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Role of Lung Ultrasound in Diagnosing and Grading Pulmonary Congestion in Heart Failure Patients

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Abstract

We enrolled 58 cardiomyopathic patients and 20 normal individuals admitted to Dar Al-Fouad hospital complaining of NYHA class III-IV, with evidence of pulmonary congestion. All patients underwent lung ultrasound. A comparison of the LUS results was done to 20 COPD patients with no history of cardiac disease. The mean age of control was 33.80; the mean age of patients was 54.03.The mean ejection fraction in the control group is 61.40, with the lowest ejection fraction 58%. The mean ejection fraction in the subject group 40.72, with the lowest ejection fraction 22% A statistical difference in lung ultrasound B lines total count (Sum) was found between the control and subjects. The mean number of B lines in the control group is 1.9, with the lowest and highest count 0 and 4 respectively. The mean number of B lines in the subject group is 54.95 with the lowest and highest count 13 and 130 respectively. The number of B-lines correlated well with E/e' value with a positive correlation coefficient ($r=0.837$ $p<0.0001$) and a positive linear curve, which indicates its usefulness in diagnosing hemodynamic and pulmonary congestion. The number of B-lines correlated well with NT-proBNP >2000 pg/mL for congestion with a positive correlation coefficient ($r=0.638$, $p<0.0001$) and a positive linear curve, which indicates its usefulness in diagnosing pulmonary congestion. When compared to results of COPD patients, the difference was significant with ease of differentiation using lung ultrasound.

Keywords: Lung ultrasound; Pulmonary congestion; Dyspnea

Abbreviations: NYHA: New York Heart Association; NT-pro BNP: N-terminal pro b-type natriuretic peptide; COPD: Chronic Obstructive Pulmonary Disease

Introduction

Advancing technology has allowed for increasingly miniaturized and portable ultrasound systems to the point where exams can be performed quickly at the bedside, often by the rounding physician. The more common standard of care for quantifying pulmonary congestion has been a chest radiograph which, depending on the institution, may require more time to perform and a more formal interpretation than a portable ultrasound [1]. Even when it is obtained, chest radiograph can have a low sensitivity for common causes of dyspnea such as pulmonary congestion [2,3]. This may be due in part to poor radiographic windows of the patient or the intra observer variability and skills of those interpreting the x-ray [4,5].

Lung ultrasound was introduced in 1997 and still has on-going studies to evaluate its accuracy in reaching an immediate diagnosis of pulmonary congestion by excluding other chest conditions, and is also of great value in evaluation of pulmonary congestion improvement in heart failure patients after initiating medical therapy, using a low cost and reliable tool [1].

In the case of acute pulmonary congestion, the practitioner using techniques of lung ultrasound, can actually visualize the extravascular lung fluid, classify it semi quantitatively, and prescribe interventions before other traditional diagnostic techniques such as chest radiograph can even occur [5].

Artifacts are the key in lung ultrasound, these artifacts are found when the air content decreases as in pulmonary congestion, pulmonary fibrosis, and the acoustic mismatch needed to reflect the ultrasound beam is created, and some images appear [6].

In the presence of extravascular lung water (EVLW), the ultrasound beam finds sub pleural interlobular septa thickened by fluid leading to a distinctive artifact called B-Lines comet tails [6].

The lung ultrasound finding of "Comet Tails" has been studied in how it relates to alveolar interstitial syndromes. These syndromes include conditions with diffuse involvement of the pulmonary interstitium which lead to respiratory distress through impairment of alveolar capillary exchange. Chronic conditions include pulmonary fibrosis, whereas acute entities are acute respiratory distress syndrome (ARDS), interstitial pneumonia, and acute pulmonary edema. With careful attention paid by the examiner at the bedside to the patient's history and monitoring the response to treatment, the ultrasonography finding of comet tails can be extremely useful in narrowing the differential diagnosis [5].

Aim of the study

A case control study to test Lung ultrasound in diagnosing pulmonary congestion among patients complaining of dyspnea NYHA class III and IV, evaluate the usefulness of lung ultrasound as a new tool to grade congestion in heart failure patients admitted to hospital with NYHA class III and IV, and value of lung ultrasound in differentiating between cardiogenic and non-cardiogenic causes of dyspnea.

Materials and Methods

Study population

Fifty eight cardiomyopathic patients (subject group) complaining of dyspnoea NYHA class III to IV on admission and twenty normal individuals (control group) with no history of any clinical illness, were recruited from Al-Azhar University hospitals and Dar Elfouad hospital. After obtaining written informed consent each patient was subjected to full medical history, clinical examination, resting 12 lead ECG, lab; Pro BNP, chest X-ray, and lung ultrasound. Patients of the subject group were excluded if they have any of the following: coexisting chronic lung condition, previous CABG, history of thoracic surgery, pregnancy or acute pulmonary edema. A comparison of the LUS results was done to 20 COPD patients with no history of cardiac disease.

Study procedure

Transthoracic Echocardiography was performed to all patients using a Vivid 7 GE with a cardiac probe (3.5 MHz). The candidate was asked to lie in the semi recumbent position on his or her left side with the head elevated. The left arm is tucked under the head and the right arm lies along the right side of the body. The transducer was variably positioned for different ECHO views. Standard positions on the chest wall were obtained such as the long and short left parasternal views, apical view and subcostal or suprasternal views for difficult windows. Most of the studies were started with the parasternal long axis view. Traditionally the dimensions of the left ventricle, aortic root and left atrium were measured using M-mode scan. Ejection fraction was assessed by modified biplane Simpson's method in ischemic patients with RWMA, while others by M-mode at the parasternal long axis. E/e' Ratio of early trans-mitral flow velocity to early diastolic mitral annulus velocity, the measurement of (E) velocity is derived from pulsed-wave (PW) Doppler, usually in the apical 4-chamber view, a 1-3-mm sample volume is placed between the mitral leaflet tips during diastole and averaged over more than three consecutive beats [7,8].

The measurement of e' using annular pulsed wave Doppler tissue imaging (DTI) is also obtained from the apical 4-chamber view, using a 1 to 2 mm size sample volume, averaging of e' velocity from the septum and lateral side of the mitral annulus [7,8].

Lung ultrasound (LUS) was performed to all patients using a Vivid 7 GE with a cardiac probe (3.5 MHz), the same identical one used to perform echocardiography. All patients were supine and arms abducted.

The Transducer in longitudinal orientation with marker in cephalic position, the scanning process starting with the left hemi thorax anteriorly and laterally, is scanning along parasternal, midclavicular, anterior axillary, mid axillary lines. Then shift to the right hemi thorax and repeat. The number of B lines in each scanning site in its corresponding box are calculated and then summed. B lines are defined as vertical lines arising from the pleural line to the edge of the ultrasound screen and move with the sliding lung [9].

According to the international evidence-based recommendations for point-of care lung ultrasound this method of examination is more quantitative than the 8 region method in which the anterior and lateral hemi thorax is divided into 2 regions each. [9].

A positive (or pathologic) test was defined as bilateral multiple comet-tail artifacts, either disseminated (defined as all over the anterolateral lung surface) or lateral (defined as limited to the lateral lung surface) [10].

A negative test was defined as the absence of comet-tail artifacts (B lines), replaced by the horizontal artifacts (A lines), or when rare, isolated comet-tail artifacts were visible or when multiple comet-tail artifacts (B lines) were confined laterally to the last intercostal space above the diaphragm. In the present study comparing cardiogenic pulmonary congestion and normal individuals, the unilateral presence of lateral multiple comet-tail artifacts was also considered negative [10].

Statistical analysis

Values were presented as means +SD or numbers and proportions, as appropriate. The relations between qualitative variables were evaluated by Chi-square test or Fisher's exact test, as indicated. Means were compared with unpaired Student's test. Quantitative data were correlated with the coefficient of correlation "r". All tests were bilateral and a P value of 5% was the limit of statistical significance. Analysis was performed by statistical package software IBM-SPSS for MAC, version 23.

Results

Baseline data

This study enrolled a total of 78 patients, divided into a control and a subject group, the control group is 20 patients, and the subject group is 58 patients. A total of 66 male patients and 12 female patients are shown in Table 1.

Variable	N (%)
Gender	
Male	66(84.6%)
Female	12(15.4%)
Hypertension	37(63.7%)
Diabetes mellitus	43(74.1%)
Dyslipidemia	34(58.6%)
Ischaemic Heart Disease	53(91.3%)
Renal Impairment	19(32.7%)
NYHA III	25(43.1%)
NYHA IV	33(56.9%)
Elevated JVP	14(24.1%)
Orthopnea	56(96.5%)
Lower Limb Edema	
Mild	4(6.9%)
Moderate	36(62.0%)
Severe	17(29.3%)
Ascites	
Mild	5(8.6%)

Moderate	5(8.6%)
Severe	4(6.9%)

Table 1: Baseline characteristics of enrolled patients

Comparison of quantitative variables between the 2 groups

Comparison of quantitative variables between the 2 groups is listed in Table 2.

Echocardiographic Findings

The mean ejection fraction in the control group is 61.40, with the lowest ejection fraction 58%. The mean ejection fraction in the subject group 40.72, with the lowest ejection fraction 22% The mean E/e' in the control group is 6.85, in the subject group the mean E/e' is 22.23, with lowest E/e' 8.04 and highest 37.33

The mean LVESD and LVEDD in Control are 3.70 cm and 4.56 cm respectively, in the subject group it is 5.22 cm and 6.17cm respectively.

	Group	Number	Mean	P Value
Age	Control	20	33.8	0
	Patients	58	54.03	
LVEDD (cm)	Control	20	4.56	0
	Patients	58	6.17	
LVESD (cm)	Control	20	3.7	0
	Patients	58	5.22	
EF%	Control	20	61.4	0
	Patients	58	40.72	
E/e'	Control	20	6.85	0
	Patients	58	22.23	
B Lines	Control	20	1.9	0
	Patients	58	54.95	

Table 2: Comparison of quantitative variables between the 2 groups.

Lung ultrasound B Lines count

The mean number of B lines in the control group is 1.9, with the lowest and highest count 0 and 4 respectively, all lines were found in the lateral aspects of the lungs above the diaphragm and was considered a negative test for pulmonary congestion. The mean number of B lines in the subject group is 54.95 with the lowest and highest count 13 and 130 respectively, all lines were distributed bilaterally along the anterior and lateral aspects of the lungs (Diffuse pattern), with no patchy occurrence at any specific areas.

Correlation between B lines and Pro BNP in the subject group

The number of B-lines correlated well with NT-pro BNP>2000 pg/mL for congestion with a positive correlation coefficient (r=0.638, p<0.0001) and a positive linear curve, there was discordance in four patients were the NT-pro BNP value was >2000 and total number of B lines 15 but chest X ray did not show signs of congestion as shown in Figure 1.

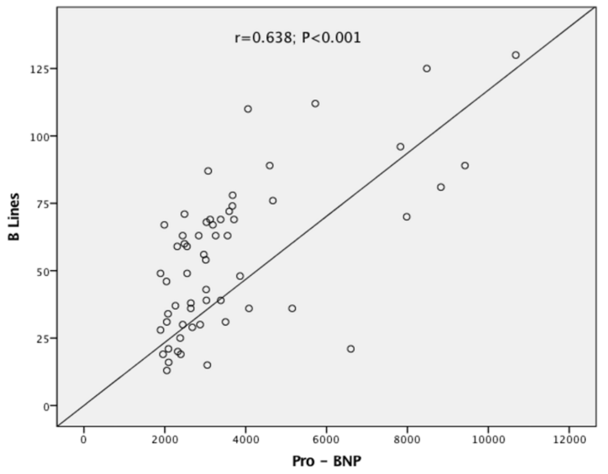

Figure 1: Linear Correlation graph between B lines and Pro BNP in subject group

Correlation between B lines and E/e' in the Subject group

The number of B-lines correlated well with E/e' value with a positive correlation coefficient (r=0.837 p<0.0001) and a positive linear curve, there was a discordance in two patients, all two patients had NT-Pro BNP values >2000, but E/e' was 15 as shown in Figure 2.

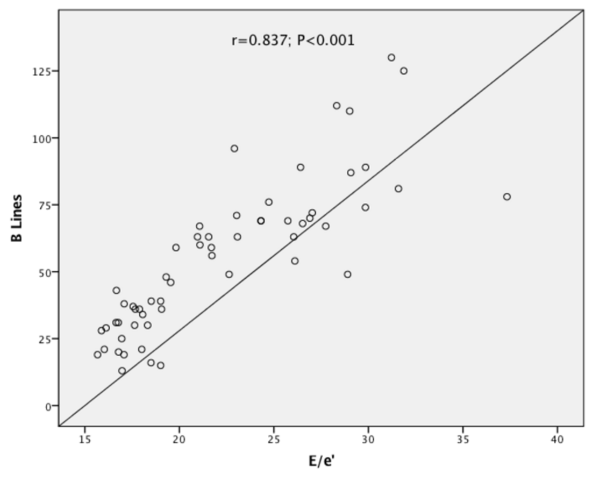

Figure 2: Linear Correlation graph between B lines and E/e' in subject group

Lung ultrasound B line count comparison of subject group to COPD patients

Twenty COPD patients were included as a comparison to the subject group for further evaluation of lung ultrasound effectiveness in differentiating between exacerbated COPD and pulmonary congestion. Lung ultrasound was performed on all 20 patients (18 men and 2 women, mean age 64, ranging between 51-75 years), the diagnosis of COPD was confirmed by respiratory history, clinical presentation, abnormal blood gases, radiologic data with signs of lung distension, hyperinflation, and echocardiography revealing alterations in right ventricular function. Four of these patients were mechanically ventilated. In the COPD patients, 8 patients showed B lines in the lateral aspects of the lungs above the diaphragm and was considered a negative test for pulmonary congestion. 9 patients did not show any B lines and no horizontal A lines 2 patients showed bilateral diffuse multiple B lines with a count of 47 and 59 lines each which is considered a positive test, 1 patient showed unilateral diffuse multiple B lines and considered a negative test. These patients were later diagnosed with pneumonia that was confirmed by lab results including sputum culture and sensitivity, elevated total leucocyte count and CRP. Given these results a ROC analysis yielded a cut off value of 10 lines is considered a positive test for pulmonary congestion given the criteria used as distribution and position of these lines as described in the discussion section. The ultrasound test was positive in 100 % of patients with pulmonary congestion, negative in 90% of patients with COPD, and negative in 100 % of patients without clinical or radiologic respiratory anomalies. The Lung ultrasound had a sensitivity of 100% and a specificity of 90 % in the diagnosis of pulmonary congestion when compared with COPD.

Discussion

Several studies have shown the value of lung ultrasound in diagnosis and evaluation of pulmonary congestion, and a one study has shown that lung ultrasound is capable of detecting subclinical congestion, [11] by detecting extravascular lung water amount which is proportional to the total number of B line count.

In this study we focus on the value of lung ultrasound in diagnosing pulmonary congestion in comparison to other important diagnostic and prognostic investigations of heart failure as E/e' and pro-BNP which are the current modalities in diagnosing, evaluating and grading pulmonary congestion of cardiogenic origin, although lung ultrasound is still controversial in grading pulmonary congestion by semi quantification of the number of B lines, this study used the quantification of E/e' which is directly proportional to LA atrial pressure i.e. the higher the pressure the more severe the pulmonary congestion, with the number of B lines, and the purpose of this is to determine whether the quantification of B lines will hint the degree or grade of pulmonary congestion and aid in management options and drug dosing.

Pro-BNP which is an important marker of hemodynamic congestion was also used in comparison, noting that pro BNP levels rise with right sided heart failure it was important to compare it to the number of B lines in biventricular heart failure and to exclude ascites for instance as the cause of dyspnea rather than actual pulmonary congestion in heart failure.

This study was also extended by addition of COPD patients in order to evaluate its use to distinguish between different causes of dyspnea, it was crucial to compare the lung ultrasound findings to the control and subject groups in order to find its sensitivity and specificity in diagnosing cardiogenic pulmonary congestion, as proposed by Dr. lichenstein, and review of his study on pulmonary congestion and COPD [12] the results were very similar to his studies, this is in fact due to that lung ultrasound depends on findings that depend on the physics of waveforms i.e. presence of B lines due to acoustic mismatch between fluid and air, and so these findings cannot be altered nor modified.

General characteristics, history and risk factors

This study enrolled a total of 78 patients, divided into a control and a subject group, the control group is 20 patients, and the subject group is 58 patients. A total of 66 male patients and 12 female patients

The control group were normal individuals with no history of risk factors or chronic illnesses; hence the risk factors were only in the subject group.

Hypertension was present in 47.4%; diabetes mellitus was present in 55.1%, Dyslipidemia in 43.6%, history of renal impairment in 24.4%, and ischaemic heart disease in 67.9% of total number of subjects.

In our study 32.1% showed NYHA functional class III and 42.3% showed NYHA class IV according to the NYHA Functional Classification for Congestive Heart Failure definitions.

Lung ultrasound B lines count

The number of B lines increased significantly in the subjects and distributed all over the lungs, when compared to the control group, the number of B lines was less than 5 lines in all individuals, and the lines were distributed laterally. These findings are similar to Dr. Lichtenstein study [13].

Correlation between B lines and pro BNP in the subject group

The number of B lines correlated well with NT-pro BNP which indicates its usefulness in diagnosis of pulmonary congestion due to volume overload, a positive linear curve implies that B lines have a prognostic value, and can be used in the evaluation and follow up of patients with pulmonary congestion. The discordance that was found in patients with high pro BNP values and low B line count was due to initiation of diuresis prior to performing the lung ultrasound, and since the lung ultrasound and echocardiography was done in the same setting the value of E/e' was also <15.

Correlation between B lines and E/e' in the subject group

In hemodynamic congestion, pulmonary congestion may or may not occur, as in cases of right sided heart failure were the NT – proBNP levels are elevated yet pulmonary congestion is minimal, E/e' is a noninvasive method to calculate left sided pressures yet it does not quantify pulmonary congestion, and precisely alveolar edema, as elevated Left ventricular pressures can cause interstitial edema which precedes alveolar edema and often causes none to mild symptoms.

NT-proBNP values describe hemodynamic congestion rather actual pulmonary congestion, and hemodynamic congestion or volume overload does not quantify degree of pulmonary congestion.

There is no doubt that these tests are of high importance in evaluating a heart failure patient but they do not specifically quantify pulmonary congestion, and for this sole reason lung ultrasound plays a valuable role in diagnosing the severity of pulmonary congestion.

This study shows a direct relationship between the B-lines count and degree or severity of pulmonary congestion, and if used in a regular practice it can aid in management strategies and medical treatment. Lung ultrasound can play an important role in semi quantifying interstitial edema which usually precedes alveolar edema, thus preventing episodes of severe pulmonary congestion and acute pulmonary edema, by a more effective medical treatment before development of symptoms.

Lung ultrasound B line count comparison of subject group to COPD patients

A Positive Test or pathologic test for pulmonary congestion was defined as bilateral multiple B lines (comet-tail artifacts), either disseminated (defined as all over the anterolateral lung surface) or lateral (defined as limited to the lateral lung surface). A negative test was defined as the absence of comet-tail artifacts, replaced by the horizontal artifacts, or when rare, isolated comet-tail artifacts were visible or when multiple comet-tail artifacts were confined laterally to the last intercostal space above the diaphragm. The unilateral presence of lateral multiple comet-tail artifacts were also considered negative.

In this comparison and using the description of a positive and negative tests, there is a significant difference between the COPD patients and the pulmonary congestion patients, this difference is logical when one considers that the interstitial compartment reaches the lung surface, whereas the bronchial compartment does not. In our study, pulmonary congestion was detected in all the patients, due to the presence of acoustic mismatch as explained in the review, and thickened interlobular septa due to the congestion.

It is important to note that not only the presence of B lines is what is important to diagnose pulmonary congestion, whether these lines are unilateral or bilateral, the distribution of these lines are also important , a patchy appearance would suggest pneumonia and a generalized distribution would suggest pulmonary congestion.

Two of the COPD patients had a positive test by definition, the B lines were bilateral, distribution is generalized in both lung with no patchy appearance, although those patients had bilateral pneumonia, yet the results were similar to that of the pulmonary congestion, which is logical as pneumonia causes increased capillary permeability which will lead to extravasation of fluid into the extravascular compartment, while the other COPD patients who did not have pneumonia showed a negative result this is because the pathology of COPD does not involve the interstitium which is visualized by lung ultrasound.

One patient had a unilateral B line which is diagnostic of pneumonia, as cardiogenic pulmonary congestion never affects one lung only. This explains the use of the term Interstitial syndrome which is a radiological description of the presence of extravascular lung water regardless the causes as increased capillary hydrostatic pressures as in volume overload, or decreased capillary oncotic pressure as hypo-albuminemia, increased capillary permeability as in infections or lymphatic obstruction, all these causes will lead to presence of B lines, and it is often difficult to differentiate between these causes by lung ultrasound alone, and as described before the affection of one or both lungs can hint to a diagnosis but there will be situations that it won't be possible as seen in this study. Interstitial pulmonary fibrosis will also yield a high B line count with even distribution as seen in cardiogenic pulmonary congestion and it has been described in literature that these B lines are more than 7 mm apart, this was not tested in this study and still requires further studies due to lack of sufficient studies.

Although it was previously proposed in literature that the presence of A lines diagnoses COPD, this was not seen in this study, this is due to that the horizontal A lines were not present in most of these patients, while their presence denotes a healthy interstitium with no congestion and thickened interlobular septae, their absence does not denote a specific disease or condition.

Lung ultrasound usefulness in differentiating between different lung conditions

The use of lung ultrasound in differentiating between different lung conditions has been discussed before in chapter one of the reviews, further details will be discussed in this section for further emphasis on the role of lung ultrasound.

An algorithm was proposed to aid physicians using lung ultrasound to reach a diagnosis, this algorithm was proposed by Dr. Lichtenstein [10], and it is a decision tree to reach a diagnosis by presence or absence of lung ultrasound signs.

It can be challenging to differentiate between all these conditions with similar presentations and similar lung ultrasound findings but history and physical examination can be of great importance, echocardiography can also exclude cardiac cause of congestion.

Lung ultrasound is an evolving new tool that has proved to be of great value for diagnosis of acute pulmonary edema and quantification of chronic pulmonary congestion and its few limitations can be avoided by careful examination and knowledge, its use will be fundamental in the upcoming years as it's easy to perform and learn appeals to physicians of different specialties.

Conclusion

Lung ultrasound B lines correlated significantly to E/e’ with a positive correlation coefficient ($r=0.91$ $p<0.0001$) and a positive linear curve and NT-proBNP with a positive correlation coefficient ($r=0.638$, $p<0.0001$) and a positive linear curve concluding that severity of congestion can be graded using the number of B lines.

Lung ultrasound B lines is useful in diagnosis of extravascular lung water as a cause of the dyspnea whether this is caused by heart failure, infection or any other causes of pulmonary congestion.

Lung ultrasound B lines should be considered a useful tool for a quick and reliable assessment of pulmonary congestion in patients with decompensated heart failure.

It is the only tool that can quantify pulmonary congestion rather than hemodynamic congestion as elevated left ventricular and pulmonary capillary pressure.

Lung ultrasound is an easy to use new tool with a very fast learning curve.

Study Limitation

Lack of patients in acute setting as pulmonary edema a small number of patients received medical therapy prior to evaluation using lung ultrasound.

References

1. Zanobetti M, Poggioni C, Pini R (2011) Can chest ultrasonography replace standard chest radiography for evaluation of acute dyspnea in the ED. Chest 139: 1140-1147.

2. Wang CS, Fitz Gerald JM, Schulzer M, Mak E, Ayas NT, et al. (2005) Does this dyspneic patient in the emergency department have congestive heart failure? JAMA 294: 1944-1956.
3. Cremona G, Asnaghi R, Baderna P, Brunetto A, Brutsaert T, et al. (2002) Pulmonary extravascular fluid accumulation in recreational climbers: a prospective study. Lancet. 359: 303-309.
4. Milne EN, Pistolesi M, Miniati M, Giuntini C (1985) the radiologic distinction of cardiogenic and noncardiogenic edema. AJR Am J Roentgenol 144: 879-894.
5. Volpicelli G, Alessandro M, Giorgio G, Cardinale L, Casoli G, et al. (2006) Bedside lung ultrasound in the assessment of alveolar interstitial syndrome. Am J Emerg Med 24: 689-696.
6. Picano E, Frassi F, Agricola E, Gligorova S, Gargani L, et al. (2006) Ultrasound lung comets: A clinically useful sign of extravascular lung water. J Am Soc Echocardiogr 19: 356-363.
7. CriticalEcho, 2009 Lung ultrasound tutorial [ONLINE] Available at: http://www.criticalecho.com/content/tutorial-9-lung-ultrasound.
8. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, et al. (2009) Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiography 10: 165-193.
9. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, et al. (2012) International Liaison Committee on Lung Ultrasound (ILC-LUS) for International Consensus Conference on Lung Ultrasound (ICC-LUS). International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med 38: 577-591.
10. Lichenstein DA, Meziere GA (2008) Relevance of Lung Ultrasound in the Diagnosis of Acute Respiratory Failure. Chest July 2008 134: 117-125.
11. Pingitore A, Garbella E, Piaggi P, Menicucci D, Frassi F, et al. (2011) Early subclinical increase in pulmonary water content in athletes performing sustained heavy exercise at sea level: ultrasound lung comet-tail evidence. Am J Physiol Heart Circ Physiol 301: 161-167.
12. Lichtenstein D, Mauriat P (2012) Lung Ultrasound in the Critically Ill Neonate. Curr Pediatr Rev 8: 217-223.
13. Lichtenstein D, Mézière G, Biderman P, Gepner A, Barré O (1997) The Comet-tail Artifact. Am J Respir Crit Care Med 156: 1640-1646.