.5		
Static compliance of the chest wall, ml/cm H_2O							
	5	201 (123–251)	196 (172–251)	196 (120–241)	206 (101–280)	0.997	0.239
	15	186 (123–242)	175 (111–227)	185 (129–298)	197 (107–273)		
End-expiratory lung volume, ml							
	5	811 ± 269	892 ± 234	839 ± 354	697 ± 170	0.363	<0.001
	15	1,563 ± 493	1,792 ± 521	1,484 ± 549	1,423 ± 370		
Lung weight, g							
	5	1,378 ± 432	1,177 ± 168	1,164 ± 231	1,825 ± 472	<0.001*‡	0.011
	15	1,426 ± 4551	1,205 ± 168	1,195 ± 203	1,912 ± 483		

Definition of abbreviations: Dav_{O_2} = arteriovenous oxygen difference; PEEP = positive end-expiratory pressure; Sv_{O_2} = venous oxygen saturation.
Data are expressed as mean ± SD or median (interquartile range) as appropriate. Two-way repeated measures analysis of variance (one-factor repetition) or two-way repeated measures analysis of variance (one-factor repetition) on ranks was used to compare the physiological values obtained among the groups and within each PEEP applied. Interaction was reported only when significant.
* $P < 0.05$ for third versus second tertile.
† $P < 0.05$ for PEEP 5 cm H_2O versus PEEP 15 cm H_2O.
‡ $P < 0.05$ for first versus third tertile.
§ $P < 0.05$ for second versus first tertile.

CT −700 and −900 HU at 5 cm H_2O PEEP significantly increased at 15 cm H_2O PEEP. A median of 72% (52–104%) of the total gas due to the higher PEEP entered these two CT compartments, with the remainder distributed in the others (*see* online supplement).

Recruitment thresholds. Recruitment at the HU thresholds of 0, −100, −200, and −300 HU was, respectively, 49 ± 83, 77 ± 87, 86 ± 85, and 87 ± 78 g. As shown, the recruitment at the commonly used threshold of −100 HU (method A) was similar to the ones computed at −200 and −300 HU (*see* online supplement). The recruitment computed at the −500 HU threshold (method B) averaged 80 ± 67 g and was weakly correlated with the recruitment measured at the traditional threshold of −100 HU (Table 3 and Figure 2).

Respiratory mechanics–based gas lung recruitment. The gas recruitment measured using the P–Vrs curve was significantly higher than that with the EELV and static compliance of the respiratory system (EELV-Cst,rs) method (Table 3). Although the two methods provided significantly different amounts of recruitment, they were closely correlated ($R^2 = 0.93$; $P < 0.0001$), as shown in Figure 3, which reports the relationship between the two methods (Figure 3A) and the Bland–Altman analysis (Figure 3B).

Comparison of the methods. Table 3 summarizes the recruitment measured using the four methods. Measured with

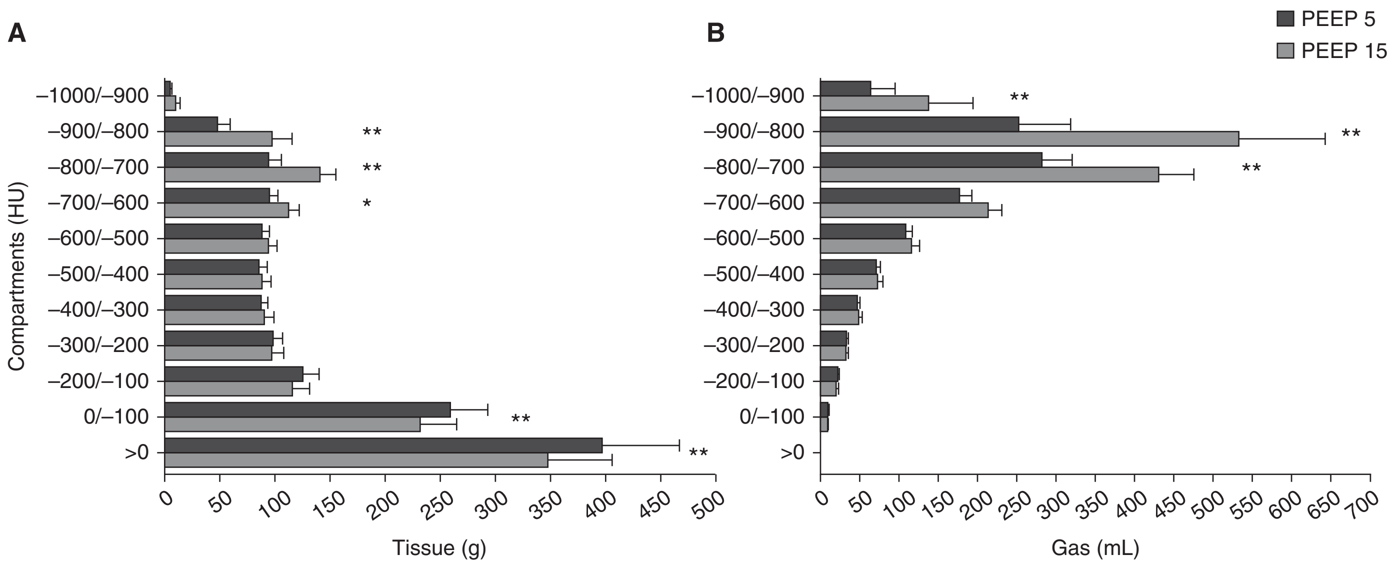

Figure 1. (*A*) Tissue distribution (in grams) in 11 computed tomography (CT) compartments from greater than 0 to −1,000 (100–Hounsfield unit [HU] steps). *Dark gray bars* represent 5 cm H_2O positive end-expiratory pressure (PEEP), and *light gray bars* represent 15 cm H_2O PEEP. $^*P < 0.05$ and $^{**}P < 0.01$ for comparison of CT scans performed at 5 and 15 cm H_2O PEEP in the same HU range. (*B*) Gas distribution in 11 CT compartments from greater than 0 to −1,000 (100-HU steps). *Dark gray bars* represent 5 cm H_2O PEEP, and *light gray* bars represent 15 cm H_2O PEEP. $^*P < 0.05$ and $^{**}P < 0.01$ for comparison of CT scans performed at PEEP 5 and 15 cm H_2O in the same HU range.

respiratory mechanics–based methods, recruitment averaged 423 ± 223 ml (54 ± 28%) with multiple P–V curves and 315 ± 201 ml (39 ± 25%) with the EELV-Cst,rs method. Previously degassed lung tissue (threshold, −100 HU) reinflated with PEEP was 77 ± 86 g (5 ± 5%) with 129 ± 148 ml of gas (16 ± 20%). Applying a threshold of −500 HU, the tissue recruited was 80 ± 67 g (6 ± 6%) with 163 ± 165 ml (16 ± 13%) of gas. Recruitment measured by CT scan expressed either as grams of tissue or milliliters of gas entering that tissue was unrelated to the recruitment measured using the respiratory mechanics methods (Figure 4).

Recruitment and baseline CT scan variables. Recruitment computed using the respiratory mechanics methods was significantly related to the amount of well-inflated tissue at 5 cm H_2O PEEP ($R^2 = 0.25$; $P = 0.02$) (*see* Figures 5B and 5C). In contrast, recruitment computed using the CT scan (threshold, −100 HU) was significantly related to the amount of noninflated tissue at 5 cm H_2O PEEP ($R^2 = 0.44$; $P < 0.001$) (*see* Figure 5A).

Recruitment and gas exchange. At constant F_{IO_2}, Pa_{O_2} improved and venous admixture decreased significantly when

Table 3. Comparisons between Different Methods in Assessing Lung Recruitment

Methods	Overall Population (*n* = 22)	First Tertile (*n* = 7)	Second Tertile (*n* = 8)	Third Tertile (*n* = 7)	*P* Value for Tertile	*P* Value for Interaction
Pa_{O_2}/F_{IO_2} at 5 cm H_2O PEEP	161 (140–193)	216 (193–273)	161 (152–169)	126 (86–140)		
Respiratory mechanics (gas)						
P–Vrs curve, ml (%)	423 ± 223 (54 ± 28%)	499 ± 247 (57 ± 26%)	333 ± 233 (43 ± 31%)	450 ± 178 (65 ± 25%)	0.364 (0.356)	0.296 (0.223)
EELV-Cst,rs, ml (%)	315 ± 201 (39 ± 25%)	395 ± 230 (45 ± 24%)	247 ± 200 (29 ± 26%)	323 ± 167 (45 ± 25%)		
P value for methods	<0.001 (<0.001)					
CT scan (tissue)						
CT (not inflated), g (%)	77 ± 86 (5 ± 5%)	49 ± 77* (4 ± 7%)*	69 ± 61 (6 ± 5%)	114 ± 115* (5 ± 5%)	0.983 (0.549)	0.012 (0.019)
CT (not + poorly inflated), g (%)	80 ± 67 (6 ± 6%)	108 ± 95 (9 ± 9%)	82 ± 51 (7 ± 4%)	50 ± 43 (3 ± 2%)		
P value for methods	0.856 (0.298)					
CT scan (gas)						
CT (noninflated gas), ml (%)	129 ± 148 (16 ± 20%)	134 ± 205 10 ± 15%*)	138 ± 128 (12 ± 10%)	114 ± 123 (25 ± 29%*)	0.496 (0.834)	0.070 (0.014)
CT (not + poorly inflated), ml (%)	163 ± 165 (16 ± 13%)	236 ± 230 (22 ± 19%)	179 ± 133 (14 ± 9%)	73 ± 74 (10 ± 9%)		
P value for methods	0.160 (0.990)					

Definition of abbreviations: Cst,rs = static compliance of the respiratory system; CT = computed tomography; EELV = end-expiratory lung volume; PEEP = positive end-expiratory pressure; P–Vrs curve = pressure–volume curve of the respiratory system.

Data as absolute values, as percentage of total lung volume (EELV for respiratory mechanics–derived variables and total gas from CT scan for gas recruited by CT scan), and as lung weight (for tissue) (as a percentage), are expressed as mean ± SD. Pa_{O_2}/F_{IO_2} at 5 cm H_2O PEEP is expressed as median (interquartile range). Two-way repeated measures analysis of variance (one-factor repetition) was performed to obtain *P* values and all pairwise multiple comparisons procedures (Bonferroni *t* test).

$^*P < 0.05$ for first versus second method.

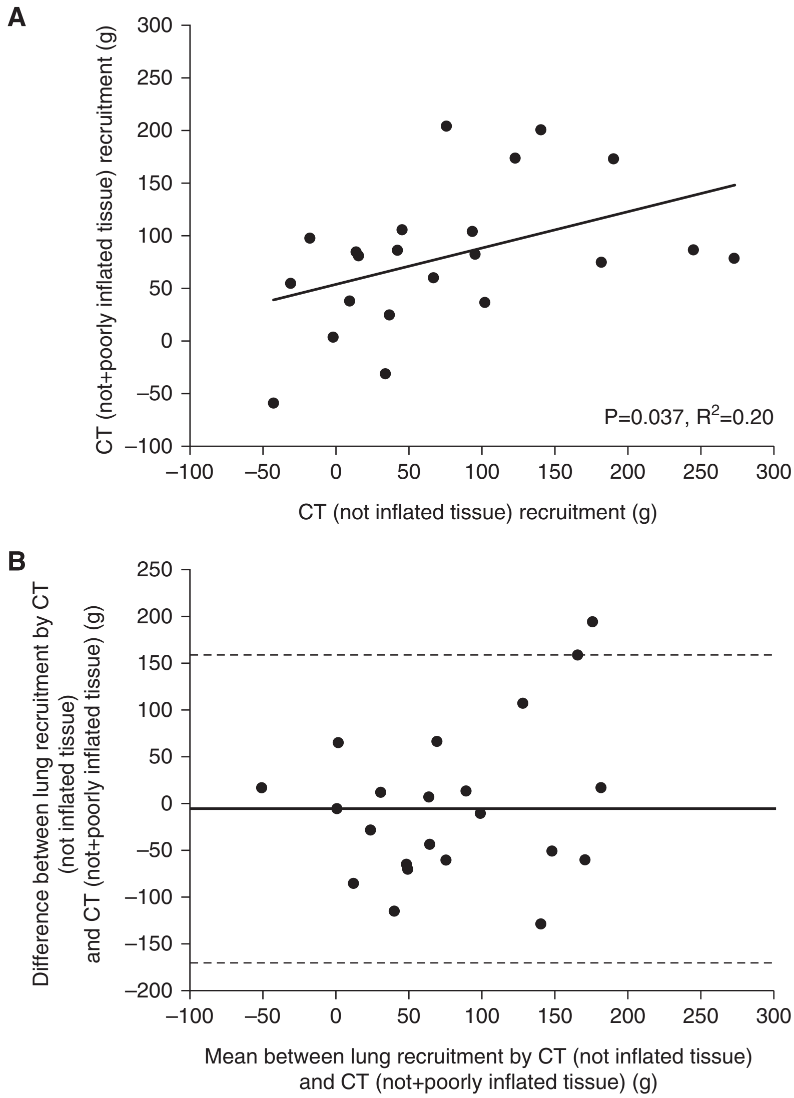

Figure 2. (*A*) Relationship between lung recruitment estimated by computed tomography (CT), expressed in grams of lung tissue. The *solid line* represents linear regression: CT (not + poorly inflated tissue) recruitment = 53 + 0.35 × CT (noninflated tissue) recruitment. $R^2 = 0.20$; $P = 0.037$. (*B*) Bland–Altman analysis of lung recruitment evaluated by CT, expressed in grams of lung tissue. The *x-axis* represents the mean of the two measurements, and the *y-axis* represents the difference between the recruitment assessed by CT methods. *Horizontal lines* represent the mean difference (*solid line*) and at the limits of agreement (mean difference ± 1.96 × SD of the differences [*dashed lines*]).

PEEP was raised from 5 to 15 cm H_2O (Table 2). CO_2 clearance slightly deteriorated with significant increases in Pa_{CO_2} and dead space. The improvement in gas exchange was unrelated to recruitment, however measured. The sole exception was a weak but significant relationship between recruitment measured with the CT scan (threshold, −100 HU) and the Pa_{O_2} improvement ($R^2 = 0.26$; $P = 0.01$) (*see* online supplement for all regressions).

Discussion

The word "recruitment" over the years has come to refer to different concepts, each relying primarily on one of the simultaneous phenomena occurring when pressures are applied to an ARDS lung, such as the opening of new pulmonary units (16) or better inflation of already open units (2). Consequently, different methods to measure recruitment have led to different results just because the word, as interpreted by different authors, does refer to different entities (2, 17). Basically, the CT scan method measures the recruitment of lung tissue to a new inflation status (16) whose extent depends on the threshold used, while the respiratory mechanics method measures both the gas entering the newly recruited lung units and that entering already open units whose mechanical properties are improved at higher PEEP.

The CT scan methods are based on voxel-by-voxel analysis. Each voxel of the dimension we used (0.002625 ml [2.625 mm^3]) may include up to 10–15 completely collapsed pulmonary acini or 1/30 of a single acinus at total lung capacity. We grouped all the voxels in the whole lung contour in 11 compartments of decreasing density (100-HU steps) from greater than 0 HU (i.e., fully degassed) to −1,000 HU (only air) (*see* Figure 1). In method A, we applied a threshold of −100 HU. We introduced this threshold decades ago (11), and it has been widely adopted up to now (*see* Table E2 in the online supplement). However, in the noninflated tissue, it includes pulmonary units with inflation up to 10% (11). We arbitrarily set this limit to account for the pulmonary units collapsing because of distal airway compression, in which some gas is left behind the occlusion, requiring lower opening pressures and probably undergoing intratidal collapse and decollapse. In our series (*see* Figure 1), the total recruitment measured at −100 HU (77 ± 86 g) included 49 ± 83 g of completely degassed tissue (threshold > 0 HU) and 28 ± 41 g of tissue nearly degassed (0 to −100 HU).

Reske and colleagues (18) and Mush and colleagues (19), using positron emission tomography, recently proposed thresholds of, respectively, −200 and −300 HU to define recruitment. Applying these thresholds to our patient population, the recruitment did not change significantly (*see* Figure 1 and online supplement). These findings first of all suggest that (*1*) a threshold up to −200 or −300 HU only marginally changes the recruitment calculation and (*2*) within this threshold range, the recruitment of completely degassed or nearly degassed units is quantitatively small, averaging only 10% of lung tissue. This fraction probably undergoes intratidal collapse and decollapse if adequate PEEP is not provided, however (20, 21).

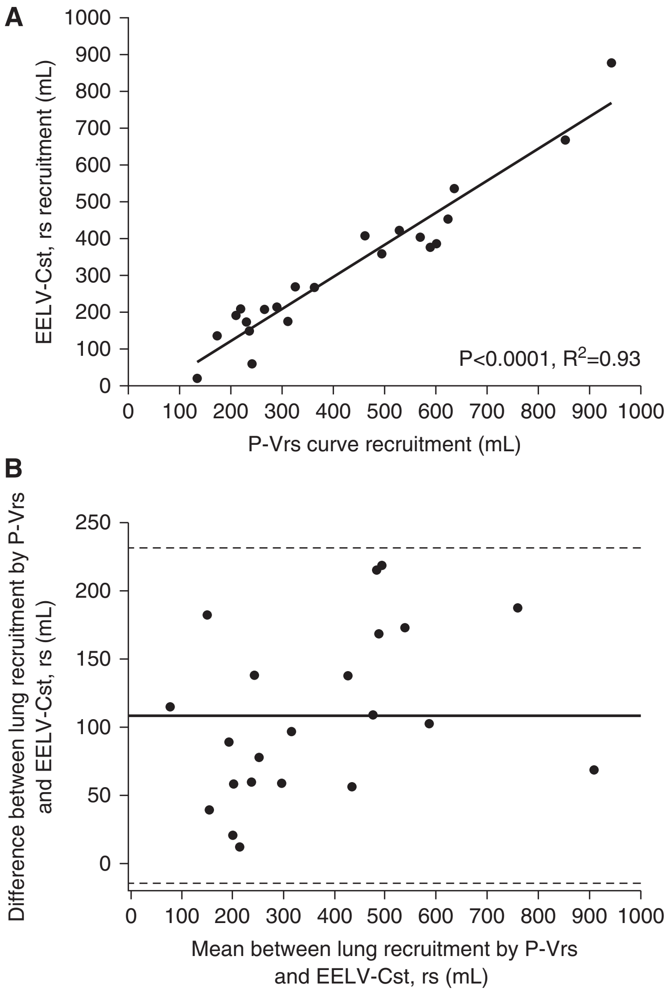

Figure 3. (*A*) Relationship between lung recruitment estimated by pressure–volume curve (P–Vrs curve recruitment) and by end-expiratory lung volume and static compliance of the respiratory system (EELV-Cst,rs). The *solid line* represents linear regression: EELV-Cst,rs recruitment = $-52 + 0.87 \times$ P–Vrs curve recruitment. $R^2 = 0.93$; $P < 0.0001$. (*B*) Bland–Altman analysis of lung recruitment computed with the P–Vrs curve and with EELV-Cst,rs methods. The *x-axis* represents the mean of the two measurements, and the *y-axis* represents the difference between the P–Vrs curve and EELV-Cst,rs methods. *Horizontal lines* represent the mean difference (*solid line*) and at the limits of agreement (mean difference $\pm$ 1.96 $\times$ SD of the differences [*dashed lines*]).

Extending the CT threshold to −500 HU, adding the poorly inflated tissue to the recruitment introduced a confounding factor. In fact, method B does not distinguish the tissue that is presumably opening and closing, as inflation up to 50% includes pulmonary units that are always open. Method B, however, is different from the method proposed by Rouby and colleagues (2), although they used the same HU threshold (−500 HU). In method B in the present study, we used a voxel-by-voxel analysis, while the Rouby method measures how much gas enters a given anatomical lung region where the contiguous voxels have an HU value less than −500 at zero end-expiratory pressure (2). In theory, if in a given anatomical region applying PEEP increases the inflation from 10% to 49.9%, the Rouby method would measure a considerable recruitment while the voxel-by-voxel analysis with a −500 HU threshold would find recruitment equal to 0, as all the inflation changes occur within the poorly aerated compartment. Therefore, Rouby's method measures both the opening of pulmonary units and better inflation of already open units.

The first method based on respiratory mechanics that we applied in this study requires measurement of the EELV at 5 and 15 cm H_2O PEEP (helium dilution) and of cord compliance at 5 cm H_2O PEEP. If the compliance does not change at 5 and 15 cm H_2O PEEP, the expected EELV at 15 cm H_2O [i.e., 5 cm H_2O EELV + compliance $\times$ (15 cm H_2O − 5 cm H_2O)] should be equal to the measured one. A measured volume that is higher than expected implies that compliance from 5 to 15 cm H_2O improved, and this has been attributed primarily to recruitment. The dual P–V curve method, proposed by several authors (4, 7), measures as recruitment the gas difference at the same pressure between two P–V curves starting from different PEEP levels. A positive difference indicates that compliance is increased, and the increase has been attributed to the recruitment of new pulmonary units.

Being based on the same principle (i.e., the improvement in compliance), the two methods provide similar recruitment figures and are extremely well related. The key issue, however, is that respiratory system compliance when the lung volume increases may improve for reasons other than enrollment of new units.

That open pulmonary units starting from different volumes inflate differently is implicit in the sigmoid P–V curve of the normal lungs. At the beginning of the inflation, it takes more pressure to reach a given volume starting from a low volume than from a higher one. This is due, independently of recruitment, to differences in surface force and lung tissue resistance at different volumes (22). Therefore, the gas increase for a given pressure increase reflects not only the possible recruitment but also the greater natural inflation of the units starting at higher volume. Actually, in the present study, we found that recruitment measured by the P–V curve was proportional to the amount of well-inflated lung, as is also suggested by gas distribution at higher PEEP in already well-aerated compartments (Figure 1). Therefore, our data suggest that the CT scan method at a threshold of −100 HU (and possibly −200 and −300 HU) measures as recruitment the amount of tissue completely degassed or nearly degassed that reinflates with higher PEEP. The respiratory mechanics method instead measures as recruitment the amount of gas

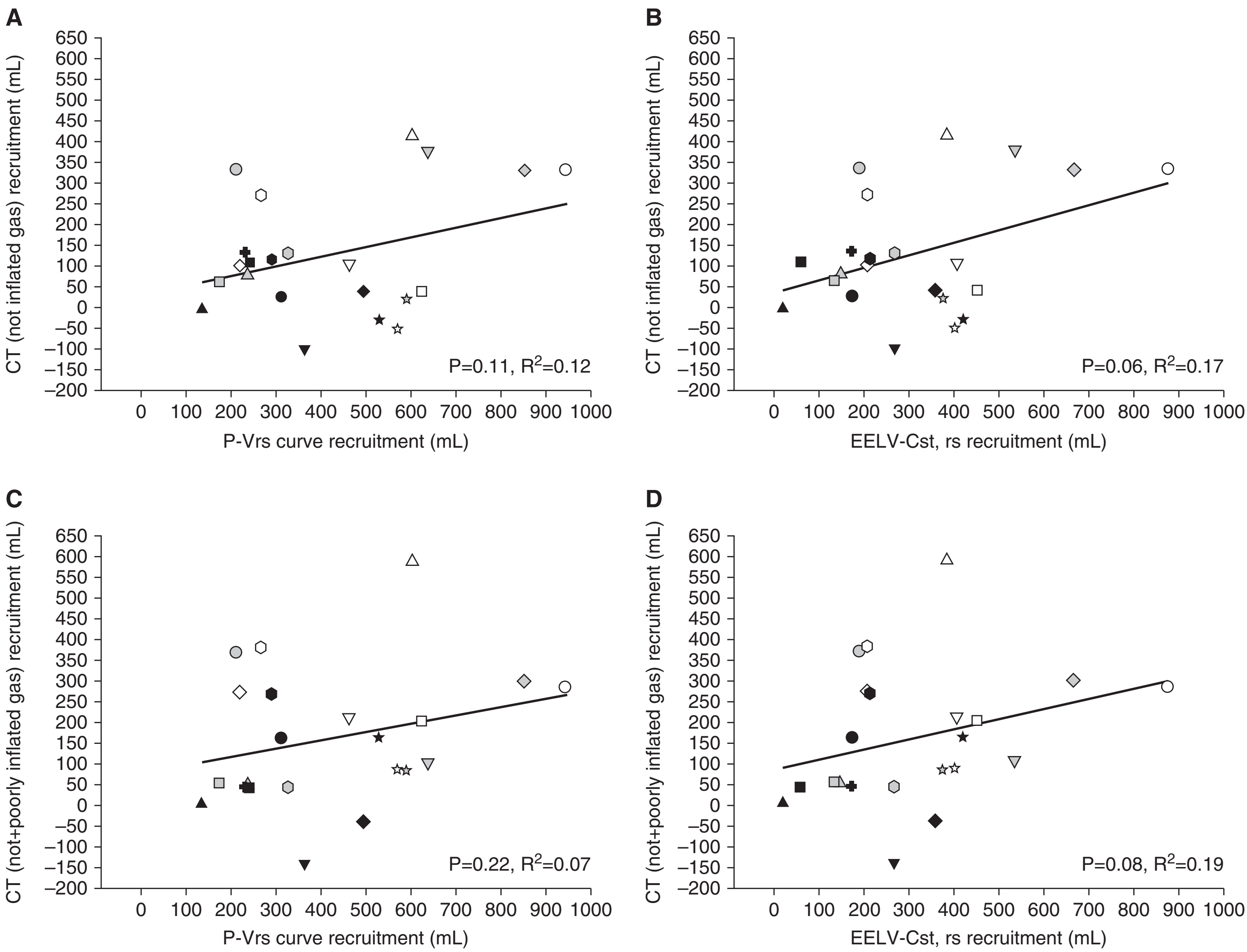

Figure 4. Comparison of respiratory mechanics–based methods and computed tomography (CT)–based methods expressed as milliliters of gas. *Solid lines* represent linear regressions. (*A*) Gas associated with recruited tissue (noninflated) versus lung recruitment estimated by pressure–volume curve (P–Vrs). $y = 31 + 0.23 \times x$. $R^2 = 0.12$; $P = 0.11$. (*B*) Gas associated with recruited tissue (noninflated) versus end-expiratory lung volume and static compliance of the respiratory system (EELV-Cst,rs). $y = 35 + 0.30 \times x$. $R^2 = 0.17$; $P = 0.06$. (*C*) Gas associated with recruited tissue (not + poorly inflated) versus P–Vrs curve recruitment. $y = 78 + 0.20 \times x$. $R^2 = 0.07$; $P = 0.22$. (*D*) Gas associated with recruited tissue (not + poorly inflated) versus EELV-Cst,rs recruitment. $y = 88 + 0.24 \times x$. $R^2 = 0.19$; $P = 0.08$. Individual patients are identified by the symbols.

entering newly opened units and the amount that inflates better, according to the improvement of mechanical properties of some pulmonary units at higher volume. Not surprisingly, these recruitments are quantitatively different and unrelated. The original method proposed by Rouby and colleagues (2), which measures all gas entering the previously poorly and/or noninflated lung regions, would measure a recruitment similar to that given by the P–V curve (i.e., newly opened units and better mechanical properties of already open lung units going from zero end-expiratory pressure to 15 cm H_2O PEEP, as shown in the comparative study by Lu and colleagues [17]). However, in the study by Lu and coworkers (17), where the P–V curve and Rouby's method were very well related, the changes in noninflated tissue (threshold, −100 HU) were unrelated to the P–V curve recruitment, as we found in our study.

Researchers in many studies have found a positive relationship between recruitment and oxygenation improvement (4, 23, 24). In our population, although the oxygenation increased with PEEP, its changes were weakly related only to the recruitment measured with CT scans (threshold, −100 HU). This is not surprising, as PEEP may affect oxygenation with mechanisms different from recruitment, such as V_A/Q changes, oxygen tension in venous blood levels (25), total cardiac output (26) and its distribution (27), and true shunt changes (28). These data suggest caution in equating any improvement in oxygenation with recruitment while setting PEEP.

In conclusion, we found that the different methods used to measure recruitment actually measure different phenomena related to the pressure increase.

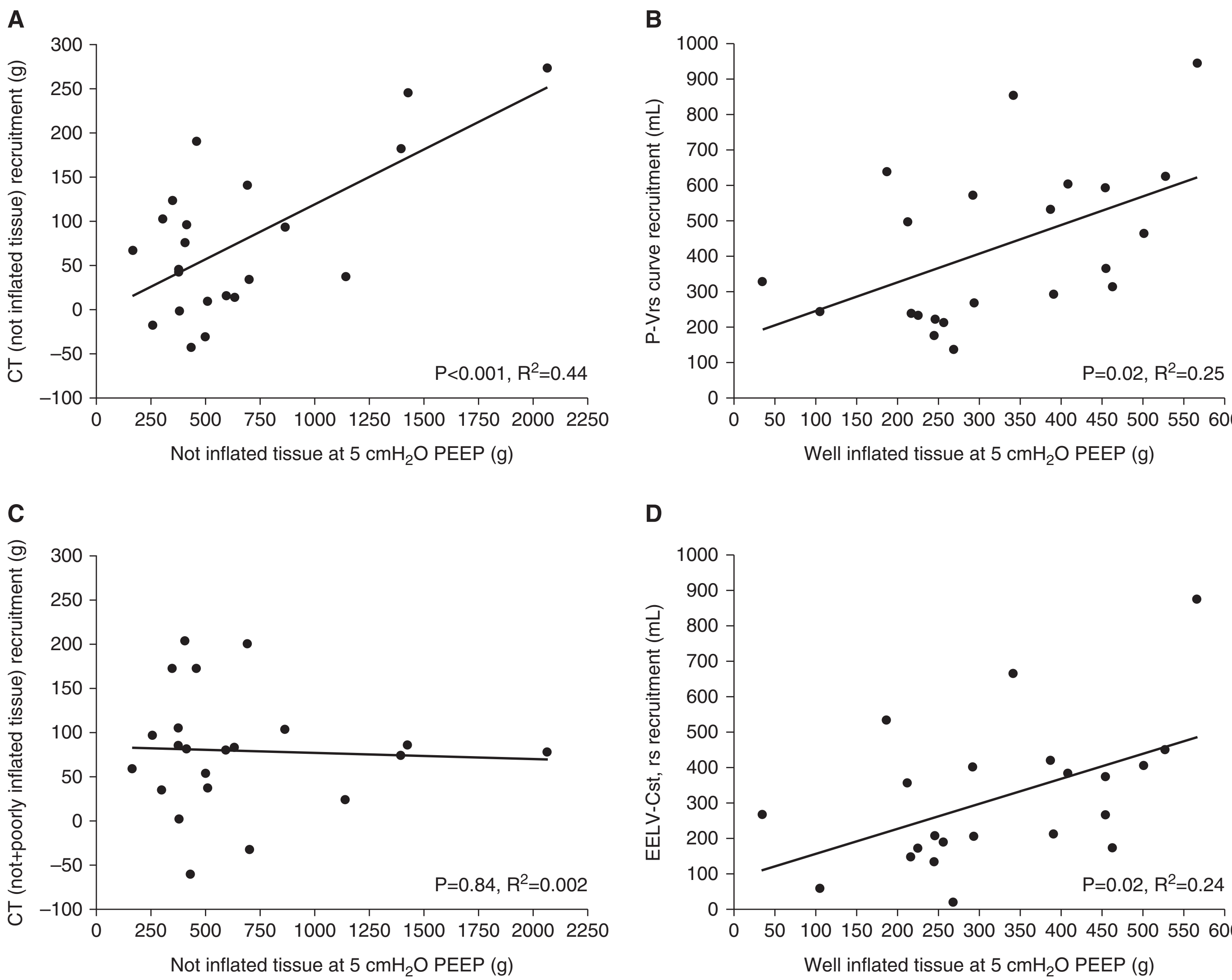

Figure 5. (*A*) Recruited tissue (not inflated) versus not inflated tissue at 5 cm H_2O positive end-expiratory pressure (PEEP). $y = -4.47 + 0.12 \times x$. $R^2 = 0.44$; $P < 0.001$. (*B*) Lung recruitment estimated by pressure–volume curve (P–Vrs) versus well-inflated tissue at 5 cm H_2O PEEP. $y = 157 + 0.85 \times x$. $R^2 = 0.25$; $P = 0.02$. (*C*) Recruited tissue (not + poorly inflated) versus noninflated tissue at 5 cm H_2O PEEP. $R^2 = 0$; $P = 0.84$. (*D*) End-expiratory lung volume and static compliance of the respiratory system (EELV-Cst,rs) recruitment versus well-inflated tissue at 5 cm H_2O PEEP. $y = 86 + 0.71 \times x$. $R^2 = 0.24$; $P = 0.02$. CT = computed tomography.

CT scan methods, at a −100 HU threshold, measure tissue that is potentially opening and closing. At a lower threshold, −500 HU, applying voxel-by-voxel analysis, introduces a confounding factor with no apparent advantage. The respiratory mechanics methods clarify to what degree raising PEEP may improve overall inflation by increasing lung compliance through enrollment of new units and possible mechanical improvement of the already open ones. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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