Ultrasound lung comets as prognostic determinant in heart disease

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(3) University of Palermo, Department of Cardiology, Palermo, Italy
(4) University of Naples Federico II, Naples, Italy.
No conflict of interest to be disclosed
Background (1): Ultrasound lung comets (ULC) are a simple echographic sign of abnormally increased extravascular lung water, that originate from water-thickened interlobular septa.

Background (2):

lung, no fly zone for echo?

«The possibility to detect pulmonary edema before it becomes clinically apparent is so inherently attractive that the effort to develop and validate such techniques still continues.»


«Because ultrasound energy is rapidly dissipated in air, ultrasound imaging is not useful for evaluation of the pulmonary parenchyma.»

Background (3): lung ultrasound

Background (4): the incredible ULC

- **Experimental correlations**
  - Zoltan et. al *submitted*

- **Hemodynamic correlations**
  - Agricola et al. Chest 2005
  - Agricola et al. JASE 2006

- **Radiographic correlations**
  - Jambrik et al. Am J Cardiol 2006
  - Gargani L et al. Rheumatology 2010

- **Echocardiographic correlations**
  - Frassi et al. JASE 2007
  - Agricola et al. JASE 2006

- **Clinical correlations**
  - Frassi et al. EJE 2007

- **Biochemical correlations**
  - Gargani et al. Eur J Heart Fail 2008

- **Underwater**
  - Frassi et al. JASE 2008

- **On the mountain**
  - Fagenholz Chest 2008
  - Pratali et al. Crit Care Med 2010
Background (5): prognosis - 290 pts

Subjects at risk

<table>
<thead>
<tr>
<th></th>
<th>No ULC</th>
<th>Mild ULC</th>
<th>Moderate ULC</th>
<th>Severe ULC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects at risk</td>
<td>137</td>
<td>51</td>
<td>33</td>
<td>69</td>
</tr>
<tr>
<td>Time (months)</td>
<td>46</td>
<td>15</td>
<td>13</td>
<td>13</td>
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<tr>
<td></td>
<td>39</td>
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<td>4</td>
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<tr>
<td></td>
<td>8</td>
<td>4</td>
<td>2</td>
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</tr>
</tbody>
</table>

Events (n=62): 39 deaths (19 cardiac), 3 non-fatal myocardial infarction, 20 acute heart failure requiring new hospitalization

Aim

To assess the prognostic value of ULC in a large population of consecutive patients, with a heterogeneous spectrum of heart disease, compared to clinical parameters.
Methods

CARDIOLOGY DEPARTMENT

1,102 in-hospital patients (age 69±12 years, 751 females)

Cardio-pulmonary ultrasound

Follow-up

<table>
<thead>
<tr>
<th>Mid-axillary</th>
<th>Anterior axillary</th>
<th>Mid-clavicular</th>
<th>Parasternal</th>
<th>Inter-costal space 2</th>
<th>Parasternal</th>
<th>Mid-clavicular</th>
<th>Anterior axillary</th>
<th>Mid-axillary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>2</td>
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<td>3</td>
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<td>4</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results (1)

PATIENTS POPULATION

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>stable angina</td>
<td>219 (20%)</td>
</tr>
<tr>
<td>acute coronary syndrome</td>
<td>216 (19%)</td>
</tr>
<tr>
<td>primary cardiomyopathy</td>
<td>74 (6%)</td>
</tr>
<tr>
<td>ischaemic cardiomyopathy</td>
<td>132 (12%)</td>
</tr>
<tr>
<td>valvular heart disease</td>
<td>134 (12%)</td>
</tr>
<tr>
<td>arrhythmias</td>
<td>154 (14%)</td>
</tr>
<tr>
<td>other</td>
<td>173 (17%)</td>
</tr>
</tbody>
</table>

Follow-up (median 14 months, interquartile range: 4-25)

158 events:
- 87 deaths
- 10 non-fatal myocardial infarctions
- 61 worsening of dyspnoea
<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>p</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>.88 (.62-1.24)</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.27 (1.13-1.42)</td>
<td>&lt;.0001</td>
<td>1.02 (1.01-1.03)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>NYHA class at admission</td>
<td>1.41 (1.23-1.59)</td>
<td>&lt;.0001</td>
<td>1.28 (1.13-1.43)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>1.004 (.73-1.37)</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.75 (1.28-2.41)</td>
<td>&lt;.0001</td>
<td>1.47 (1.08-2.06)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>.78 (.57-1.07)</td>
<td>ns</td>
<td></td>
<td></td>
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<tr>
<td>Hypercholesterolemia</td>
<td>.74 (.54-1.005)</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1.05 (.77-1.44)</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1.10 (.8-1.51)</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein C reactive (mg/l)</td>
<td>1.04 (1.01-1.01)</td>
<td>&lt;.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.26 (1.12-1.34)</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe ULC</td>
<td>3.34 (2.43-4.67)</td>
<td>&lt;.0001</td>
<td>2.17 (1.78-2.64)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Results (3): prognosis – 1,102 pts

No ULC (< 5)
Mild/moderate ULC (6-30)
Severe ULC (>30)

N = 1,102
p < .001
Log rank = 67.8

<table>
<thead>
<tr>
<th>Subjects at risk</th>
<th>616</th>
<th>483</th>
<th>462</th>
<th>437</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>342</td>
<td>291</td>
<td>267</td>
<td>249</td>
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<tr>
<td></td>
<td>144</td>
<td>117</td>
<td>106</td>
<td>96</td>
</tr>
</tbody>
</table>
History and clinical data

Echo-cardiography

History and clinical data

ULC

Results (4): stepwise model

- p < .001
- p = ns
- p < .001
Conclusions

• ULC are a simple, user-friendly, bedside sign of extravascular lung water, that provide useful information for the prognostic stratification in a heterogeneous spectrum of patients with heart disease.

• Their prognostic value is similar to the one provided by a comprehensive echocardiogram.
Monseur Babinet prévenu par sa portière de la visite de la comète.
Limitations

• Some potentially significant parameters are not included in the model (chest X-ray, natriuretic peptides).

• ULC evaluation not at the same time-point in all patients.

• Lack of ULC assessment at discharge.
## Echo data

<table>
<thead>
<tr>
<th></th>
<th>Unit</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td>.95 (.94 - .96)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic diameter (mm)</td>
<td></td>
<td>1.05 (1.03 - 1.07)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wall motion score index</td>
<td></td>
<td>2.9 (2.2 – 3.8)</td>
<td>&lt;.001</td>
<td>4.5 (3.0 – 6.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Significant mitral regurgitation</td>
<td></td>
<td>2.3 (1.7 – 3.2)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial area (cm²)</td>
<td></td>
<td>1.07 (1.05 – 1.08)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td></td>
<td>2.3 (1.7 – 3.2)</td>
<td>&lt;.001</td>
<td>1.02 (1.01 – 1.04)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td></td>
<td>2 (1.3 – 3.1)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ULC &gt; 10</td>
<td></td>
<td>4.2 (3 – 5.8)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PASP = pulmonary artery systolic pressure; ULC = ultrasound lung comets
## Left-sided heart failure

N = 489

<table>
<thead>
<tr>
<th></th>
<th>univariate</th>
<th>multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Male (n)</td>
<td>.4 (.5 - 1.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.03 (1.01 - 1.04)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>NYHA class admission</td>
<td>1.3 (1.1 - 1.4)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Diabetes Mellitus (n)</td>
<td>1.7 (2.2 - 2.4)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>.9 (.6 - 1.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Known coronary heart disease (n)</td>
<td>1.1 (.8 - 1.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.3 (1.2 - 1.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>.96 (.94 - .98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>End-diastolic diameter (mm)</td>
<td>1.2 (.7-2.1)</td>
<td>.545</td>
</tr>
<tr>
<td>ULC &gt; 10</td>
<td>2.9 (1.9 – 4.4)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Left-sided heart failure: death and decompensation

104 events (64 death, 40 decompensated heart failure)

N = 489
p < .0001
Log rank = 24.6
Left-sided heart failure: decompensation

Events: 40 decompensated heart failure

Event-free survival (%)

Time

N = 489
p < .0001
Log rank = 14.73

B-lines < 10

B-lines ≥ 10

B-lines < 10

B-lines ≥ 10
Left-sided heart failure: decompensation

N = 489

Global x squared

EF  PASP  WMSI  ULC

p < .0001  p = ns  p < .0001
Acute coronary syndrome

ULC ≤ 30

ULC > 30

N = 470 pts
Log rank 27,3
p < .0001

56 hard events: 36 deaths; 20 non-fatal MI

log rank = 35.9
p < .0001

mean follow-up: 8±11 months

Methods

<table>
<thead>
<tr>
<th></th>
<th>Mid-axillary</th>
<th>Anterior axillary</th>
<th>Mid-clavicular</th>
<th>Parasternal</th>
<th>Intercostal space</th>
<th>Parasternal</th>
<th>Mid-clavicular</th>
<th>Anterior axillary</th>
<th>Mid-axillary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid-axillary</td>
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<tr>
<td>Anterior axillary</td>
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<tr>
<td>Mid-clavicular</td>
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<tr>
<td>Parasternal</td>
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<td></td>
<td></td>
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<tr>
<td>Intercostal space</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasternal</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-clavicular</td>
<td>4</td>
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<tr>
<td>Anterior axillary</td>
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<tr>
<td>Mid-axillary</td>
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</tr>
</tbody>
</table>

**Comet score = total number of ULC**

Water-thickened septa
- left-sided heart failure
- ARDS
- interstitial pneumonia
- alveolitis …

Collagen-thickened septa
- interstitial lung disease
- sarcoidosis
- scleroderma …
Comparison with HRCT: Warrick score

Furosemide stress test

Cardiogenic dyspnoea

ULCs (number)

Before treatment

After treatment

n=66

p<0.0001

Before treatment

After treatment

Furosemide stress test

Pneumogenic dyspnoea

ULCs (number)

Before treatment

After treatment

Before treatment

After treatment

ULC and EVLW

ULC and PCWP

\[ R = 0.48, p = 0.001 \]
Entro pochi minuti

Radiografia del torace

Ecografia del torace

121 pazienti/ 135 controlli

Normal subject

Feasibility for echo 100%

Interstitial edema

Time needed: <3 minuti

ULC vs radiographic score

![Graph showing the correlation between chest X-ray score and echo score. The graph includes a linear trend line with the following statistics:

- Sample size (n) = 135
- Correlation coefficient (r) = 0.78
- Significance level (p) < 0.01]
Intra-patient variation

Chest X-ray and echo comets at admission

Chest X-ray and echo comets after 3 days

ULC and natriuretic peptides

Sensitivity

1-Specificity

n=149
AUC (NT-proBNP)= 0.978
AUC (ULCs)= 0.893

Pulmonary congestion stress-echo

- PASP (r = 0.69, p = 0.0001)
- E/Em (r = 0.70, p = 0.0001)
- estimated PCWP (r = 0.69, p = 0.0001)

- ∆PCWP (r = 0.62, p = 0.0001)
- peak stress E/Em (r = 0.71, p = 0.0001)

Pulmonary congestion stress-echo

Baseline

Peak stress

WMSI

ULC

n = 72
p = .0001

Serial assessment of pulmonary congestion

Individual data analysis

NYHA class improved (≥1)
n=87

NYHA class worsened or unchanged
n=16

p<.001

p=ns

Gargani L, Picano E. European heart journal 2009;vol.30 (Abstract Supplement):290
ULC in ARDS: pigs

Experimental pig model of oleic acid induced-ALI/ARDS

Training-time: 60 minuti

- university
- stress echo
- secondary school
- color/Doppler echo
- elementary school
- 2D echo
- kindergarten
- Ultrasound lung comets
ULC and diastolic dysfunction

*p<0.0001*

- Normal
- Abnormal Relaxation
- Pseudonormal
- Restrictive

ULC and dyspnea

Physical basis

A-lines

B-lines

Ultrasound lung comet

Normal lung

Pulmonary edema
Lung comets and technology

(<1 hour experience)

High-tech veteran

R Sq Linear = 0.91

n=20
p<.0001
r=.958

(>2 years experience)

How to quantify B-lines?
The da Pisa Code

Additive risk of cancer/exam

1 in 2,000
1 in 1000
1 in 500
1 in 200
1 in 100
1 in 75
1 in 50
1 in 25
1 in 10
1 in 5
1 in 2
1 in 1

Equivalent number of chest x-rays

50 250 500 750 1000

# Radiographic score

<table>
<thead>
<tr>
<th></th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hilar vessels</strong></td>
<td></td>
</tr>
<tr>
<td>Enlarged</td>
<td>1</td>
</tr>
<tr>
<td>Increased in density</td>
<td>2</td>
</tr>
<tr>
<td>Blurred</td>
<td>3</td>
</tr>
<tr>
<td><strong>Kerley lines</strong></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>4</td>
</tr>
<tr>
<td>B</td>
<td>4</td>
</tr>
<tr>
<td>C</td>
<td>4</td>
</tr>
<tr>
<td><strong>Micronoduli</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Widening of interlobar fissures</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Peribronchial/perivascular cuffs</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Extensive perihilar haze</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Subpleural effusion</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>Diffuse increase of density</strong></td>
<td>5</td>
</tr>
</tbody>
</table>

Comete ed ecocardiografia

n=185

![Graph showing ULC number with Ejection Fraction <40% and Diastolic dysfunction ≥2](image)

Ejection Fraction <40%
- - + +
Diastolic dysfunction ≥2
- - + +

(n= 96) (n= 27) (n= 15) (n= 45)

Comete e peptidi natriuretici

N = 149
P < 0.0001

Pazienti con dispnea cardiogena

Pazienti con dispnea non cardiogena

NT-proBNP

Comete e peptidi natriuretici

Comete ultrasoniche polmonari

N= 149
P< 0.0001

Comete e peptidi natriuretici

N=149
P<0.0001
R=0.69

Alveolar capillary membrane

<table>
<thead>
<tr>
<th>Pulmonary Capillary Wedge Pressure (mmHg)</th>
<th>CXR</th>
<th>Physical Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-12</td>
<td>Normal</td>
<td>-</td>
</tr>
<tr>
<td>12-18</td>
<td>Inversion of flow</td>
<td>-</td>
</tr>
<tr>
<td>18-25</td>
<td>Interstitial edema</td>
<td>-</td>
</tr>
<tr>
<td>&gt;25</td>
<td>Alveolar edema</td>
<td>+</td>
</tr>
</tbody>
</table>
Extravascular lung water

«The possibility to detect pulmonary edema before it becomes clinically apparent is so inherently attractive that the effort to develop and validate such techniques still continues.»


Yu CM et al. *Circulation* 2005;112:841-848
Lung comets and ARDS

ULCs (n°) vs. Wet/dry ratio

- N = 17
- p < .001
- R = .911

Jambrik Z, Gargani L, Picano E, submitted
Mitral regurgitation

Delta PASP (mmHg)

Delta ULC (n°)

n = 20
r = .70
p < .001

Methods: 3 persons in a boat

Ultrasound Lung Comets and symptoms (n=14)

ULC in underwater

Chest Ultrasonography For Hape

Himalayan Rescue Association Clinic
Pheriche, Nepal

Fagenholz P.J. Chest 2007
Lung comets at different quotes

Pratali L et al. Crit Care Med 2010
Lung Comets in subjects with clinical HAPE

Pratali L et al. Crit Care Med 2010
Lung comets and O2 Saturation

O2 saturation %

Quotes 0 m s.l. 3440 m s.l. 4800 m s.l. 5130 m s.l. 1350 m s.l.

97 ± 1.5 91 ± 2.1 81.8 ± 4.5 84.1 ± 3.0 97 ± 1.7

R = -0.7; p < 0.001

Pratali L et al. Crit Care Med 2010