Prognostic Value of Extravascular Lung Water Assessed With Ultrasound Lung Comets by Chest Sonography in Patients With Dyspnea and/or Chest Pain

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ABSTRACT

Background: Ultrasound lung comets (ULCs) consist of multiple comet tails originating from water-thickened interlobular septa. They are a new echographic tool to assess the pathologic increase in extravascular lung water, which is a possible harbinger of impending acute heart failure. The objective was to assess the prognostic value of ULCs in patients with dyspnea and/or chest pain syndrome at hospital admission.

Methods and Results: A total of 290 consecutive in-hospital patients (aged 68 ± 13 years) admitted for dyspnea and/or chest pain syndrome were evaluated on admission with a comprehensive two-dimensional and Doppler echocardiographic evaluation and chest sonography with ULC assessment. A patient ULC score was obtained by summing the number of comets from each of the scanning spaces in the anterior right and left hemithoraxes, from the second to fifth intercostal spaces. All patients were followed up for a median period of 16 months (interquartile range: 2.8−29.1 months). During the follow-up, 62 events occurred: 19 cardiac deaths, 3 nonfatal myocardial infarctions, 20 acute heart failures requiring hospitalization, and 20 noncardiac deaths. The 16-month event-free survival was highest in patients with no ULCs and lowest in patients with severe (>30) ULCs at entry (70% vs 19%, $P = .0007$). At univariate analysis, ULCs (hazard ratio [HR] 2.349; confidence interval [CI] 1.364−4.044) were more powerful predictors than other echocardiographic variables of recognized prognostic value, including ejection fraction (HR 0.974; 95% CI 0.958−0.99) and wall motion score index (HR 1.628; CI 1.15−2.304). On multivariable analysis, ULCs provided additional prognostic information (HR 1.9; 95% CI 1.1−3.4) on diabetes (HR 2.05; 95% CI 1.2−3.5) and New York Heart Association class (HR 1.3; 95% CI 1.0−1.6).

Conclusion: ULCs are a simple user-friendly, radiation-free bedside sign of extravascular lung water. They provide useful information for the prognostic stratification of patients with dyspnea and/or chest pain syndrome. (*J Cardiac Fail 2007;13:830−835*)

Key Words: Chest sonography, extravascular lung water, prognosis, ultrasound lung comets.

Pulmonary congestion is a major predictor of both morbidity and mortality in heart failure. The majority of patients with high filling pressure do not have clinical congestion, defined as dyspnea, orthopnea, pulmonary rales, jugular vein distension, or peripheral edema.[1,2] It must also be recognized that even when present, heart failure signs and symptoms are not specific or properly assessed.[2,3] Pulmonary congestion may be manifested on chest x-ray as cardiomegaly, redistribution of pulmonary vessels, increased density and enlarged hilar vessels, perihilar haze, perivascular and peribronchial cuffs, Kerley lines, and sometimes alveolar edema. Although these radiologic manifestations of congestion are often present in patients with heart failure, they are relatively slow to respond to either increases or decreases in pulmonary capillary wedge pressure.[4] Furthermore, the absence of radiologic findings does not exclude the presence of pulmonary congestion and has a high interobserver variation.[5] Potentially,

pulmonary congestion may be evaluated by obtaining an ultrasound scan of the lung.[6] The lung has traditionally been considered poorly accessible to ultrasound techniques, but in patients with pulmonary congestion, images defined as ''ultrasound lung comets'' (ULCs) can be depicted by scanning with cardiac probes along the intercostal spaces.[7] This technique is a reliable, regional, quantitative, and an easy method to assess the presence of extravascular lung water.[6]

A significant correlation exists between the number of ULCs and pulmonary congestion by radiographic signs, interstitial edema documented by computed tomography (CT), measurement of extravascular lung water by the indicator dilution technique, and pulmonary capillary wedge pressure.[8−10] In a previous study from our laboratory, Jambrik et al.[8] found a linear correlation ($r = 0.78$) between the number of ULCs and the radiologic lung water score semiquantitatively assessed on chest x-ray. Intrapatient variations recorded before and after therapy showed an even stronger correlation ($r = 0.83$) between changes in ULCs and radiologic lung water score.[8] Because pulmonary congestion is a recognized unfavorable prognostic sign, the aim of our study was to assess the prognostic meaning of ULCs in patients with dyspnea and/or chest pain at hospital admission.

Methods

Patients

A total of 290 consecutive patients (age 68 ± 13 years, 96 female) with dyspnea and/or chest pain syndrome who were admitted to the adult cardiology-pneumology department of the Institute of Clinical Physiology of the Italian National Research Council, Pisa, were prospectively enrolled from January 1, 2003, to August 31, 2005.

Known coronary artery disease was present in 246 patients, reflecting previous myocardial infarction in 106 patients (37%) and revascularization in 140 patients (48%). Risk factors for coronary heart disease were highly prevalent, with 48% of the patients having hypertension, 37% having hypercholesterolemia, and 26% having diabetes. Twenty-five patients (9%) also had chronic obstructive lung disease, and 34 patients (12%) had chronic kidney failure.

Echocardiographic Study

All patients underwent comprehensive transthoracic echocardiography examinations at rest. Transthoracic echocardiographic studies were performed with a commercially available ultrasound machine (Sonos 5500-7500 Philips Ultrasound, Sequoia C256 Acuson Siemens Mountain View, California; Esaote Mylab, Genoa, Italy; and Vivid System 7, GE/Vingmed, Milwaukee, Wisconsin) equipped with a 2.5 to 3.5-MHz phased-array sector scan probe (S3-S8 or V3-V7) and second harmonic technology. All standard echocardiographic views were obtained when possible. Left ventricle end-diastolic and end-systolic diameters were measured from the M-mode trace obtained by parasternal long-axis view. Left ventricular volumes were measured, and ejection fraction (EF) was obtained by two-chamber and four-chamber views using the biplane area-length method, according to the recommendations of the American Society of Echocardiography.[11] Left

ventricular mass was calculated by the Devereux formula[12] indexed to body surface area. Mitral regurgitation was assessed semiquantitatively (from 1 to 4) by color flow Doppler. Diastolic function was determined from the pattern of mitral and pulmonary venous flow velocity by pulsed Doppler echocardiography,[13] complemented by mitral annular velocity by tissue Doppler imaging when needed.[14] Diastolic dysfunction was staged as ''absent'' (grade 0), ''mild'' (grade 1, impaired relaxation), ''moderate'' (grade 2, pseudonormalized filling pattern), and ''severe'' (grade 3, restrictive filling pattern). The systolic pulmonary artery pressure was derived from the maximal velocity of tricuspid Doppler tracing adding the value of the right atrial pressure. The right atrial pressure was estimated on the basis of inspiratory collapse index of the inferior vena cava.[15]

Chest Sonography

The echographic examinations were performed during the first day of the hospitalization (8 ± 4 hours from admission) with patients in the supine or near-to-supine position (Fig. 1, middle), at the end of the standard two-dimensional echocardiogram as previously described.[8] Briefly, the ultrasound scanning of the anterior and lateral chest was obtained on the right and left hemithoraxes, from the second to fourth (on the right side to the fifth) intercostal spaces and from the parasternal to midaxillary line. In each intercostal space, the number of ULCs was recorded at the parasternal, midclavicular, anterior axillary, and midaxillary lines (Fig. 1, middle). The sum of ULCs found at each of the scanning sites yielded a score denoting the extent of the extravascular fluid of the lung. Zero was defined as a complete absence of ULCs on the investigated area, and the presence of ULCs was staged in three grades: ''mild'' (5−14 comets), ''moderate'' (15−29 comets), and ''severe'' (≥30 comets). A lung comet was defined as a hyperechogenic, coherent bundle with a narrow basis, spreading from the transducer to the further border of the screen.[9] The ULCs described here extend to the edge of the screen and arise only from the pleural line (Fig. 1, bottom). The examinations were performed with the same probe used for the echocardiographic study.

The intra- and interobserver variability of the echo comet score were previously assessed by two independent observers in a set of 20 consecutive cases and were 5% and 7%, respectively.[8]

Observers were unaware of the results of the other scan and obtained all echocardiography and ULC measurements independently of one another. The reader who scored ULCs was blinded to the cardiac echocardiography data.

Follow-Up Data

Follow-up data were obtained in all patients by inclusion criteria. Events were defined as death for all causes, cardiac deaths, myocardial infarction, and development or progression of heart failure. In patients who died in hospital or at home, the cause of death was elucidated from the medical records, the family, and the local physician who signed the death certificate. The definition of cardiac death required documentation of significant arrhythmias or cardiac arrest, or both, or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factor. In case of deaths out of hospital for which no autopsy was performed, sudden unexpected death was attributed to a cardiac cause. The development or progression of heart failure was defined as at least one of the following: worsening of New York Heart Association (NYHA) functional class, new hospitalization for worsened or decompensated heart failure, or
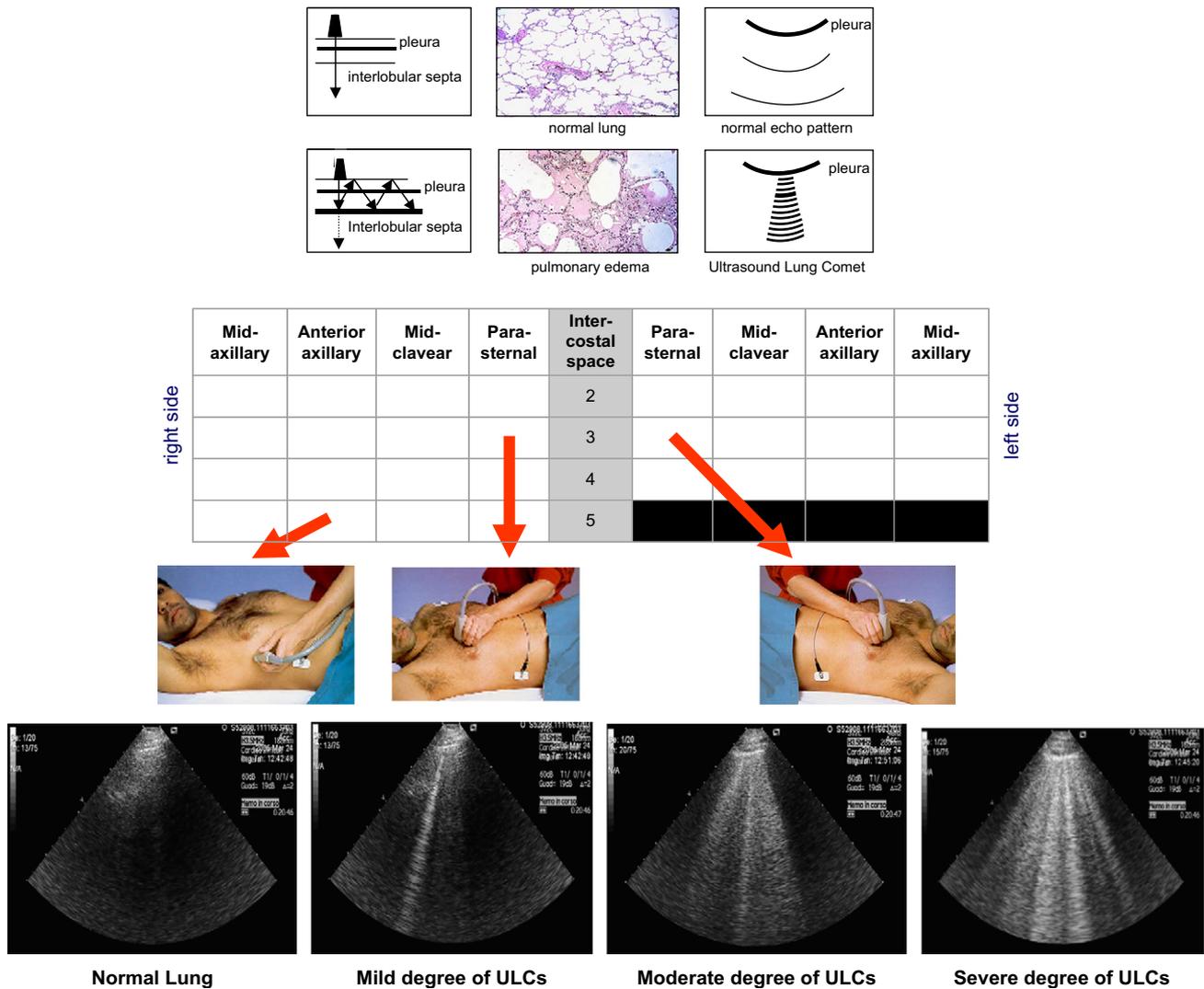
Fig. 1. ULCs by chest sonography. Top: how they are generated from thickened subpleural septa. Middle: how to scan the chest for ULC assessment. Bottom: how to score and report ULC findings. ULC, ultrasound lung comet.

cardioverter-defibrillator device implantation. Therefore, the outcome events were all causes-death (defined as cardiac and noncardiac death) for survival and spontaneous events (death and the development or progression of heart failure for spontaneous event-free survival). When more than one of these events occurred, patients were censored at the time of the most severe event.

Statistical Analysis

Data are expressed as mean ± standard deviation, and as numbers (percent) for categoric variables. Statistical analyses included descriptive statistics (frequency and percentage of categoric variables and mean and standard deviation of continuous variables), Kaplan-Meier survival curves, and Cox proportional-hazards models. The following covariates were analyzed: age, sex, hypertension, hypercholesterolemia, diabetes, smoke, NYHA class at admission, EF, wall motion score index (WMSI), and diastolic function. Differences between survival curves were compared with the log-rank test, grading ULCs from absent to severe. All analyses were performed with the Statistical Package for the

Social Sciences (SPSS Inc., Chicago, Illinois), and P values less than .05 were considered to be statistically significant.

Results

The main clinical data of the 290 patients are reported in Table 1. All chest sonography examinations were performed in less than 3 minutes. ULCs were absent (<5) in 137 patients and present in 153 patients (53 had mild ULCs, 31 had moderate ULCs, and 69 had severe ULCs).

Echocardiographic Findings

The mean value of EF on admission was 45% ± 14% (range 15%−70%); 143 patients had an EF less than 50%; the rest WMSI was 1.5 ± 0.6; and the mean value of left ventricle end-diastolic diameter was 54 ± 10 mm. The pulmonary systolic pressure was 42.4 ± 14 mm Hg. Mitral regurgitation was moderate in 22% of patients and severe in 5% of patients.

Table 1. Patients' Characteristics

No. of patients	290
Age (y)	68 ± 13
Sex (male/female)	194/96
Smoking habit, n (%)	51 (17%)
Hypertension, n (%)	139 (48%)
Diabetes, n (%)	75 (26%)
Hypercholesterolemia, n (%)	106 (37%)
Previous myocardial infarction, n (%)	106 (37%)
NYHA functional class on admission	2 ± 1.1
Family history of CAD, n (%)	90 (31%)
Coronary percutaneous revascularization, n (%)	140 (48%)
Acute pulmonary edema on admission, n (%)	20 (7%)
Angina at admission, n (%)	86 (30%)
Chronic heart failure, n (%)	143 (49%)

NYHA, New York Heart Association; CAD, coronary artery disease.

Follow-Up Data: Total Mortality

During a median of 16 months (first quartile 2.8, third quartile 29.1), a total of 62 events (21%) occurred: 39 deaths, 3 nonfatal myocardial infarctions, and 20 rehospitalizations for worsening of symptoms (leading to implantation of cardioverter-defibrillator device in 5 cases). The 16-month event-free survival showed a significantly better outcome for those patients without ULCs (Fig. 2), whereas a worse outcome was observed in patients with a severe grade of ULCs. In regard to future HF hospitalization alone, and not as part of the combined end point, the rate of new hospitalization (because of the development or progression of HF) was higher in patients with a severe ULC score and lower in patients with no ULCs (log rank = 24.4, $P <$ .0001). Univariate predictors of spontaneous events are reported in Table 2. At multivariable analysis, diabetes (hazard ratio [HR] 2.05; 95% confidence interval [CI] 1.2−3.5), NYHA functional class (HR 1.3; 95% CI 1.0−1.6), and

ULCs (HR 1.9; 95% CI 1.1−3.4) were independent prognostic predictors of spontaneous events.

Discussion

In patients admitted to the hospital with dyspnea and/or chest pain, the presence of ULCs identifies a subgroup at a higher risk of experiencing events. The higher the number of ULCs, the worse the outcome.

Comparison with Previous Studies

Previous studies showed that ULCs image extravascular lung water,[6] and that extravascular lung water (assessed with impedance-based catheters) may predict adverse prognosis.[16] ULCs are reasonably well correlated with extravascular lung water assessed by chest x-ray,[8] CT,[9] and the double-indicator dilution method.[10] Other well-established prognostic predictors include NYHA functional class[17] and systolic[18] and diastolic dysfunction.[19] In previous studies, we found that the ULC number increases with increasing degrees of diastolic dysfunction, and that the degree of diastolic dysfunction is a stronger determinant of ULC than EF.[20] These data support the use of ULCs for the purpose of prognostic stratification. More direct support to the prognostic value of extravascular lung water may be derived from intrathoracic impedance monitoring.[16] This method measures intrathoracic impedance, which is inversely correlated to pulmonary capillary wedge pressure and fluid balance. It decreases before the onset of symptoms and before hospitalization for fluid overload. A regular intrathoracic impedance monitoring provides an early warning of congestion that might allow physicians to intervene by adding or titrating medications, possibly preventing the need of hospitalization.[16]
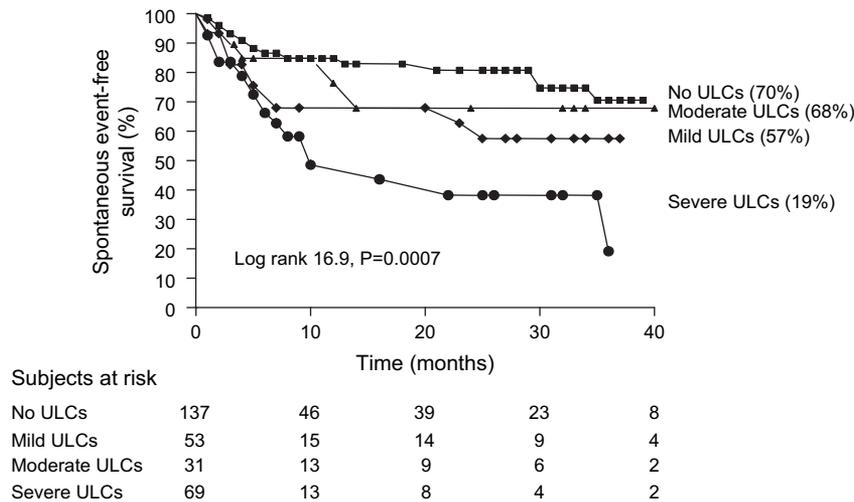

Fig. 2. Kaplan-Meier survival curves in patients stratified according to the presence or absence of ULCs, staged in 4 grades: no ULCs; mild, moderate, and severe ULCs. The best survival is observed in patients without a significant number of ULCs; the worst survival is observed in patients with a severe grade of ULCs ($P <$ .0007). ULC, ultrasound lung comet.

Table 2. Univariate Predictors of Spontaneous Events

	HR (95% CI)	P Value
Diabetes	2.204 (1.316−3.693)	.003
NYHA functional class on admission	1.491 (1.208−1.841)	.0001
Ejection fraction	0.974 (0.958−0.99)	.001
WMSI	1.628 (1.15−2.304)	.006
ULCs	2.349 (1.364−4.044)	.002

HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association; WMSI, wall motion score index; ULC, ultrasound lung comet.

Limitations

We acknowledge some limitations of the study design and the proposed method of chest sonography. Although the sample size of our study is respectable (n = 290), the number of events (n = 62), especially hard events (n = 39 deaths), is still relatively low. Confirmatory data on larger sample size, and possibly on a multicenter basis, are needed to strengthen our findings and to assess the prognostic value of ULCs when compared with other prognostic predictors missing in our evaluation (eg, cardiac natriuretic peptides).[21] A limit of ULCs may arise from the differential diagnosis between cardiogenic and pneumogenic ULCs. Cardiogenic watery comets may be difficult to distinguish from pneumogenic fibrotic comets, which are typically found in interstitial lung disease. Usually, diagnosis is obvious from a patient's history and/or from dynamic, serial evaluations, because only cardiogenic comets are cleared by diuretic therapy.[22] However, in the present study only the first assessment of ULCs at entry was considered. Future studies should consider the dynamic evaluation with several ULC assessments (at hospital admission and discharge; before and after diuretic therapy) for a more accurate assessment of the cause underlying ULCs. Echocardiographic data on the filling pressure (e/e′ ratio) were not available in the present study population. However, in a previous study from our group, Agricola et al.[23] described a linear correlation between the ULC number and the e/e′, both in resting conditions ($r = 0.70$) and during exercise stress ($r = 0.71$). Whether filling pressures and ULC provide redundant prognostic information cannot be assessed from the present study.

Clinical Implications

The current guidelines recognize cardiac natriuretic peptides, chest x-ray, and echocardiography as essential tools for the evaluation of patients with known or suspected heart failure.[5] ULCs are based on chest sonography and offer an important support to these parameters, adding insights into a variable of recognized diagnostic and prognostic value, that is, extravascular lung water.[6] They are easy to acquire, simple to measure and learn, and fast to perform (<3 minutes). ULCs require limited technology and are not restricted by cardiac acoustic window limitations or patient decubitus. The feasibility is excellent.[24] The interpretation of ULCs is also simple. At chest sonography, the "normal"

lung is "black" (no water, no signal), the lung with interstitial edema is "black-and white" (with white stripes representing ULCs), and the lung with alveolar edema is "white" (no air, only water). ULC assessment is the "kindergarten" of the ultrasound school, the simplest information to obtain, although not necessarily the least important. Therefore, ULCs are attractive for complement Doppler-echocardiography in the evaluation of patients with known or suspected heart failure in the emergency department.[6] ULCs provide important prognostic information, additive to the more established echocardiographic parameters such as EF,[18] mitral regurgitation,[25] WMSI,[26] and cardiac natriuretic peptides.[27] If our findings are confirmed in larger patient series by other laboratories, chest sonography targeted to ULC assessment will become a novel useful tool to monitor extravascular lung water in patients with dyspnea and/or chest pain. This is particularly relevant because chest radiography is not recommended by the latest guidelines for the assessment of interstitial lung water, inasmuch as changes in the radiographic assessment of pulmonary vascular congestion are too insensitive to detect but the most extreme changes in fluid status.[28] CT would be an excellent alternative but has obvious limitations in high cost, logistic burden, and considerable radiation dose (corresponding to 400 chest x-rays for a chest CT and 750 chest x-rays of a 16-slice multislice CT).[29] In conclusion, ULC assessment is a simple, user-friendly, radiation-free bedside imaging of extravascular lung water and provides useful information for the prognostic stratification in patients admitted with dyspnea and/or chest pain syndrome.

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