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Sonographic Evaluation of Pleural Fluid in a Large Group of Adult Healthy Individuals – End Trial Results

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A B S T R A C T

This partly prospective, partly retrospective trial was performed in adult healthy volunteers to confirm the prevalence of sonographically visible physiological pleural and to establish possible individual variations of the presence and amount of pleural fluid over time as well as to asses relations in between pleural fluid and individual characteristics like age, sex, body mass index, smoking history and hormone therapy (in woman). A reliable threshold between normal and pathological pleural fluid findings was determined. Prospective chest sonography of both pleural spaces was performed with 3–12 MHz transducer in 71 randomly selected healthy adults and presence of pleural fluid was evaluated and measured as an anechoic layer at least 2 mm in thickness. Each individual was reexamined three times in two to four months intervals. Another 86 individuals were prospectively re-examined for the third time, 24 to 36 months after completed previous trials while the data on the baseline and follow up examination were retrospectively acquired. Maximum thickness of the pleural fluid was measured in the elbow position after five minutes leaning in lateral decubitus position. Examinees served as their own controls, with the quantitative measurement of the fluid layer over time. The fluid layer was visible in at least one pleural space in 51/157 (32.5%) subjects, whereas 35 (22.3%) examinees had a positive finding on all three examinations. Consistency of this finding was high between each pair of examinations over time (Cohen's Kappa ≥0.8, $p<0.001$). The maximum thickness of fluid layer ranged from 2.0 to 5.2 mm, with a mean of 2.9 mm independently of left or right pleural space and unilateral or bilateral presence. Regression models indicate that odds for observing pleural fluid in an individual decrease with age ($p=0.013$) and that if observed, the fluid tends to be thicker in women ($p=0.017$) and in subjects with higher BMI ($p=0.028$). Sonography detected small amounts of pleural fluid in 32.5% of healthy individuals. If present, maximum thickness of the fluid layer doesn't exceed the threshold value of 5.2 mm with mean values around 3 mm. The amount of physiological pleural fluid is relative stable over time and is very likely an individual characteristic with lower frequencies in elders while the frequencies of sonographically detected pleural fluid in healthy adults does not correlate with sex, obesity, smoking or hormonal therapy.

Key words: *pleura, fluid, physiology, sonography, ultrasound*

Introduction

Data on the smallest amounts of pleural fluid detectable by imaging methods in pathologic conditions of pleural space vary considerably, but they are essentially within the same broad range when computed tomography, sonography or X-rays are used[1–4]. A small amount of pleural fluid (5–20 mL) is often present in the pleural space of healthy individuals[5]. It was observed that few millimeters of free pleural fluid could be detected at the level of phrenicocostal sinuses in otherwise healthy individuals[6,7]. Therefore, the quantitative analysis of normal pleural fluid in healthy adults over time might provide additional guiding information of how to improve the diagnostic approach in some patients, particularly in the intensive care unit patients.

Thus, the purpose of this trial was to confirm the prevalence of sonographically visible normal pleural fluid in large group of adult healthy individuals, to establish possible individual variations of the presence and amount

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of pleural fluid in each individual over time and to asses relations in between pleural fluid and individual characteristics like age, sex, body mass index, smoking history and hormone therapy (in woman). A reliable threshold between normal and pathological pleural fluid findings was determined.

Subjects and Methods

The protocol of the trial

Between September 2006 and January 2007 71 individuals participated in the prospective part of this study. They underwent the baseline and two follow up sonographic examinations of both pleural space in 2–4 months intervals one after another. During this period 86 participants were examined only once, while the data on baseline and follow up examinations were retrospectively acquired from the previous trials[6,8] with the same inclusion/exclusion criteria as well as an adequate examination position.

Study population

Altogether the data on 157 healthy volunteers (84 men and 73 women; 22–73 years old; mean age 43.4±12.8 years) were included in this statistical analysis. The majority of examinees had a body-mass-index (BMI) beyond 25 (112, 71.3%), and were non-smokers (108, 68.8%). Among women, 23 (31.1%) were taking either oral contraceptives or hormone-replacement therapy. All examinees were healthy according to their medical history, previous physical examination and baseline laboratory tests. Individuals with any significant clinical abnormality were excluded from the study. In all subjects, X-ray in standing position in the posterior-anterior direction was within the normal limits. Institutional Ethical Board approved both phases of the study and written informed consent was obtained from each individual prior to baseline US examination of pleural spaces.

Imaging

Sonography of both pleural spaces was performed by two experienced radiologists, following a standardized protocol. Initially, each individual was placed in the lateral decubitus position for five minutes. Then the sonographic examination of the lower pleural space was performed with the subject leaning on one elbow (Figure 1) and still in the lateral decubitus position. The possible fluid accumulation was evaluated with the probe along the mid-axillary line. Both pleural spaces of each individual were examined in baseline and two follow-up studies. In a first group of 71 individuals all three studies were carried out in 2 to 4 months intervals. In a second group of 86 volunteers the first and second study (baseline and first follow up) were performed within the previous trials 2 to 4 months after each other [6,8] while the third study (second follow up) was carried out prospectively after a delay of 24 to 36 months to the previous study.

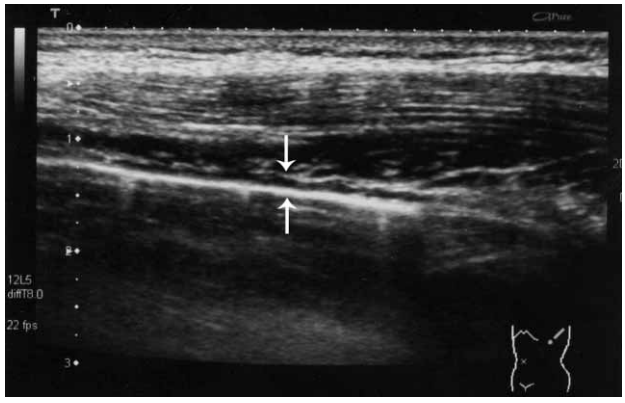

Fig. 1. Ultrasonographic image of normal left pleural space with no fluid in between the pleurae (white arrows). The patient was examined in »leaning on the elbow position«, 12 MHz transducer was used.

Two US scanners were used: Envisor HD (Philips, Best, the Netherlands) with a 3–12 MHz linear transducer, and SSA-390 (Toshiba, Tokyo, Japan) with a 9–12 MHz linear transducer. The sonographic criterion for the presence of pleural fluid was defined as follows: detection of an anechoic zone present between the parietal and visceral pleura, with a cross-section thickness of at least 2 mm, with changing appearance in inspiration and expiration status and/or with varying appearances when moving during examination[2,6,8,9]. Maximum cross-section fluid thickness between the parietal and visceral pleura was measured using calipers during suspended respiration with the position of the probe perpendicular to the thoracic wall. Examinations were performed by one of the two observers blinded to all previous results. Each subject underwent the follow-up studies and served as it's own control for what concerns the quantitative measurement of pleural fluid.

Statistical analysis

Descriptive statistics was calculated for all the studied variables. Mean differences were tested using students t-test (for independent or paired samples, as appropriate), or using one-way analysis of variance (ANOVA, when comparing three groups). Differences in proportions between groups were tested using two-sided Fisher's exact test; difference between an estimated and an assumed proportion was tested using exact binomial test. To measure concordance of detected presence of pleural fluid for the three successive follow-up studies Cohen's Kappa coefficient was calculated. Agreement was considered fair to good if κ values were between 0.40 and 0.75 and high if κ values were greater than 0.75. Presence of pleural fluid in an individual and its measured thickness were correlated with various descriptive endpoints using a multiple logistic or linear regression model. All statistical analyses were performed with Excel Windows software. A p value of less than 0.05 was considered to indicate a statistically significant difference.

Results

The number and proportion of subjects who had a sonographically detectable anechoic fluid layer in the pleural space is reported in Table 1. This finding was observed in 44 of 157 cases (28.0%) during the initial study, in 41 of 157 cases (26.1%) in the follow-up study and in 45 of 157 cases (28.7%) during the third examination. Numerical results of the fluid visible only unilaterally are also summarized in Table 1. Fluid visible in the left pleural space only prevailed, but this difference between the left and the right pleural space was not statistically significant ($p=0.678$, $p=0.503$ and $p=0.302$ for the 1st, 2nd and 3rd study, respectively).

Overall, 106 (67.5%) subjects had negative finding of pleural fluid, while 51 individuals (32.5%) presented at least one positive finding during one of the three examinations. Seven subjects (4.5%) had a positive finding only once during the three studies, 9 examinees (5.7%) were positive twice, and 35 (22.3%) had a positive finding during all three exams. The high reproducibility of the sonographic presence of pleural fluid was confirmed on an individual bases by the high κ agreement between pairs of examinations: 142 (90.4%) cases agreed between the 1st and 2nd examination (Kappa=0.758, $p<0.001$), 148 (94.3%) individuals between the 1st and 3rd examination (Kappa=0.859, $p<0.001$), and 149 (94.9%) individuals between the 2nd and the 3rd examination (Kappa=0.872, $p<0.001$).

The mean thickness of the observed fluid layer was quite similar for all follow-up studies with 2.89 mm (SD 0.53 mm, range 2.0–4.3 mm) for the 1st study, 3.0 mm (SD 0.61 mm, range 2.0–5.2 mm) for the 2nd study, and 2.85 mm (SD 0.46 mm, range 2.0–4.6 mm) for the 3rd study. More detailed data for the fluid layer thickness in relation to the affected pleural space and unilateral or bilateral presence are reported in Table 2. Overall, no significant difference of the mean fluid layer thickness in both pleural spaces is measurable on any of the follow-up examinations ($p=0.556$, $p=0.396$ and $p=0.038$ for the 1st, 2nd and 3rd study, respectively). Even if only the subjects with unilaterally present fluid are considered, there was no statistical difference ($p=0.459$, $p=0.393$ and $p=0.642$ for the 1st, 2nd and 3rd study, respectively). Finally, statistical significance is also not reached when comparing subjects with unilaterally affection with bilateral one ($p=0.175$, $p=0.802$ and $p=0.243$ for the 1st, 2nd and 3rd study, respectively). However, we found that the mean thickness of the observed fluid layer increased statistically significantly in accordance with the number of examinations with a positive finding (1st study: mean=2.34, SD=0.14; 2ndstudy: mean=2.60, SD=0.31; 3rd study: mean=2.99, SD=0.38; $p<0.001$).

The presence of physiological pleural fluid could not be correlated statistically with sex ($p=0.113$), BMI ($p=0.698$), smoking ($p=0.198$) or hormonal therapy in women ($p=0.090$), but it was less likely with increasing age ($p=0.013$; estimated odds ratio per year 0.96, 95% CI 0.93-0.99).

The mean fluid layer thickness proved to be larger for women (mean 3.0 mm, SD 0.4 mm; standardised regression coefficient=0.338; $p=0.017$) than for men (mean 2.7 mm, SD 0.4 mm) and also larger for subjects with a BMI above 25 (mean 3.0 mm, SD 0.4 mm) compared to subjects with a BMI beyond 25 (mean 2.8 mm, SD 0.4 mm; standardised regression coefficient=0.319; $p=0.028$). No

TABLE 1
NUMBER AND PROPOTION OF SUBJECTS WITH SONGRAPHICALLY DETECTED PLEURAL FLUID IN TOTALLY 157 HEALTHY INDIVIDUALS

	1st Study	2nd Study	3rd Study
Total Right Pleural Space	31 (19.7%)	29 (18.5%)	35 (22.3%)
Total Left Pleural Space	34 (21.7%)	33 (21.0%)	40 (25.5%)
Unilaterally	23 (14.6%)	20 (12.7%)	15 (9.6%)
Right / Left Pleural Space	10 / 13	8 / 12	5 / 10
Bilaterally	21 (13.4%)	21 (13.4%)	30 (19.1%)
Total	44 (28.0%)	41 (26.1%)	45 (28.7%)

TABLE 2
COMPARISON OF FLUID LAYER THICKNESS OVER TIME FOR POSITIVE FINDINGS

	1st Study X (SD)	2nd Study X (SD)	3rd Study X (SD)
PF of Right Pleural Space	2.82 mm (±0.67)	2.93 mm (±0.73)	2.73 mm (±0.61)
PF of Left Pleural Space	2.73 mm (±0.53)	3.13 mm (±0.90)	3.08 mm (±0.69)
PF Unilaterally	2.99 mm (±0.55)	2.98 mm (±0.60)	2.73 mm (±0.41)
PF Bilaterally	2.77 mm (±0.49)	3.03 mm (±0.63)	2.90 mm (±0.47)
Overall range	2 mm–4.3 mm	2 mm–5.2 mm	2 mm–4.6 mm

statistical significance could be correlated with age ($p=0.378$), smoking habits ($p=0.756$) or hormonal therapy ($p=0.505$) in women.

Discussion

Diagnostic ultrasound is frequently used to screen for pleural liquid especially in cases of contradictory X-ray or CT results. Sonography is also the ideal method for identifying the best puncture site for pleural drainage[10]. Accurate detection of small pleural effusion, possibly indicating early-stage lung disease is particularly important in cancer patients as well as in intensive care unit patients. Nevertheless, our results confirmed that a small amount of pleural fluid is often encountered also in healthy volunteers with normal maximum thickness of the fluid layer beyond a threshold of approximately 5 mm. The sonographic measurements in our study were easily reproduced over time even for thin fluid layers, indicating that this method combined with appropriate calculation may also serve to predict actual pleural effusion volumes.

Sonographic measurements are influenced by the size of the thoracic cavity. Moreover, the parietal and visceral pleura and the space in between usually measure only 0.3 to 0.4 mm[4]. On sonograms, physiological pleural fluid accumulation usually appears as a wedge-shaped echo free layer with the base orientated towards costophrenic angle[6]. Sonographic examination of the pleural space with the subject leaning on one elbow has proven to be accurate when searching for small effusions[3] and also for demonstrating physiologic pleural fluid in adults[6,7,10].

Noppen[11] and coauthors recently reported similar results with 4–18 mL of pleural fluid present in the pleural space in the small group of healthy adult individuals. If the amount is small, the fluid is mostly adherent to the pleural surface[11] and for that reason difficult to detect by ultrasound. This was the case in two thirds of healthy examinees in our study, belonging to the group with sonographically »dry pleural space« (Figure 1). Once the total amount of pleural fluid approaches to the upper level of normal range of pleural fluid volume (=18 mL according to Noppen et al.[11]) within the pleural cavity, it becomes partly free. The fluid than accumulates at various sites such as the costodiaphragmatic sinuses, around the hila and lobar margins[12] and thus could be sonographically detected. Typical images of individuals with sonographically »wet pleural space« are shown on Figure 2. Subjects with so called »wet pleural space« present already some free pleural fluid and accumulation between the lateral costal pleurae while they lean in the lateral decubitus position (Figure 3a). Such fluid tends to shift towards the lateral phrenicocostal sinus immediately after changing subject's decubitus position to elbow position and thus may easily be detected with the transducer (Figure 3b).

Our findings clearly indicate that sonographic presence of physiologic pleural fluid is a stable feature for about 22% of healthy volunteers during longer follow-up periods.

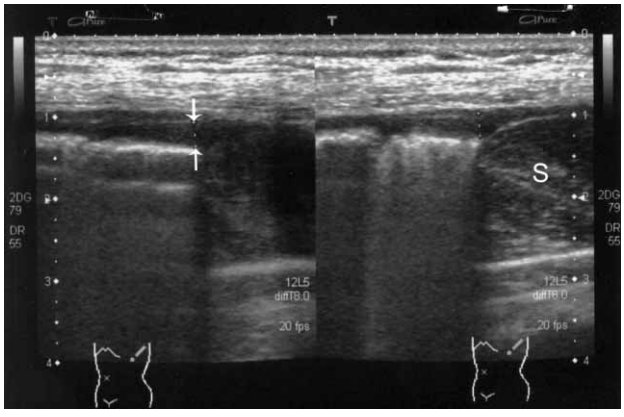

Fig. 2. Examination of the left pleural space in »leaning on the elbow« position showing a wedge shaped collection of phyisiological pleural fluid (between white arrows). This is a typical image of the individual with sonographically »wet« pleural space. S=spleen.

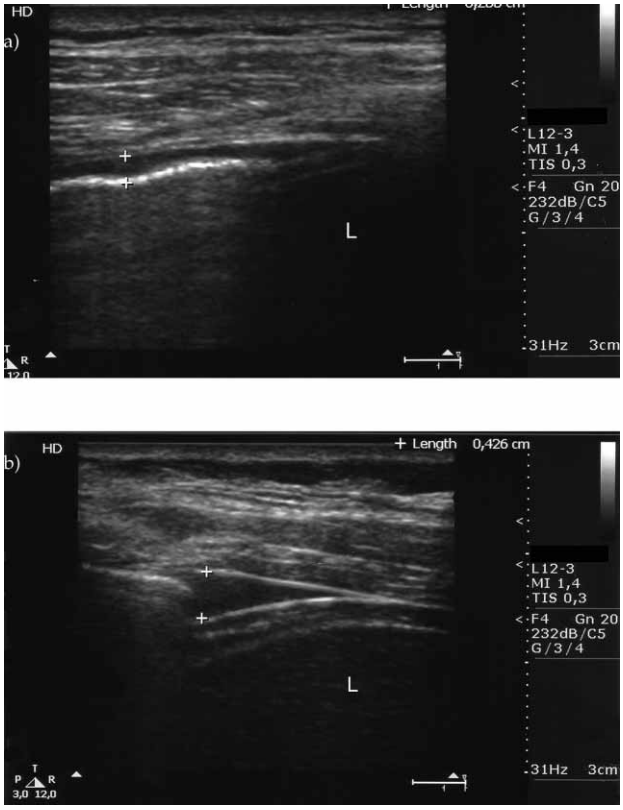

Fig. 3. Examination of the right pleural space in healthy adult individual. a) examination in leaning on a side position. Small collection of pleural fluid in between the pleurae measuring up to 2.3 mm (between the calipers). L=liver. b) the same person, the image is taken immeadiately after changing to a »leaning on the elbow« position. The collection (between the calipers) of the fluid is tipically wedge shaped and more obvious to examiner (maximum perpendicular thickness was found to be almost doubled – 4.3 mm). L=liver.

TABLE 3
PRESENCE OF US VISIBLE PLURAL FLUID ACCORDING TO VARIOUS DESCRIPTIVE ENDPOINTS

Endpoint	Statistical test	p value
Age	t-test (independant samples)	p=0.015
Sex	Fisher's exact test	p=0.396
BMI	Fisher's exact test	p=0.578
Smoking	Fisher's exact test	p=0.198
Hormonal therapy (W)	Fisher's exact test	p=0.090

The results of this trial confirm that the frequency of sonographically detected pleural fluid in healthy subjects does not correlate with sex, obesity, smoking or hormonal therapy. The pleural fluid presence is less likely with the increasing age (Table 3). This is most probably related to generally reduced volume of extra cellular fluid in elderly population[13]. The logistic regression model used to predict the presence of pleural fluid in an individual confirmed only the age to be a statistically significant predictor of US visible pleural fluid (Table 4). Thus, the reduced frequency of residual pleural fluid in older people may indicate the need to follow-up by ultrasound any positive finding in this population.

Multiple linear regression in subjects with detected fluid proved the mean thickness of the fluid to be larger for women than for men and also larger for subjects with a BMI above 25 compared to subjects with normal BMI (Table 5). Probably in women the same amount of fluid is distributed over a smaller area explaining this difference.

Several important technical points regarding the use of sonography to differentiate residual pleural fluid should be noted. Some fine echoes seen within the pleural space are artifacts due to adjacent hyperechoic parietal and visceral pleura (Figure 2). These artifacts might impede accurate diagnosis, but may well be differentiated from pleural liquid. It was shown that the prediction errors between the perpendicular maximum thickness of the fluid layer and calculation of fluid volumes are especially striking in cases of small volumes of fluid[10]. For this reason, quantification of the fluid volume of normal subjects hasn't been validated in this study by drainage or in comparison to other methods such as lateral decubitus chest X-ray radiography.

In summary, this trial demonstrates that in around 30% of healthy individuals pleural fluid is sonographically detected in the elbow position. Thus, it can be reliably concluded that pleural space in healthy individual can be sonographically without detectable pleural fluid (»dry«) or with some pleural fluid at the level of costophrenic recesses (»wet«). If present, maximum thickness of the fluid layer doesn't exceed the threshold value of 5.2 mm with mean values around 3 mm. The amount of pleural fluid is relative stable over time and is very likely an individual feature with lower frequencies in elders but not related to sex, obesity, smoking or hormonal therapy. It is important not to misinterpret the simple presence of these small amounts of pleural fluid as pathologic, since it may lead to further unnecessary diagnostic and therapeutic procedures. But on the other side the routine examination of pleural space to determine the baseline status of pleural cavity in special subgroups of patients with possible early pleural involvement (such as cancer patients, cardiac patients, ICU patients) might be justified. Further studies are necessary to evaluate the role of small pleural effusion as a predictive factor in such diseases.

TABLE 4
LOGISTIC REGRESSION MODEL CORRELATING PRESENCE OF PLEURAL FLUID IN AN INDIVIDUAL WITH VARIOUS DESRIPTIVE ENDPOINTS

	Regression coefficient	p	Estimated odds ratio (95% confid. interval)
Sex (M:F)	–0.584	0.113	0.56 (0.27–1.15)
Age	–0.038	0.013	0.96 (0.93–0.99)
BMI (N: elevated)	–0.156	0.698	0.85 (0.39–1.89)

TABLE 5
MULTIPLE LINEAR REGRESSION MODEL CORRELATING THE MEAN THICKNESS OF THE PRESENTED FLUID WITH VARIOUS DESRIPTIVE ENDPOINTS OF AN INDIVIDUAL

	Standardised regression coefficient	p
Sex (M: F)	0.338	0.017
Age	0.126	0.378
BMI (N: elevated)	0.319	0.028
Smoking (Yes: No)	0.043	0.756

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SONOGRAFSKO PROCJENJIVANJE PLEURALNE TEKUĆINE U VELIKOJ GRUPI ZDRAVIH, ODRASLIH OSOBA – KRAJNJI REZULTATI POKUSA

S A Ž E T A K

Ovaj djelomično prospektivni i djelomično retrospektivni pokus izveden je na odraslim, zdravim volonterima kako bi se potvrdila prevalencija sonografski vidljivog fiziološkog pleurala i ustanovile moguće individualne varijacije prisutstva i količine pleuralne tekućine tijekom vremena te također odnosi između pleuralne tekućine i individualnih karakteristika kao što su dob, spol, indeks tjelesne mase, povijest pušenja i hormonska terapija (kod žena). Određen je pouzdani prag između normalne i patološke pleuralne tekućine. Prospektivna sonografija pluća oba pleuralna prostora izvedena je s 3–12 MHz magnetskim pojačalom na 71 slučajno odabranim, zdravim, odraslim osobama, a prisutstvo pleuralne tekućine procijenjeno je i izmjereno kao sloj bez odjeka debeo 2 mm. Svaki ispitanik pregledan je tri puta u intervalima od dva do četiri mjeseca. Drugih 86 ispitanika je prospektivno pregledano i treći put, 24 do 36 mjeseci nakon završetka prijašnjih pokusa, dok su rezultati temeljnih i naknadnih pregleda dobiveni retrospektivno. Maksimalna debljina pleuralne tekućine mjerena je u L poziciji nakon pet minuta bočnog naginjanja pozicije dekubitusa. Ispitanici su sami sebi služili kao kontrola, sa kvantitativnim mjerama sloja tekućine tijekom vremena. Sloj tekućine bio je vidljiv u barem jednom pleuralnom prostoru među 51 od 157 (32,5%) ispitanika, od kojih je 35 (22,3%) imalo pozitivni nalaz u sva tri pregleda. Konzistencija ovih nalaza bila je visoka između svakog para pregleda tijekom vremena (Cohenov Kappa≥0,8; $p<0,001$). Maksimalna debljina sloja tekućine kretala se između 2,0 i 5,2 mm, s aritmetičkom sredinom 2,9 mm neovisno o lijevom ili desnom pleuralnom prostoru i unilateralnom ili bilateralnom prisutstvu. Regresijski modeli pokazali su da vjerojatnost za promatranje pleuralne tekućine kod pojedinca pada s dobi ($p=0,013$) i da, ako se promatra, tekućina teži većoj debljini kod žena ($p=0,017$) i kod ispitanika s većim indeksom tjelesne mase ($p=0,0287$). Sonografija je otkrila male količine pleuralne tekućine među 32,5% zdravih ispitanika. Ako je prisutna, maksimalna debljina sloja tekućine ne prelazi prag od 5,2 mm s aritmetičkom sredinom od 3 mm. Količina fiziološke pleuralne tekućine relativno je stabilna tijekom vremena te je vrlo česta individualna karakteristika s niskim frekvencijama kod starijih osoba dok frekvencije sonografski otkrivene pleuralne tekućine kod zdravih, odraslih osoba ne korelira sa spolom, dobi, pušenjem ili hormonskom terapijom.