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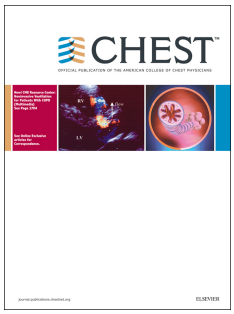

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Author contributions

Drs Corradi and Brusasco C contributed to the study design, data collection and analysis, and the writing of the manuscript and are the guarantor of the paper, *Dr Vezzani* contributed to the data collection, data analysis, reading and checking of the manuscript, *Dr Santori* contributed to the data analysis, statistical revision, reading and checking of the manuscript, *Dr Ball* contributed to the data analysis, reading and checking of the manuscript, *Drs Nicolini and Manca* contributed to the organization of the study, patients' selection and data collection, *Dr Gherli* contributed to data analysis, reading and checking of the manuscript, *Dr Brusasco V* contributed to the study design, data results interpretation and writing of the manuscript.

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Abstract

Introduction: Lung ultrasonography (LUS) has been used for non-invasive detection of pulmonary edema. Semi-quantitative LUS visual scores (V-LUS) based on B-lines are moderately correlated with pulmonary capillary wedge pressure (PCWP) and extravascular lung water (EVLW). A new quantitative computer-aided LUS analysis (Q-LUS) has been recently proposed.

Aims: This study investigated 1) whether Q-LUS better correlates with PCWP and EVLW than V-LUS; 2) to which extent positive end-expiratory pressure (PEEP) affect the assessment of pulmonary edema by Q-LUS or V-LUS.

Methods: 48 mechanically ventilated patients with PEEP of 5 or 10 cmH_2O and monitored by PCWP (n=28) or EVLW (n=20) were studied.

Results: PCWP was significantly and strongly correlated with Q-LUS Grey Unit value (r^2=0.70) but weakly with V-LUS B-line score (r^2=0.20). EVLW was significantly and more strongly correlated with Q-LUS Grey Unit mean value (r^2=0.68) than with V-LUS B-line score (r^2=0.34). Q-LUS showed a better diagnostic accuracy than V-LUS for the detection of PCWP>18 mmHg or EVLW≥10 mL/kg. With 5-cmH_2O PEEP, the correlations with PCWP or EVLW were stronger for Q-LUS than V-LUS. With 10-cmH_2O PEEP, the correlations with PCWP or EVLW were still significant for Q-LUS but insignificant for V-LUS. Inter-observer reproducibility was better for Q-LUS than V-LUS.

Conclusions: Both V-LUS and Q-LUS are acceptable indicators of pulmonary edema in mechanically ventilated patients. However, at high PEEP only Q-LUS provides data that are significantly correlated with PCWP and EVLW. Computer-aided Q-LUS has the advantages of being not only independent of operator perception but also of PEEP.

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Introduction

Pulmonary edema is a serious clinical condition resulting from a variety of causes, including inflammation, transfusion, and cardiac dysfunction.[1] The presence and severity of pulmonary edema can be invasively inferred from measurements of pulmonary capillary wedge pressure (PCWP) or extravascular lung water (EVLW). PCWP provides an indirect estimate of pulmonary edema and is dependent on both left atrial and alveolar pressures.[2] EVLW provides a direct measure of pulmonary edema, though based on some mathematical assumptions.[3,4] Owing to their invasive nature, connected risks, and costs, the use of these methods is limited to intensive care units. Therefore, the majority of patients with pulmonary edema are evaluated by imaging techniques.

Chest radiographic findings at bedside correlate weakly with pulmonary congestion and EVLW.[5,6] Thoracic computed tomography (CT) provides relevant information on morphological and functional changes resulting from increased EVLW. When analyzed quantitatively, CT can also provide measurements of lung aeration and density, from which an estimate of pulmonary edema can be inferred.[7] Because of ionizing radiation exposure and difficulty to mobilize critically ill patients, CT scanning cannot be widely used as a monitoring tool.

Lung ultrasonography (LUS) has been used for assessing pulmonary edema non-invasively and in real time by semi-quantitative visual scoring of artifacts called B-lines.[8] The presence of B-lines is a marker of pulmonary congestion, which is related to increased PCWP in patients without known pulmonary diseases.[9,10] Although the number of B-lines in patients undergoing cardiac surgery was found to be moderately correlated with the amount of EVLW, as assessed by thermo-dilution method, [9,11] the data regarding their relationship with PCWP are contrasting.[8,11] Recently, a model of pulmonary edema in isolated bovine lungs [12] showed that an objective, operator-independent, automated histogram-based quantitative analysis of LUS (Q-LUS) can provide a more accurate assessment of interstitial fluid than visual LUS based on B-lines scoring (V-LUS).

The aim of the present study was to investigate whether Q-LUS can provide estimates of pulmonary edema that are better correlated with PCWP and EVLW than V-LUS. For this purpose, mechanically-ventilated patients with otherwise healthy lung were studied following cardiac surgery. It was also investigated to which extent positive end-expiratory pressure (PEEP) affects the assessment of pulmonary edema by Q-LUS or V-LUS.

Some of the results of this study have been previously reported in an abstract form at the 35th International Symposium on Intensive Care and Emergency Medicine.[13]

Materials and Methods

Patients

Forty-eight consecutive patients requiring invasive hemodynamic monitoring after cardiac surgery were prospectively included in this observational study (Table 1). The indications for invasive hemodynamic monitoring were the following: left ventricular ejection fraction <40%, redo operation, left main coronary artery stenosis >70%, recent acute myocardial infarction, unstable angina despite medical treatment, and left ventricular hypertrophy in coronary artery disease undergoing coronary artery by-pass grafting. No patient had history, or treatment, or radiographic evidence of preexisting pulmonary disease. At ICU admittance, immediately following cardiac surgery, patients underwent LUS and hemodynamic assessment by pulmonary artery catheter to assess PCWP (n=28) or trans-pulmonary thermo-dilution method to measure EVLW (n=20), as per clinical indications. PCWP >18 mmHg was considered as an elevated left-sided filling pressure[2] and EVLW≥10 mL/kg as a marker of pulmonary edema.[14] Patients were mechanically ventilated with a tidal volume of 8±0.7 mL/kg and ventilator settings that were maintained constant except PEEP. Following a recruitment maneuver with

peak pressure of 40 cmH_2O and PEEP of 20 cmH_2O, PEEP was reduced by 5-cmH_2O steps to zero. Measurements of V-LUS, Q-LUS and PCWP or EVLW were obtained during 20 min steady-state at 10 and 5 cmH_2O PEEP. LUS and hemodynamic measurements were repeated whenever required by clinical conditions.

The study was approved by the local institutional review board (protocol Number 41429). All patients gave a written informed consent before elective cardiac surgery.

Lung ultrasonography

A Philips CX50 system (Philips Healthcare, Eindohoven, The Nederlands) with high-frequency, linear-array probe at 10 MHz was used for collecting LUS images before hemodynamic measurements by the same operator (F.C.), with the patients in a supine position. Transverse scanning was used to better visualize the pleural line avoiding acoustic interference from the ribs.

V-LUS. A total of 28 lung areas were scanned along parasternal, mid-clavicular, anterior axillary, and mid-axillary lines with focus at pleural line. A B-line was defined as a discrete laser-like vertical hyperechoic reverberation artifact extending from the pleural line to the bottom of the screen, without fading and moving synchronously with lung sliding. V-LUS was evaluated a posteriori by two operators (F.C and C.B.) blindly and separately searching for the presence, distribution, and extent of artifacts suggestive of interstitial involvement. Each lung area was carefully analyzed to count the maximum number of B-lines, ranging between 0 (complete absence) and 10 (complete confluency). In the case of confluent B-lines, the percentage of the lung area occupied by B-lines (white to black area) was calculated and divided by ten to infer an estimate number of B-lines.[15] The sum of B-lines found over the 28 zones was taken as the overall result of V-LUS.

Q-LUS. Each hemi-thorax was divided into four areas, upper and lower anterior (between sternum and anterior axillary line) and upper and lower lateral (between the anterior and posterior

axillary lines). A 12-s video clip was recorded with the probe held motionless and perpendicular maintaining pressure at the minimum needed for full adherence of transducer to skin. Q-LUS was analyzed using a custom-made computer-assisted gray-scale software (*QUANTA*^{TM} *Critical Care*, CAMELOT Biomedical Systems Srl [www.quanta.camelotbio.com]) (Figures 1 and 2). A region of interest area was chosen extending from the pleural line to the bottom of the screen and its area was maintained constant by width adaptation. Images showing signs of incomplete adhesion between probe and chest surface were discarded. The mean echo intensity of each region of interest was determined and the mean of the 8 areas was retained for analysis. Q-LUS. The ultrasound data were collected and saved as 12-s cine loops (video loops) at 33 frames per second. Thus, the total ultrasound dataset for this analysis were 8 cine loops per subject for 48 subjects totaling 384 cine loops, consisting of 399 frames per loop or a total of 153,216 frames of ultrasound data. Afterwards, a pixel-per-pixel algorithm was used to calculate the frequency distribution of 255 different echo intensities (Grey Units) of each areas considered. The mean value of echo intensity of each of 8 regions of interest was determined and their mean retained for analysis. The regions of interest were defined by the operator starting from the pleural line down to the bottom of images and excluding the fixed structures of the rib cage. The region of interest area was made constant in all images by varying the image width to compensate for differences in depth of pleural line from chest surface among patients and chest wall areas (Figure 3). Multi-frame images were acquired with the same setting (52-DB gain, focus at 6 cm with linear-array probe to maximize ultrasound beam collimation, 50% time-gain compensation, removal of 2nd harmonic and automatic post-processing to avoid artifact attenuation). Data were stored as uncompressed DICOM and then randomly rearranged for blind analysis by two anesthesiologists with LUS expertise.

Hemodynamics

A pulmonary artery catheter (141HF7, Edwards Lifesciences, Unterschlei Bheim, Germany) for conventional hemodynamic measurements was inserted via right internal jugular or subclavian vein. PCWP measurements were derived electronically from the hemodynamic monitoring system (Drager Infinity Delta XL, Dräger Medical GmbH Lübeck, Germany). Transducers were positioned at the level of the fourth intercostal space in correspondence of the mid-axillary line and were zeroed to atmospheric pressure. Blood pressure, heart rate, and central venous pressure were measured continuously. All measurements were reviewed for artifact removal. Mean end-expiratory PCWP was obtained by two investigators (A.V. and T.M.) via waveform analysis from electronically stored recordings of 3–5 PCWP tracings.

A VolumeView™ catheter (Edwards Lifesciences) for trans-pulmonary thermo-dilution measurements was inserted into the left or right femoral artery and connected to the EV1000™ Clinical Platform monitoring system (Edwards Lifesciences). Thermo-dilution measurements were performed in sets of at least three consecutive injections of 20 mL cold saline each, randomly distributed over the respiratory cycle. As required by the EV1000™ software, individual boluses of each set were manually validated by the attending physician before they were included in the data set. By protocol, boluses differing by >15% of the set average were considered faulty and excluded from the analysis. Catheters were positioned in operating room and correct placement was checked before measurements by chest X-ray.

Statistical Analysis

Data are presented as mean ± standard deviation or median and interquartile range (IQR).

Although mean LUS intensities, PCWP and visual scores were normally distributed, other continuous variables did not pass the Shapiro-Wilk test, by suggesting to use non-parametric tests for comparisons and correlation. The comparisons between continuous variables were performed with the

Wilcoxon-Mann-Whitney test. The relationships between continuous variables were tested by Pearson and Spearman rank correlation. To minimize the risk of Type I error in the evaluation of the correlation matrix, P values of the Spearman analysis were adjusted using the Holm method. A power calculation for correlation analysis was preliminarily carried out for each r coefficient from 0.5 to 0.7 ($\alpha = 0.05$, with a two-sided alternative hypothesis). The extra sum-of-squares F test was used for comparing the regression lines of repeated measures when available.

Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic accuracy and to define cutoff values for each measurement pattern. For each ROC curve, the area under curve (AUC) and its 95% confidence interval (CI) were calculated, as well as the cutoff value that maximized sensibility and specificity. The AUCs of two ROC curves were compared by applying the bootstrap test. The bootstrap test for AUC comparison implements the Hanley-McNeil method by performing 2000 replicates with resampling from the raw data. For the evaluation of intra-/inter-observer variability, coefficient of variation (CV, calculated as σ/μ), intraclass correlation (ICC), and Robinson's A were used.

Results

Of 61 patients screened, 13 were excluded for one of the following reasons: they were studied only at one PEEP level because of hemodynamic instability (n=8) or lung visualization was sub-optimal due to surgical manipulation or pleural effusion (n=5). None of the patient showed clinical, biochemical, or radiographic signs of pneumonia after surgery. A total of 96 LUS were obtained and analyzed: 56 in association with PCWP and 40 with EVLW measurements. The total time required to complete the examination was significantly shorter for Q-LUS than V-LUS (5.2±0.6 vs. 13.0±1.5 min; $p<0.001$). This was mainly due to a shorter time of analysis (2.6±0.3 vs. 8.2±1.2 min; $p<0.001$)(Table 2). The intra-class correlation was 0.966 (95% CI: from 0.945 to 0.979), with Robinson's A = 0.983.

Power calculation for correlation analysis, preliminarily performed for each *r* coefficient from 0.5 to 0.7, yielded 0.786-0.991 ranges for PCWP and 0.619-0.949 for EVLW.

Correlations with PCWP

PCWP was correlated with Q-LUS Grey Units mean value (r^2=0.697; p<0.0001) and less strongly with V-LUS B-line score (r^2=0.201; p=0.0005) (Figure 4, Table 3). By ROC analysis (Table 4), Q-LUS showed a higher diagnostic accuracy [AUC: 0.90; 95% CI (0.81-0.99)] than V-LUS [AUC: 0.61: 95% CI (0.46-0.75)] for the detection of PCWP>18 mmHg, with cutoff values of 76 Grey Units and 15 B-lines, respectively.

With a PEEP of 5 cmH_2O, the correlation with PCWP was stronger with Q-LUS Grey Units mean value (r^2=0.797; p<0.0001) than V-LUS B-line score (r^2=0.351; p=0.0009). With a PEEP of 10 cmH_2O, the correlation with PCWP was still significant for Q-LUS Grey Unit mean value (r^2=0.563; p<0.0001), but insignificant for V-LUS B-line score (r^2=0.079; p=0.1471) (Figure 4).

Correlations with EVLW

EVLW was significantly correlated with Q-LUS Grey Unit mean value (r^2=0.683; p<0.0001) and less strongly with V-LUS B-line score (r^2=0.339; p<0.0001) (Figure 5, Table 3). By ROC analysis (Table 5), Q-LUS showed a better diagnostic accuracy [AUC 0.93, 95% CI (0.79-1.00)] than V-LUS [AUC 0.85, 95% CI (0.67-1.00)] for the detection of EVLW≥10 mL/kg, with cutoff values of 39 Grey Units and 9 B-lines, respectively.

With a PEEP of 5 cmH_2O, the correlation with EVLW was stronger for Q-LUS Grey Unit mean value (r^2=0.807; p<0.0001) than V-LUS score (r^2=0.639; p<0.0001). With a PEEP of 10 cmH_2O, the correlation with EVLW was still significant for Q-LUS Grey Unit mean value (r^2=0.662; p<0.0001), but borderline for V-LUS score (r^2=0.200; p=0.0482) (Figure 5).

Changes within patients

Eleven patients monitored with PCWP and six with EVLW had repeated measurements at the same PEEP, because of hypotension requiring hemodynamic re-evaluation. There were no significant differences in slope (p=0.27-0.86) or intercept (p=0.34-0.96) among individual regression lines between Q-LUS and PCPW or EVLW at any PEEP level (Figure 6).

Discussion

The main results of this study are that: 1) Q-LUS correlated with PCWP and EVLW better than V-LUS, 2) Q-LUS showed a greater diagnostic accuracy in identifying PCWP>18 mmHg or EVLW≥10 mL/kg than V-LUS; 3) with high PEEP application, Q-LUS but not V-LUS remained significantly correlated with PCWP and EVLW.

Comments on methodology

Quantification of B-lines has been performed by techniques using different types of transducers (curved, linear, micro-convex, phased array), scanning frequencies,[12,16-18] and acoustic windows.[19] These differences might in theory represent important source of variability. Using linear probes, Baldi et al [7] showed that V-LUS can determine semi-quantitatively EVLW with the same accuracy as CT by exploring only sub pleural areas. Thus, in this study, linear probes and transverse scan were used to facilitate visualization of pleural line.

In a number of studies V-LUS was used to detect and quantify pulmonary edema in patients with congestive heart failure.[20] However, V-LUS has limitations due to the difficulty of counting single artifacts on moving images over the whole chest.

Q-LUS is a computer-aided method to analyze LUS images that is independent of inter-

observer variability and proved to be more sensitive than either V-LUS or CT in detecting EVLW in isolated lungs.[12] Moreover, Q-LUS provides the analysis of 399 frames over a 12 s video-clip, thus including at least two whole breathing cycles.

For V-LUS, scoring was based on 28-zone, which presumably can give more quantitative information than protocols based on lower numbers of zones.[15] For Q-LUS, only 8 zones were considered in order to shorten the time of analysis, on the expectation that no information is lost thanks to the computer-aided analysis.

Comments on results

The results of the present study show a strong correlation between lung echo intensity, as assessed by Q-LUS, and pulmonary congestion, as inferred from high levels of invasively determined PCWP or EVLW. This result can be reasonably explained by the increase of reflective interfaces between air and fluid, which are the major determinant of echo intensities. Overall, also V-LUS was significantly correlated with PCWP and EVLW, but less strongly than Q-LUS. This data confirm the superiority of Q-LUS over V-LUS in the assessment of pulmonary edema in humans, as previously reported in isolated lungs.[12] The greater accuracy of Q-LUS than V-LUS in predicting PCWP and EVLW cutoffs may be the result of a greater sensitivity of Q-LUS to small amounts of EVLW,[12] and also to the random error associated with subjective scoring with V-LUS. Therefore, it is not surprising that Q-LUS was better correlated than V-LUS with quantitative objective measurements like PCWP and EVLW.

To best of our knowledge, this is the first study examining the effect of PEEP on LUS in cardiogenic edema of otherwise healthy lung. The results show that the ability of either V-LUS or Q-LUS to assess pulmonary edema was impaired when PEEP level was raised, which can be reasonably attributed to an increase of air-to-water ratio. This may be due to the opening of peripheral lung units

by PEEP, thus changing the distribution of EVLW between the deep central and peripheral lung regions, even if the total amount of EVLW remains constant. However, whereas the correlations of V-LUS with either PCWP or EVLW disappeared at PEEP of 10 cmH_2O, those of Q-LUS was weakened but remained significant. The attenuation of B-lines with increasing PEEP was previously reported in ARDS [21] and attributed to the effect of lung recruitment. A physiological mechanism may be that the alveolar recruitment is associated with a more homogeneous distribution of EVLW or geometric changes [22], which may result in a reduction of highly reflecting sub-pleural interfaces even if the overall air-to-water ratio is in part preserved. Where this occurs, the number or size of water particles may not achieve the critical values for generating B-lines in relation to the LUS waive-length. The physical mechanisms underlying this phenomenon is a matter of speculation but "scattering" may be a reasonable explanation based on ex-vivo animal studies [12,22]. According to basic physics of ultrasonography, [23] the attenuation of ultrasound intensity is not only dependent on absorption and reflections, but also on beam scattering, whereby energy propagates in several different directions. The amplitude, shape, and spatial distribution of the internal echo signal are dependent on the nature and state of the lung parenchyma examined. If the structures encountered are smaller than the ultrasonic wavelength, the so-called "Rayleigh scattering" may occur. In this case, the microstructure act as point reflectors so that the energy is scattered in all directions (without B-lines appearance). When the scale of tissue inhomogeneity is similar to the ultrasound wavelength "Tyndall scattering" may occur (with B-lines appearance). In this case the scattering is more unidirectional and attenuation is dependent on the frequency of the ultrasonic wave. For the above reasons, Q-LUS reflects the air-to-water ratio irrespective of artifacts visible to naked eye, i.e., B-lines. On the other hand, in the case of "white lung", when confluent B-lines cannot be counted, Q-LUS can still be able to distinguish between different amount of EVLW.

Interestingly, B-lines correlated better with EVLW than PCWP, which is in agreement with a

recent report by Volpicelli et al.[11] and apparently due to an increased PCWP without B-lines. A possible explanation for this finding could be that PCWP does not reflect hemodynamic congestion only but also alveolar pressure. This mechanism would be confirmed by the loss of correlation between B-lines and PCWP when PEEP, and in turn alveolar pressure, was increased. However, in the present study Q-LUS Mean Grey Units correlated similarly with EVLW and PCWP even when PEEP was increased. It can be speculated that Q-LUS is able to detect interstitial edema associated with increased PCWP before alveolar edema occurs and B-lines can be seen. Q-LUS in this study was faster than 28-zone V-LUS. We recognize that there are faster V-LUS scores that may be competitive in terms of time, but unsuitable for quantitative information.

This study has some limitations. First, the study was conducted in a limited number of patients monitored for pulmonary congestion by PCWP or EVLW. Measurements of both PCWP and EVLW in the same patients would have been ideal for the study but not done to limit invasiveness. More patients had PCWP than EVLW because more patients had Swan-Ganz than EV-1000 catheter already positioned in the operating room. Second, parameters and settings of ultrasound device potentially affect the echo intensity analysis, thus different cutoff values of V-LUS or Q-LUS may be obtained with different systems, probes and scanning planes. Further studies are needed to develop software with second-order analysis to make Q-LUS independent of ultrasound device and pre-settings. Measurements were obtained at PEEP of 5 and 10 cmH_2O only, because these levels represent the best compromise between ventilation distribution, oxygenation, and hemodynamic stability in these patients. [24] It was not possible to evaluate over-distended lung units, which remains a major limitation of ultrasonography irrespective of the method of analysis. Third, our results are ventilator-setting specific and cannot be extrapolated to other ventilation strategies. Finally, this was a validation study of a bedside method that can be used prior to, but not substituting for, invasive methods that can provide additional hemodynamic information.

In conclusion, the results of the present study show that both V-LUS and Q-LUS are acceptable indicators of pulmonary edema in patients mechanically ventilated with low PEEP. However, when high PEEP is applied the relationships between B-lines and the usual measurements of pulmonary edema PCWP and EVLW is lost, whereas the correlations with Q-LUS data remain significant. Although computer-aided Q-LUS represents just a new software application to LUS, it offers the advantages of extracting more information without increasing complexity and examination time and of increasing operator perception because human retina can differentiate only 30 shades of gray, whereas computer-aid quantitative ultrasonography (Q-LUS) can differentiate 255 shades of gray, thus providing more detailed quantification of ultrasound intensity.

Table 1. Patients Characteristics

	EVLW	PCWP	
Sex (m/f)	15/5	22/6	0.729
Age (yr)	69 ± 8	70 ± 8	0.782
Type of surgery (n)			
Coronary Artery Bypass Grafting	12	18	0.902
Valve Replacement	5	7	
Aortic Surgery	3	3	
Simplified Acute Physiology Score	28 ± 12	28 ± 11	0.947
Body Mass Index (kg/m^2)	27 ± 4	27 ± 4	0.853
Euroscore	6 ± 3	6 ± 3	0.933
Transfusion (RBC units)	3 ± 5	4 ± 5	0.659
Inotropic Score	3 ± 2	4 ± 3	0.602
Vaso-Inotropic Score	28 ± 11	16 ± 13	0.105
Ejection Fraction (%)	42 ± 12	44 ± 13	0.622
CI ($l/min/m^2$)	2.7 (1.8-3.5)	2.5 (2.1-2.9)	0.416
SVI ($ml/m^2/beat$)	29 (21-44)	28 (22-35)	0.106
SVRI (dynes $s/cm^5/m^2$)	1745 (1283-3540)	2307 (1879-2708)	0.935
PCWP (mmHg)	-	13 (10-17)	
GEDI (ml/kg)	735 (533-835)	-	
ITBVI (ml/m^2)	917 (645-1032)	-	
PVPI	2.85 (2.42-3.47)	-	
EVLW (ml/kg)	14 (12-16)	-	

Mechanical Ventilation (h)	24 (16-85)	48 (12-300)	0.155
Intensive care unit length of stay (d)	6 (5-7)	8 (3-16)	0.818
Hospital length of stay (d)	16 (11-22)	15 (12-32)	0.818
Intensive care unit mortality (n)	0	3	0.138
In hospital deaths (n)	0	3	0.138

Data are presented as mean ± SD or median (IRQ).

CI, cardiac index; SVI, stroke volume index; SVRI, Systemic vascular resistance index; PCWP, pulmonary capillary wedge pressure; GEDI, Global End Diastolic Index; ITBVI, Intra Thoracic Blood Volume Index; PVPI, Pulmonary Vascular Permeability Index; EVLW, Extra Vascular Lung Water; RBC, red blood cell.

Table 2. Times for quantitative lung ultrasonography (Q-LUS) and visual lung ultrasonography (V-LUS) examinations.

Time (min)	V-LUS	Q-LUS	*p*
Acquisition	4.6±0.9	2.5±0.5	<0.001
Analysis	8.2±1.2	2.6±0.3	<0.001
Total	13±1.5	5.2±0.6	<0.001

Data are mean ± SD

Table 3. Correlation coefficients obtained by parametric (Pearson's) and non-parametric (Spearman's) analysis.

PCWP					
		Spearman (r)	*p*	Pearson (r)	*p*
PEEP 5 and 10	Q-LUS	0.801	<0.0001	0.835	<0.0001
	V-LUS	0.440	0.0007	0.448	0.0005
PEEP 5	Q-LUS	0.859	<0.0001	0.893	<0.0001
	V-LUS	0.636	0.0003	0.593	0.0009
PEEP 10	Q-LUS	0.700	<0.0001	0.750	<0.0001
	V-LUS	0.202	0.3029	0.281	0.1471
EVLW					
		Spearman (r)	*p*	Pearson (r)	*p*
PEEP 5 and 10	Q-LUS	0.671	<0.0001	0.826	<0.0001
	V-LUS	0.564	<0.0001	0.581	<0.0001
PEEP 5	Q-LUS	0.732	0.0002	0.898	<0.0001
	V-LUS	0.907	<0.0001	0.800	<0.0001
PEEP 10	Q-LUS	0.820	<0.0001	0.813	<0.0001
	V-LUS	0.371	0.1074	0.447	0.0482

PCWP, pulmonary capillary wedge pressure; EVLW, Extra Vascular Lung Water; Q-LUS, quantitative lung ultrasonography; V-LUS, visual lung ultrasonography.

Table 4. Accuracy of quantitative lung ultrasonography (Q-LUS) and visual lung ultrasonography (V-LUS) for PCWP >18 mmHg (28 patients and 56 measurements)

	Predictors	**Cutoffs (Sn, Sp)**	**AUC (95% CI)**	**P***	**P#**
Overall (PEEP 5 and 10)	Q-LUS	76 (0.91, 0.70)	0.90 (0.81-0.99)	0.002	<0.0001
	V-LUS	15 (0.73, 0.44)	0.61 (0.46-0.75)	0.006	
PEEP 5	Q-LUS	76 (0.91, 0.80)	0.92 (0.79-1.00)	0.004	0.9048
	V-LUS	15 (0.83, 1.00)	0.91 (0.81-1.00)	0.003	
PEEP 10	Q-LUS	69 (0.90, 0.89)	0.894 (0.77-1.00)	0.004	0.0376
	V-LUS	15 (0.50, 0.72)	0.608 (0.40-0.82)	0.012	

AUC: Area under Receiver Operating Curve; CI: confidence intervals; Sn: Sensitivity; Sp: Specificity. P*, significance of ROC curves, P#, significance of AUC differences between Q-LUS and V-LUS.

Table 5. Accuracy of quantitative lung ultrasonography (Q-LUS) and visual lung ultrasonography (V-LUS) for EVLW≥10 mL/kg (20 patients and 40 measurements)

	Predictor	**Cutoff (Sn, Sp)**	**AUC (95% CI)**	**P***	**P#**
Overall (PEEP 5 and 10)	Q-LUS	39 (0.83, 1.00)	0.93 (0.79-1.00)	0.005	0.4448
	V-LUS	9 (0.83, 0.77)	0.85 (0.67-1.00)	0.008	
PEEP 5	Q-LUS	61 (1.00, 0.86)	0.97 (0.90-1.00)	0.001	0.8566
	V-LUS	13 (1.00, 0.81)	0.96 (0.89-1.00)	0.001	
PEEP 10	Q-LUS	39 (1.00, 1.00)	1.000 (0.99-1.00)	<0.001	0.0447
	V-LUS	9 (0.50, 0.72)	0.47 (0.00-1.00)	0.133	

AUC: Area under Receiver Operating Curve; CI: confidence intervals; Sn: Sensitivity; Sp: Specificity. P*, significance of ROC curves, P#, significance of AUC differences between Q-LUS and V-LUS.

Figure legends

Figure 1. Representative Q-LUS images and analysis in a patient with increased extra vascular lung water (EVLW) during ventilation with different pulmonary end-expiratory pressure (PEEP) levels. Left panels: images showing B-lines at high (top) but not low (bottom) PEEP; Right panels: grey-texture analysis showing Gray Scale Units distributions.

Figure 2. Representative images and Q-LUS data of four patients with different levels of EVLW at PEEP 10.

Figure 3. Representative images of two patients with different body composition showing how the region of interest (ROI) was delineated. Note that the ROI in the fat subject (lower panel) was made wider than in the lean subject (upper panel) to obtain the same areas.

Figure 4. Correlations between pulmonary capillary wedge pressure (PCWP) and Q-LUS or V-LUS at PEEP levels of 5 or 10 cmH_2O.

Figure 5. Correlations between EVLW and Q-LUS or V-LUS at PEEP levels of 5 or 10 cmH_2O.

Figure 6. Relationships between changes of Q-LUS and EVLW or PCWP in patients with repeated measurements. Each symbol represents a patient. Shown are the regression lines for pooled patients as no significant differences were observed among individual regression lines at any PEEP level.

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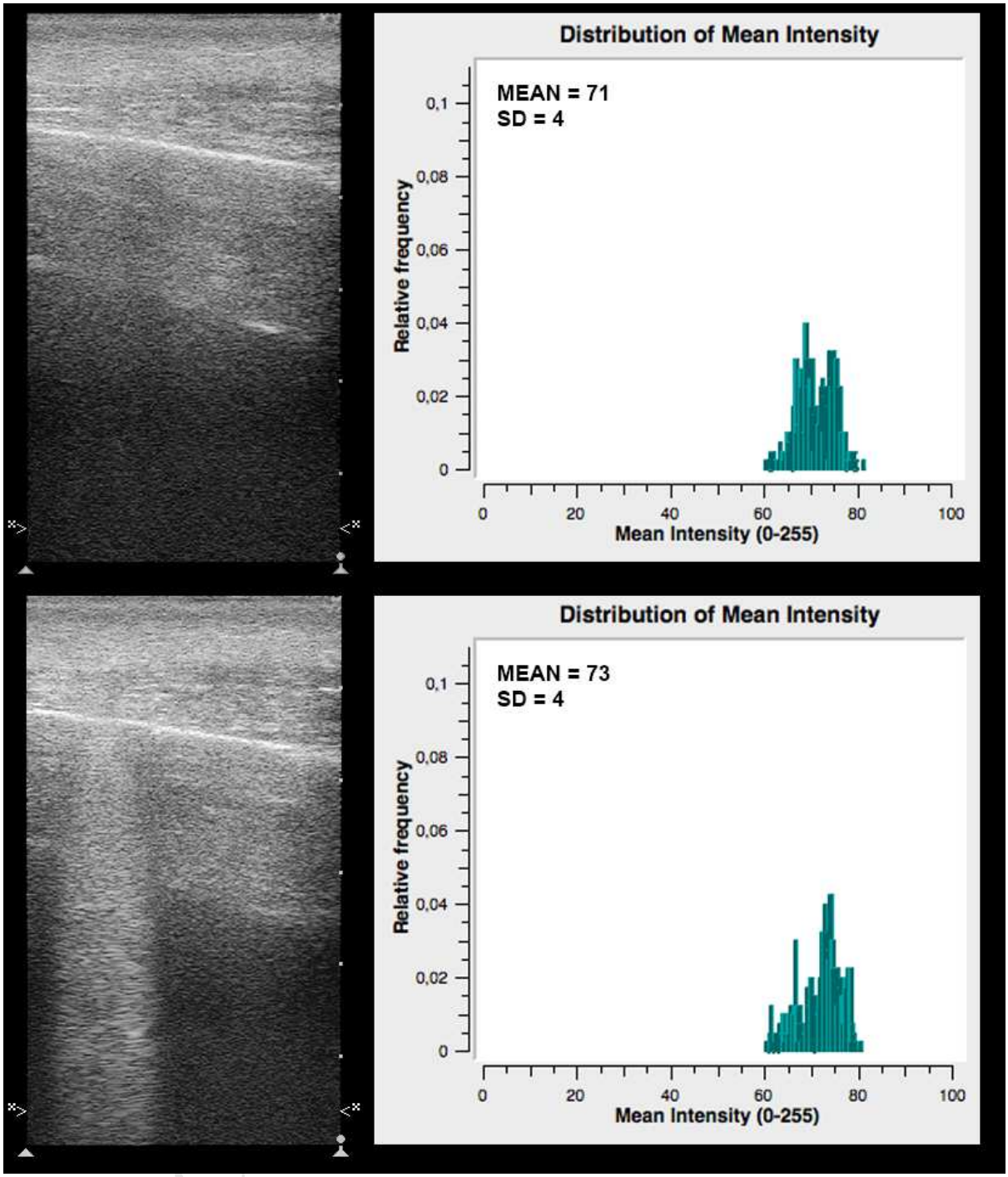
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80
100
Mean Intensity (0-255)
Distribution of Mean Intensity
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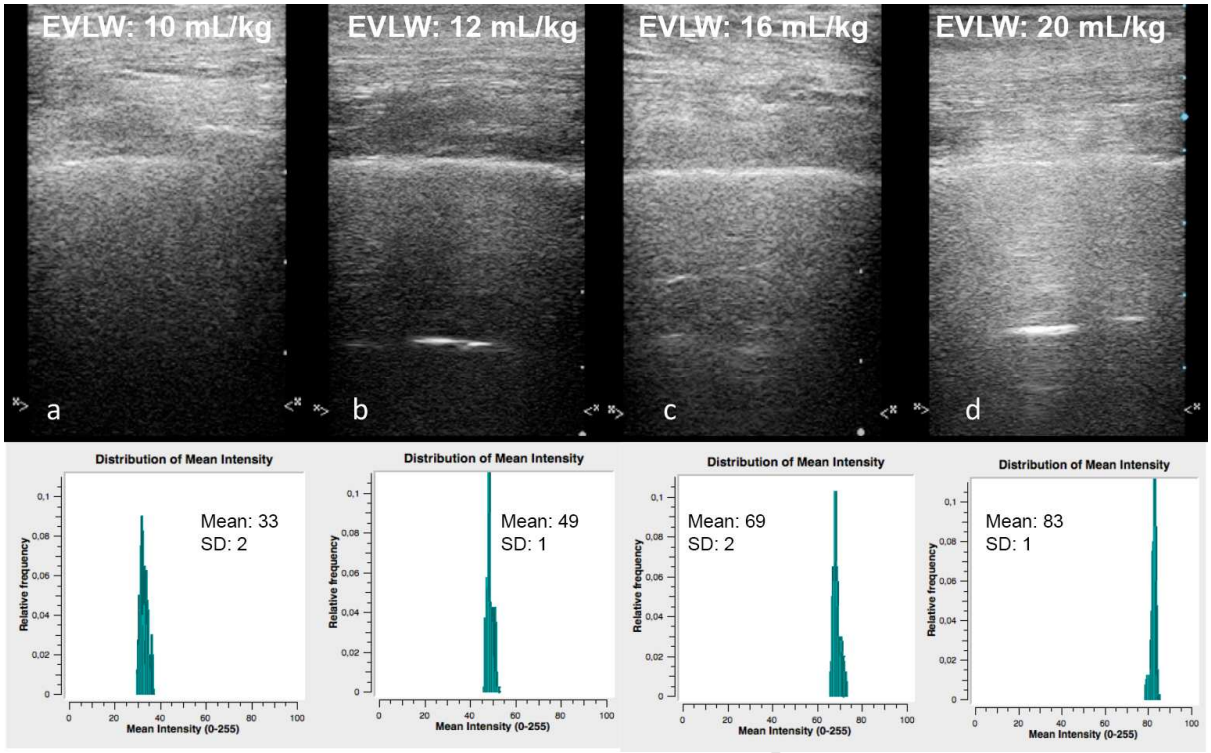

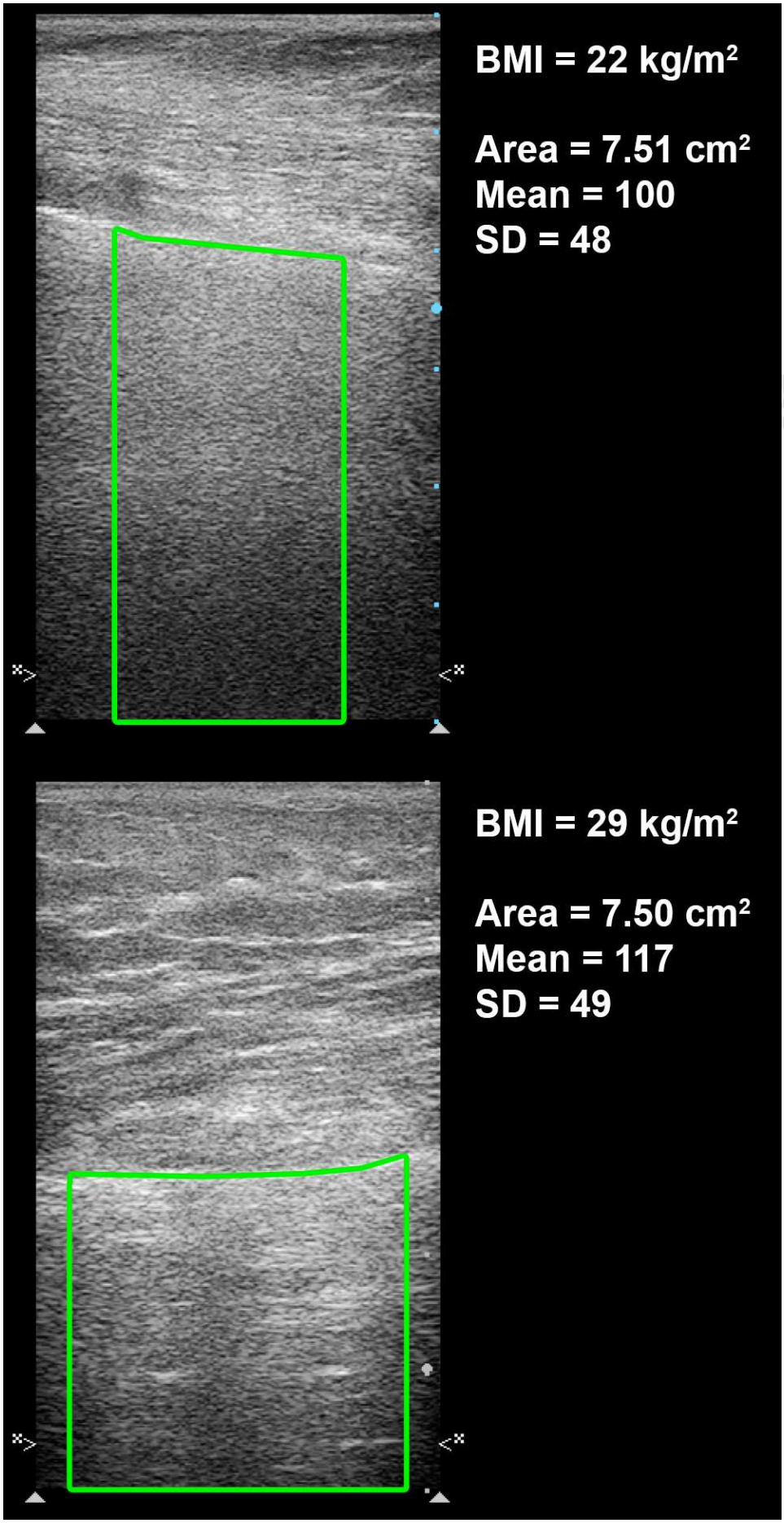
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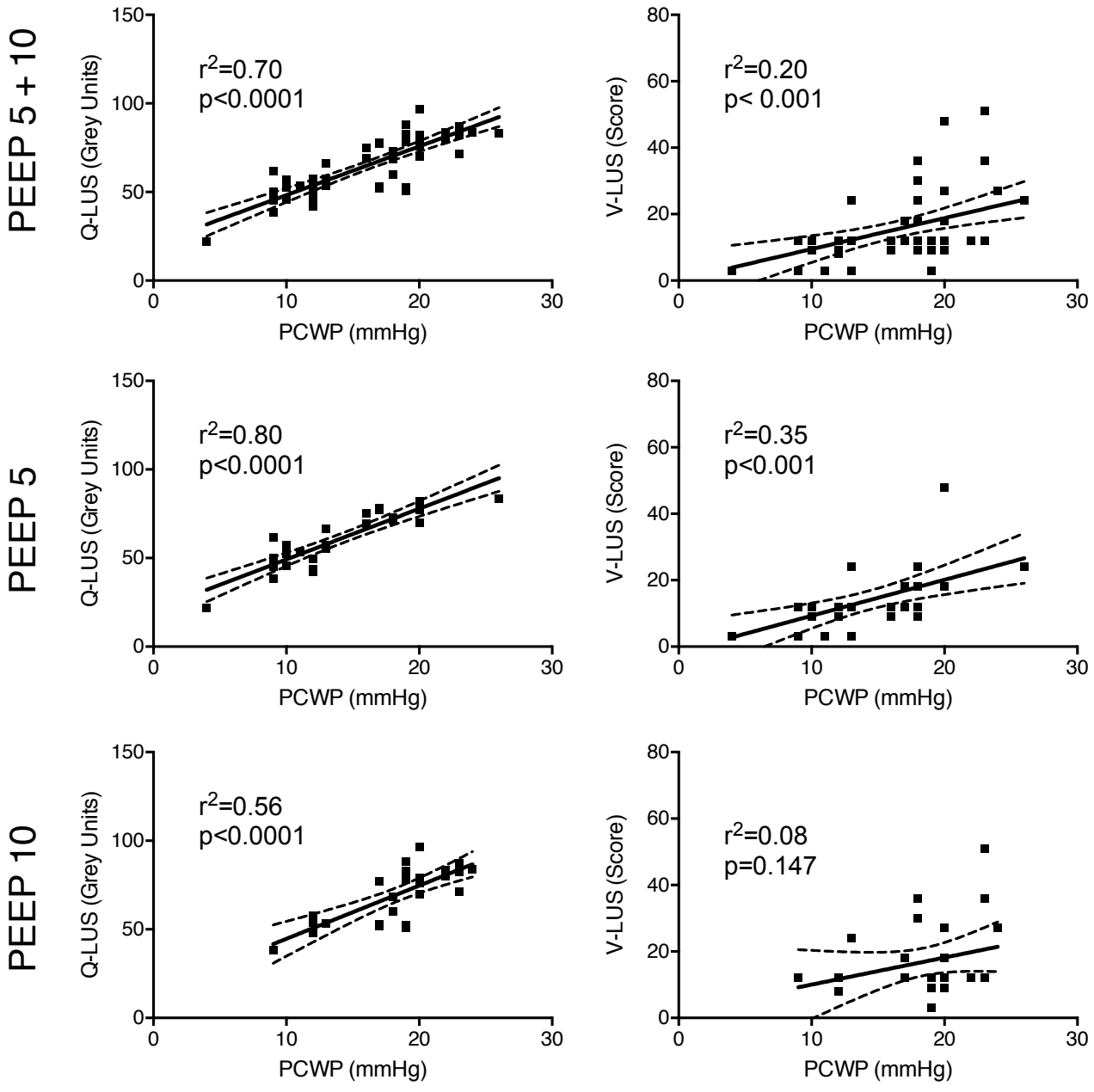
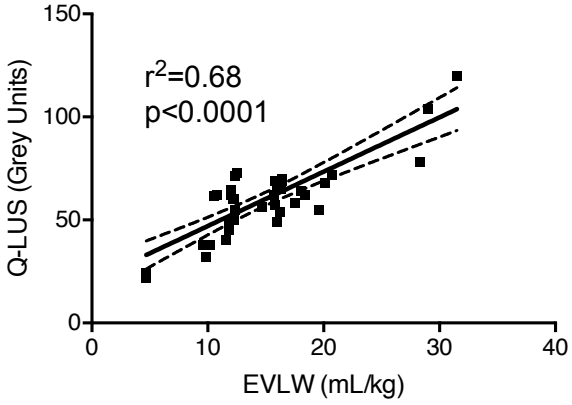
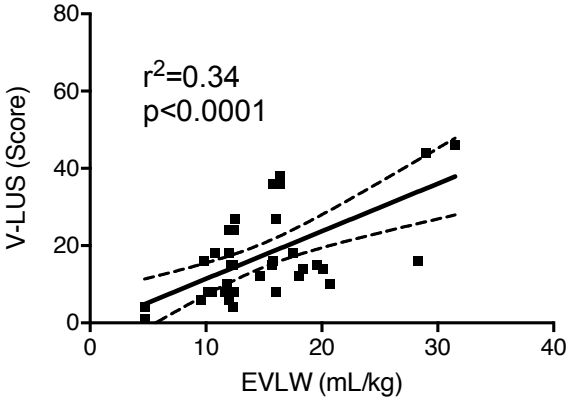
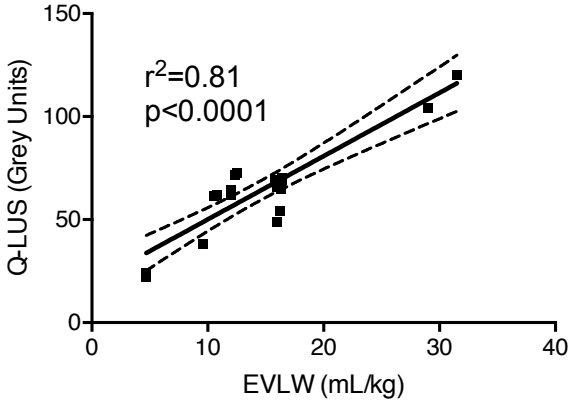


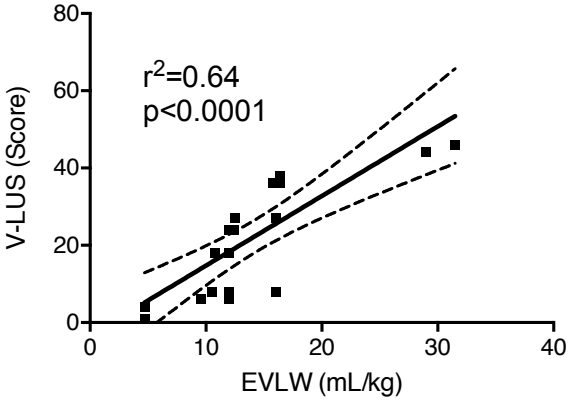
PEEP 5 + 10





PEEP 5





PEEP 10