Title

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Permalink

https://escholarship.org/uc/item/8727959x

Journal

Blood Purification, 39(1-3)

ISSN

0253-5068

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Publication Date

2015

DOI

10.1159/000368973

Original Paper

Blood Purification

Blood Purif 2015;39:37–44
DOI: 10.1159/000368973

Quantitative Lung Ultrasound Comet Measurement: Method and Initial Clinical Results

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Key Words
Dialysis · Hemodialysis · Lung · Ultrasound · Comet · Fluid · Ultrafiltration · Blood volume

Abstract

Background/Aims: Recently, ultrasound signals termed 'lung water comets' associated with pulmonary edema have been correlated with adverse clinical events in dialysis patients. These comets fluctuate substantially during the ultrasound exam highlighting the need for objective quantitative measurement methods. ***Methods:*** We developed an image-processing algorithm for the detection and quantification of lung comets. Quantification measures included comet number (comet count) and the fraction of the ultrasound beams with comet findings (comet fraction). We used this algorithm in a pilot study in 20 stable dialysis outpatients to identify associations between ultrasound comets and clinical parameters including blood pressure (BP), percent blood volume reduction on dialysis (%BV), ejection fraction (EF), and ultrafiltration on dialysis (UF). ***Results:*** Positive findings included associations with lung comet measurements with pre-dialysis Diastolic BP ($r = 0.534$, $p = 0.015$), subject age ($r = –0.446$, $p = 0.049$), and a combination of EF and end dialysis %BV reduction ($r = –0.585$, $p = 0.028$). Comet fraction and comet count were closely correlated due to the inherent relationship between these two metrics ($r = 0.973$, $p < 0.001$). Negative findings included ultrasound comets that did not change from beginning to end of dialysis ($p = 0.756$), and were not significantly correlated with single dialysis treatment UF ($p = 0.522$), subject body weight ($p = 0.208$), or BMI ($p = 0.358$). ***Conclusions:*** Ultrasound signal processing methods may help quantify lung ultrasound comets. Additional findings include algorithmic lung comet measurement that did not change significantly during single dialysis sessions in these stable outpatients, but were associated with cardiovascular and fluid status parameters.

Background/Aims

While the extensive cardiovascular burden associated with end-stage renal disease (ESRD) is well known [1–3], the importance of fluid management is steadily gaining more attention [4–6]. This is strikingly shown by recognizing that across the 350,000 patients in the United States about 280,000 episodes per year develop due to flu-

KARGER 125

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0253–5068/15/0393–0037$39.50/0

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id overload, over 80% of which require hospitalization and cost our country around $1.7 billion annually. Management of patients with dialysis, and preventing fluid overload between dialysis treatments while avoiding hypovolemia during dialysis, is a complicated task requiring improved assessment of fluid status [7–9].

Lung ultrasound (USN) has recently been reported to be useful in evaluating pulmonary edema [10–12]. Acoustic reverberations, identified visually as lung water 'comets', due to pulmonary edema have been correlated with mortality, incidence of cardiac events, and hospitalization [12], and patients with severe congestion exhibited a 4.2× higher mortality and 3.2× increased risk of cardiac morbidity compared to patients without lung congestion. At the same time, the validity of using lung comets as a quantitative tool is disputed [13]. The current common practice of estimating comets has relied on the observation of still frame ultrasound images; yet our own clinical observations and others [13] are that lung comets vary during the real time ultrasound lung examination. We therefore sought to develop and test an objective and quantitative image-processing method that would estimate comet count and comet signal strength captured over a series of frames stored in standard ultrasound cine loops. We further sought to investigate if this objective algorithmic approach would detect clinically meaningful associations between lung comet counts and parameters associated with fluid status in hemodialysis outpatients.

Methods

Clinical

Clinical Data Collection

Twenty stable hemodialysis outpatients (17 men and 3 women) were enrolled at the University of Michigan Dialysis outpatient program after Institutional Review Board approval and informed consent. Lung ultrasound was performed using a commercially available ultrasound device (7.5 MHz, vascular or small parts probe, Interson Corporation, Pleasanton, Calif., USA). Ultrasound scanning was performed through the intercostal (IC) spaces in the anterior and lateral chest for the right and left hemi-thorax at the beginning and end of dialysis treatment using data collection methods modeled after other investigators [12]. Patients were recumbent in their dialysis reclining chairs during the ultrasound examination. To preserve modesty, privacy curtains were drawn in the dialysis unit for all subjects and data collection was limited to the anterior apex of the chest for women subjects. The ultrasound data were collected and saved as 2 s cine loops (video loops) at 16 frames per second, or 32 frames for each IC space (generally 32 IC spaces for men and 12 for women). Early in the study, abundant lung comets were observed in the apical and parasternal IC spaces; therefore, to construct a uniform dataset for analysis from men and women, the bilateral parasternal IC spaces 1 through 4 bilaterally (eight IC spaces per subject) were used for clinical study data analysis. Thus, the total ultrasound dataset for this analysis were 16 cine loops per subject (eight at the beginning and end of dialysis per subject) for 20 subjects totaling 320 cine loops per observer for two observers (640 cine loops), consisting of 32 frames per loop or a total of 20,480 frames of ultrasound data. Additional cine loops were archived for future analysis.

Clinical Data Analysis

Clinical data collected for evaluation were prescribed and delivered Ultrafiltration (UF), beginning dialysis BP, dialysis treatment blood volume monitoring data using the CritLine® Monitor (CLM, Fresenius Medical Care North America) and if present in subject's clinical data echocardiographic ejection fraction (EF); EF was present for 13 of the 20 subjects. Since blood volume monitoring data were stable (no C profiles) in this clinically stable outpatient population, the percent blood volume (%BV) data collected for analysis used for analysis were the final BV reduction (final BV) and the mean BV reduction per hour (BV slope). The lung comet score (comet count, comet fraction) was generated in MATLAB (Mathworks, Natick, Mass., USA) with our laboratory image-processing algorithms. The pre-dialysis comet scores were analyzed against the clinical parameters available by multiple linear regression. In addition, the pre-dialysis comet scores were compared to the post-dialysis comet scores using a two-sided t test.

Laboratory

Algorithms

Algorithms were developed to provide quantification of comet number and strength. In addition, these computer-detection techniques provide efficient and repeatable assessment of comet activity in an ultrasound image loop. The complexity of lung USN images, including variation in comet position and strength, as well as a variety of image artifacts associated with lung imaging (mostly stemming from secondary reflections from the lung surface) were accommodated by the algorithms. Unlike previous approaches [10–12] that depended on human observer assessment of lung comets, the approach described here provides more precise quantification of comet activity and excludes observer bias.

The image-processing architecture was developed using Matlab (Mathworks, Natick, Mass., USA) and image loops were processed off-line, after ultrasound acquisition. An Interson (Pleasanton, Calif., USA) ultrasound imaging system utilizing a mechanically driven, single element probe was used to collect image data. B-mode image loops were acquired at 16 frames/s and stored in an image buffer for subsequent processing. The buffer length was ~2 s. B-mode images were stored in the polar format (i.e., range, beam coordinates), before scan conversion. This is advantageous for comet detection since the resolution is spatially invariant in this representation, resulting in consistent comet widths regardless of lateral position or depth. Figure 1a shows the relationship between polar coordinates (right) and physical pixel (left) locations. To acquire image data, the Interson system mechanically sweeps a single element transducer across the ±30 degree field of view and back. As the transducer moves, it transmits and receives ultrasound sig-

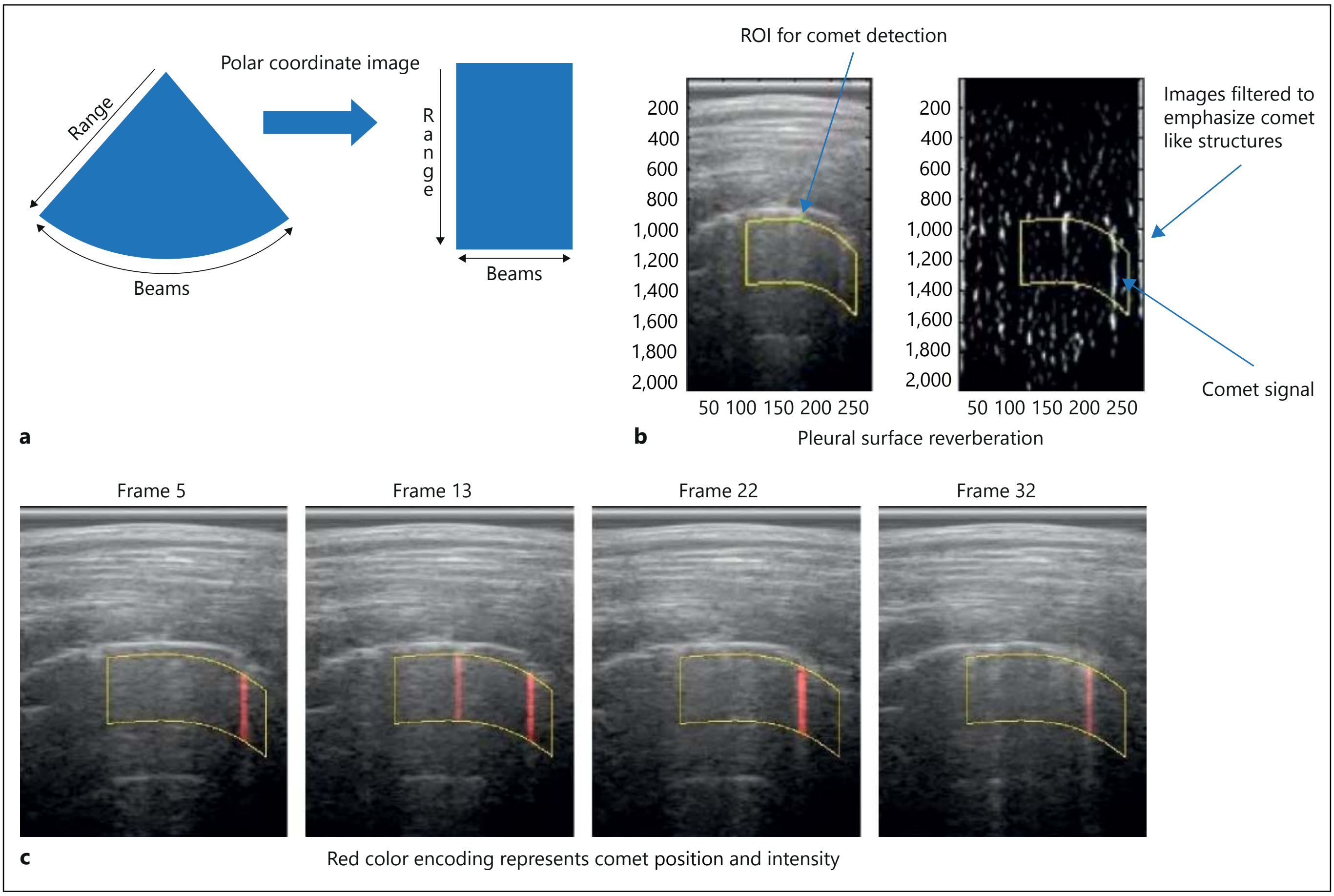

Fig. 1. Polar coordinate representation of image (**a**); Image filtering for comet detection (**b**); Combined B-mode and comet detection images for visualization and assessment (**c**).

nals at a regular rate to form image frames. The mechanical acquisition results in slower sweep speeds near the edges of the field of view compared to the center, producing spatially varying beam spacing. Correction of this distortion is necessary to properly measure comet strength, size, and position. Using analytically determined beam positions provided by the manufacturer, a uniform beam sampling is produced by linear interpolation of B-mode images.

Region of Interest Definition

Comet detection is performed in a region of interest (ROI) defined by the user. In this system, the operator defines points on the lung surface. The analysis software creates the upper border of the ROI by spline fitting the user-defined points and extending the ROI by 1 cm (for 5 cm scan depth) or 1.5 cm (for 10 cm scan depth) below the boundary. The same contour shape is used in figure 1b. The operator also sets the lateral (i.e., across beam) extent of the ROI. ROI processing is critical to accommodate image quality variation. For example, the lung surface may occupy only a portion of the image field of view. In addition, lung border definition is the only user input needed for the comet assessment method presented here, which can improve reproducibility and consistency compared to techniques relying on the comet counting by the user. Also, the ROI allows for consistent analysis of multi-frame data, an improvement of the previous, single frame analysis techniques.

Spatial and Temporal Filtering

Distortion corrected B-mode image loops are processed to detect comets. This is accomplished by applying spatial and temporal finite impulse response (FIR) filters tuned to pass comet spatial and temporal frequencies, thereby accentuating comet-like features in the image loop. In this case, the across beam FIR is a 5-beam, moving average filter (i.e., the assumed comet width is 5 beams). The along beam FIR is ~0.25 cm (or ~100 samples at sampling frequency of 30 MHz). The combination of these filters requires the comet shape to be long and narrow. Temporally, a 3-frame FIR is applied to reduce noise and spurious image artifacts. An example of B-mode and filtered images is presented in figure 1b. The right (filtered) image is shown using a positive dynamic range. As seen by the processed image, comet-like structures are emphasized by the spatial and temporal filtering. Notice also in figure 1b that the horizontal line appearing approximately at depth 1,700 from width 100–175 is the pleural surface reverberation seen when a comet is not present, and the comet B-line extending down approximately from depth 1,000 through 1,700 occurs with

DOI: 10.1159/000368973

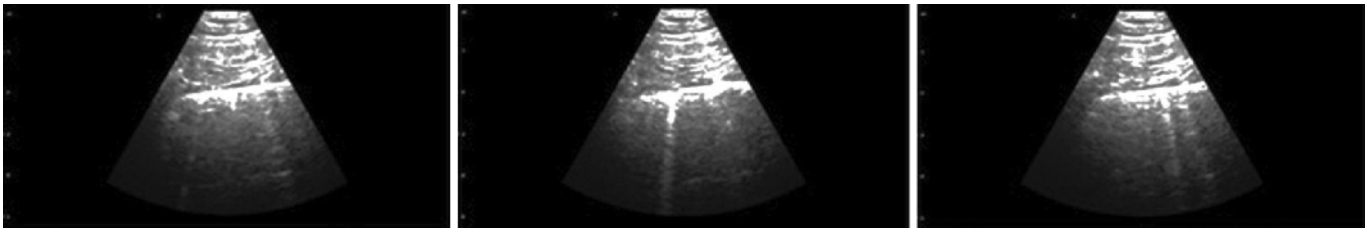

Fig. 2. The three images show consistent character of the ultrasound speckle pattern from stable tissue above the pleural line, indicating very slight motion of the transducer, and the high degree of variation of the comet character, location, and number below the pleural line during a few seconds duration lung exam.

loss of the horizontal A-line, findings typically described as features of lung comets [11]. The horizontal A-lines are also seen to disappear below the vertical comets highlighted in figure 1c.

Calculation of Comet Energy

Comet energy is calculated for each beam within the ROI by summing the signal of filtered images along columns (y-dimension). The process is repeated for all frames, producing a map of comet energy across the ROI for each frame (time). The total comet energy (energy score) for a particular image loop is the average signal strength within this image, normalized by the standard deviation. The normalization factor accounts for the overall strength of the ultrasound signal, which may vary between image loops and subjects due to changing acquisition conditions, as well as emphasizing the stronger variance of images (i.e., spikiness) associated with comets. This helps avoid false detection from strong reverberation artifacts, which are typically wider with less across beam variance (e.g., less spiky).

Comet Detection

A threshold was applied to the normalized spatial-temporal comet energy map described above, producing a binary image representing location and frames of strong comets. This process eliminates spurious low strength signals. The comet detection score is the average value of the thresholded binary image, and represents the fraction of the ROI in which a strong comet is present throughout the entire ultrasound loop. The detected comet signals can be mapped onto B-mode images for comet visualization as shown in the series of images in figure 1c. In this case, the comet position and size is indicated by the red color-encoding derived from the thresholded binary comet energy map. This kind of image output could potentially guide real-time acquisition and comet assessment. The comet count is then derived from the matrix of detected comet fractions. Only discrete comet fractions will be counted as comets: that is, either a thick comet or a thin comet will be counted as one comet. Both the comet fraction and comet count were displayed by the program used for analysis.

Results

Early in the study we confirmed the observation that B-scan images show considerable variation in comet character and number with slight motion of the transducer during the real time ultrasound examination (fig. 2).

Table 1. Demographic and clinical data

	Range (mean ± SD)
Age, years	53±14
Weight, kg	96±24
BMI, kg/m^2	31.5±7.6
Male gender, %	85 (17/20)
Diabetes, %	55 (11/20)
Hypertension documented, %	95 (19/20)
Congestive heart failure documented, %	5 (1/20)
Coronary artery disease documented, %	20 (4/20)
Diastolic blood pressure, mm Hg	75±11
Systolic blood pressure, mm Hg	134±29
Ejection fraction, %	51±17

From the consistent character of the ultrasound speckle pattern, stable tissue is observed above the pleural line. This indicates that very slight motion of the transducer or slight motion with normal respiration is associated with a high degree of variation of the comet character, location, and number below the pleural line. So comets, while somewhat distinct, are shown to be not completely 'discrete' phenomena; they vary in brightness/intensity, width, length, and reverberation pattern. We adjusted for the ambiguity on comet counting and interpretation with the algorithm-based approach outlined in the methods section above. All of the twenty patients were able to successfully complete the ultrasound scanning during their standard dialysis treatment. The demographic and clinical parameters of the twenty patients are included in table 1.

The output of the analysis program was stored in a plain text file and then analyzed using OriginPro 9 (OriginLab Corporation, Northampton, Mass., USA) for correlation. A series of relationships between comet

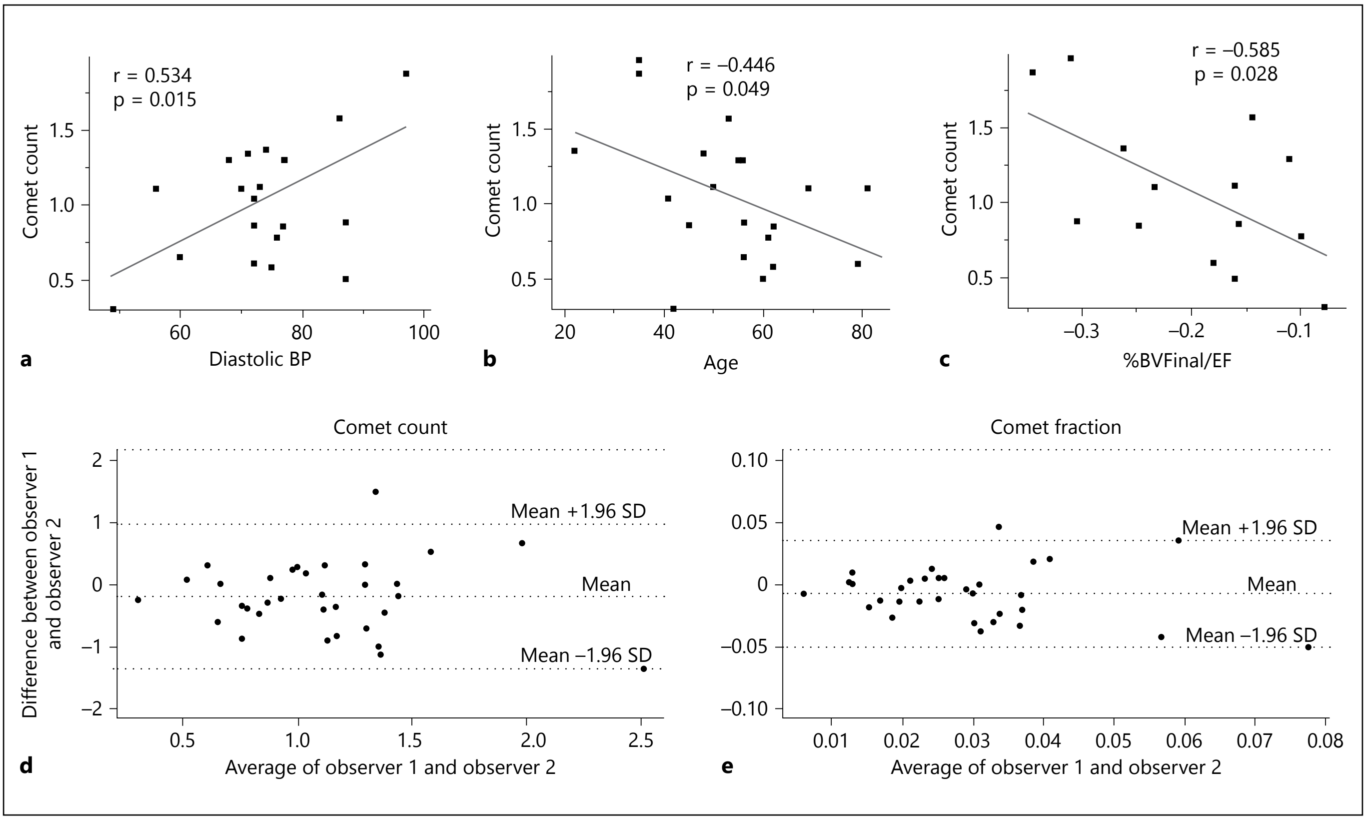

Fig. 3. Correlation between pre-dialysis comet count and clinical parameters diastolic BP (**a**), age (**b**), ratio %BVFinal to EF (**c**), Bland-Altman plot of two observers for comet count (**d**), and comet fraction (**e**).

count and clinical parameters were examined. The pre-dialysis comet count was analyzed against the following parameters using linear regression: blood pressure (BP), ejection fraction (EF), subject body weight, subject age, BMI, and blood volume (BV) indicators during the course of dialysis such as final BV reduction (final BV), and mean BV reduction per hour (BV slope). Among these parameters, diastolic blood pressure (fig. 3a: r = 0.534, p = 0.015), and subject age (fig. 3b: r = –0.446, p = 0.049) showed significance at the 0.05 level. A combination of Final %BV and EF (Final BV divided by EF) was also found significant (fig. 3c: r = –0.585, p = 0.028), although Final BV (r = –0.427, p = 0.061) and EF (r = –0.377, p = 0.184) both showed borderline significance. Systolic blood pressure (r = 0.249, p = 0.289), BV slope (r = –0.360, p = 0.119), subject body weight (r = 0.294, p = 0.208), and BMI (r = 0.217, p = 0.358) were not found to be significant.

Comet fraction and comet count were closely correlated as a result of the inherent inter-relationship between these two metrics (r = 0.973, p < 0.001). Therefore, comet fraction yielded similar results. Diastolic blood pressure (r = 0.570, p = 0.009), subject age (r = –0.461, p = 0.041), and Final %BV/EF (r = –0.602, p = 0.023) were found to be significant (fig. 3a–c). Other parameters mentioned above were not found to be significant with comet fraction. To examine if comet counts or fractions changed during dialysis, a two-sided, paired t test was performed. The results were negative with p = 0.921 for comet count, and p = 0.874 for comet fraction. A separate linear regression model suggested the decrease in comet count during the dialysis period (defined as the comet count at the beginning of dialysis minus the comet count at the end of dialysis) strongly correlates neither with the UF achieved (r = 0.109, p = 0.522) nor with the change in mean arterial BP (r = 0.035, p = 0.843). The full results of the analysis can be found in table 2.

To examine the amount of error introduced by different observers, an inter-observer analysis was performed. The correlation coefficient between the two observers did not show a high agreement on either comet count (r = 0.368) or comet fraction (r = 0.310) and the Bland-Alt-

Table 2. Full results of comet analysis

Comet	Clinical parameter	Unit	Range	R-value	p value	Signif.
Pre-dialysis comet count	Diastolic BP	mm Hg	75±11	0.534	0.015	*
	Systolic BP	mm Hg	134±29	0.249	0.289	NS
	Final %BV (final BV)	percent	–8.5±4.7	–0.427	0.061	NS
	Mean BV/h (slope)	percent/h	–2.2±1.2	–0.360	0.119	NS
	Ejection fraction	–	51±17	–0.377	0.184	NS
	Final BV/EF	–	–	–0.585	0.028	*
	Subject dry weight	kg	96±24	0.294	0.208	NS
	Subject age	years old	53±14	–0.446	0.049	*
	Subject BMI	kg/m^2	31.5±7.6	0.217	0.358	NS
Pre-dialysis comet fraction	Diastolic BP	mm Hg	75±11	0.570	0.009	**
	Systolic BP	mm Hg	134±29	0.268	0.253	NS
	Final %BV	percent	–8.5±4.7	–0.355	0.124	NS
	Mean BV/h (slope)	percent/h	–2.2±1.2	–0.283	0.226	NS
	Ejection fraction	–	51±17	–0.447	0.109	NS
	Final %BV/EF	–	–	–0.602	0.023	*
	Subject dry weight	kg	96±24	0.279	0.234	NS
	Subject age	years old	53±14	–0.461	0.041	*
	Subject BMI	kg/m^2	31.5±7.6	0.167	0.480	NS
Comet fraction	Comet count	–	–	0.973	<0.001	***
Decreased comet count	UF achieved	l	3.1±1.7	0.109	0.522	NS
	Mean BP change (begin to end HD)	mm Hg	2.23±11.55	0.035	0.843	NS
Pre- vs. post-dialysis comet count		–	–	–	0.921	NS
Pre- vs. post-dialysis comet fraction		–	–	–	0.874	NS

man plot of the observers is shown in figure 3d, e. The inter-observer variation for both comet count and comet fraction observations were within two standard deviations for most measurements (fig. 3d, e), even though the inter-observer variation was high.

Discussion

There is increasing evidence for the potential value of ultrasound lung comets in assisting with pulmonary fluid status assessment [10–12, 14, 15]. However, the variation and fluctuation of comet character as well as questions about using them as a quantitative measure [13] highlight the need for automated and objective tools such as the algorithm in this study. Fundamentally, lung water comets result from acoustic reverberation caused by acoustic impedance mismatches [14–17]. This reverberation results in multiple 'comet tail' artifacts generated in the image at the lung surface; water-thickened interlobular septa near the pleural surface may be the source of this reverberation pattern in the ultrasound images [14–17]. However, this explanation of comet generation does not necessarily mean that some 'quantity' of comet number or character can be translated directly into a quantitative measure of pulmonary edema. Additional fundamental work is yet to establish the basis for lung water quantification and to relate this quantity to ultrasound comet generation, and to clinical findings. Notwithstanding this observation, the clinical ultrasound data and correlations with clinical findings that we observed points to the fact that further work be performed using this approach or similar approaches.

In this pilot project, our purpose was to develop and clinically test an objective measurement algorithm-based approach to detect comet patterns in standard DICOM ultrasound B-mode cine loops (video sequences) and calculate various metrics associated with these artifacts. This type of approach allows the processing of considerably more data than can be performed manually by the clinician. For example, in this study more than 20,000 frames of data were processed for these 20 subjects, offering the possibility of extracting considerably more information from a rich ultrasound dataset that may be routinely collected in a short lung ultrasound examination. While algorithm-based quantification standardizes ultrasound comet analysis and allows for large amounts of data to be incorporated into the examination, additional sources of measurement variation remain. Bland-Altman analysis showed comparable measurements between observers, yet the inter-observer spread indicated differences in image acquisition between observers likely from small differences in probe position. The comet fluctuation during the measurements we observed and the inter-observer variation do suggest that standardization of acquisition will improve quantification. The user-defined ROI may also be a source of measurement variation although this appeared more consistent during the analysis. Both of these variables require more study.

We had hypothesized that if the lung ultrasound comets were related directly to lung fluid content that there would be a detectable difference from beginning to end of dialysis using this approach. However, we did not detect such a difference in this stable patient population. This is in contrast with other investigators' findings that comets were reduced with fluid removal during dialysis [18] in hospitalized patients. One possible explanation is this smaller pilot study was underpowered to detect this change in this stable outpatient population. We have started a study in hospitalized dialysis patients to investigate this further. The positive findings are interesting in that lower cardiac ejection fraction accompanied by higher-end dialysis reduction in intravascular blood volume was associated with greater pre-dialysis comets counts. This occurred in the absence of greater ultrafiltration targets for these patients. Patients with low ejection fraction may have reduced redistribution of fluids from extravascular compartments, including lungs and extremities, and manifest this as greater intra-dialytic reduction in relative blood volume during dialysis. This is interesting to consider in light of the greater mortality associated with greater lung water comets independently observed [12]. More study is needed to better understand the relationship between fluid compartments and the rate at which fluid shifts between compartments. Similarly, elevated blood pressure is associated with increased fluid, and this is supported by these findings of greater lung comet counts and comet fractions in patients with pre-dialysis diastolic hypertension. The reason lower comet counts were seen in patients with increasing age is uncertain. Future studies may benefit from intravascular or other volume status monitoring to determine how much reduction in lung water will occur with what degree of intravascular contraction during dialysis in different patient populations.

Conclusions

Algorithm-based ultrasound signal-processing methods may help objectively quantify lung ultrasound comets. This initial analysis suggests that such approaches to lung comet measurement allow operator-independent objective processing of large amounts of video ultrasound (cine loop) data; so while inter-observer ultrasound data collection remains a variable, the data analysis step may be objectively conducted. Our pilot data from this small series of stable dialysis outpatients did not detect a change in comets during single dialysis sessions, but lung comets were associated with clinically relevant cardiovascular and fluid status parameters. Further studies are required to both explain the quantitative relationship between comets and lung water and to determine the role of lung ultrasound in the clinical setting for dialysis patients.

Acknowledgment

This work was supported by an Investigator-Initiated Research Study (IIRS) Grant from Fresenius Medical Care Renal Therapies Group, Waltham, Mass., and funding from The University of Michigan Center for Integrative Research in Critical Care Grand Challenge: Sepsis Initiative and we wish to thank Barbara Santuci for help with manuscript preparation.

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