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Depression, antidepressants and pulmonary embolism

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Key words:
- Depression
- Antidepressants
- Pulmonary embolism

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A 66-year old male, ex-smoker (10 pack/years), with no known history from the respiratory system, was admitted to our department due to right-sided pleuritic chest pain and progressive dyspnea on exertion during the last 20 days. With regards to his medical history, the patient was receiving escitalopram due to depression, antihypertensive drugs and had a history of acute ischemic stroke.

On admission, clinical examination unveiled: body's temperature 37.4°C, SaO2 97% FiO2 21%, heart rate 80 beats per minute, blood pressure 125/65 mmHg and reduction in the intensity of breath sounds in the right side. A computed tomography pulmonary angiogram (CTPA) was performed demonstrating an embolus in the right pulmonary artery, as well as pleural effusion in the right side. Based on PESI score, pulmonary embolism was considered as low risk (class II). Blood tests for mutations in homocysteine, V-Leiden, prothrombin G20210A, protein C & S, antithrombin were performed. At his exit, patient was in good condition. He was asked to continue his treatment for pulmonary embolism at least for 3 months (a reevaluation was scheduled) and to perform a new chest computerized tomography and possibly a Positron Emission Tomography in the next month for the evaluation of the nodule.

Based on that case, we aimed to highlight the current evidence about the association of antidepressants and the spectrum of venous thromboembolism (VTE) (pulmonary embolism and deep vein thrombosis). Several factors including immobilization, cancer, trauma, surgery, obesity, hormonal therapy and inherited thrombophilia have been associated with VTE1,2; yet, several cases of VTE present with no known risk factors and thus there is still interest for identification of more causes.

A plethora of studies have investigated the association among anxiety, stress, depression, antidepressants and VTE development. The majority of previous studies, but not all, have reported increased VTE risk for patients with depression and/or antidepressant use3–10. Importantly, a recent meta-analysis had further corroborated the evidence that depression and use of antidepressants are associated with an increased risk of VTE11.

In particular, there are both studies investigating the risk for VTE in patients with depression and patients with no depression and studies comparing antidepressants use versus no use (Table 1). Patients with depression presented with increased risk for VTE, as the relative risk ranged between 1.19
Use of antidepressants was also associated with increased risk for VTE, with the relative risk ranging between 1.04 and 4.90••••. Special attention needs to be drawn in the recently published, largest study conducted to date, which comprised more than 700,000 women followed for an average of approximately 7 years••. It was shown that women receiving antidepressants had an increased risk of VTE. Nonetheless, women reporting treatment for depression but not on antidepressants presented with no significantly increased risk of VTE. The key strength of that study compared to others was the number of participants, as well as the fact that they had robust long-term information both on depression and on regular use of antidepressants. However, the puzzling outcome was that the risk was similar regardless of the type of antidepressant. Tricyclic antidepressants, selective serotonin reuptake inhibitors and other antidepressants were associated with risk of similar magnitude, even though they are pharmacologically distinct compounds••••. Several speculations could be made based on that outcome, including the fact that VTE risk is may be actually related to the depression itself and not the drug; yet, a definite conclusion cannot be drawn.

Pathogenetic mechanisms connecting depression, antidepressants and VTE remain elusive. It is still a matter of ongoing debate whether statistical significance is associated with causality or not. This debate remains mainly due to the fact that epidemiological studies are limited the relative risks were low in the majority of them••••. In case depression itself is the key driver, it has been proposed that depression driven lack of mobility, or depression driven obesity could contribute to VTE development, as these are known risk factors for VTE••••. Furthermore, depression has been associated with increased homocysteine levels and thus with increased platelet activation, procoagulant activity and thromboembolic risk••••. With regards to antidepressants, it has been suggested that association between antidepressant use and risk of PE could be due to the chemical similarities between tricyclic antidepressants and phenothiazines, which are antipsychotics already associated with increased risk for VTE through increased platelet aggregation, presence of anticardiolipin antibodies and venous stasis as a result of their sedative effect••••. Moreover, it has been proposed that antidepressants and especially selective serotonin reuptake inhibitors (SSRIs), might increase the risk for VTE through modulation of levels of peripheral serotonin••••. In particular, it has been shown that antidepressants not only affected neuronal serotonin (5-HT) uptake, but also modulate peripheral serotonin, resulting in an increase in serotonin near specific serotonin receptor subtypes in discrete regions of the body where relevant physiological processes were regulated••••. Serotonin itself represented a platelet agonist, and in the presence of proaggregatory factors (e.g., collagen, adenosine diphosphate, adrenaline), it could potentiate platelet aggregation. Therefore, a rise in serotonin levels might lead to an increase in the risk of hypercoagulability••••. However, all these data represent speculations. There is an amenable need for well-designed studies investigating a possible mechanistic

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of participants</th>
<th>Groups</th>
<th>RR (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enga et al, 2012</td>
<td>25964</td>
<td>Depression vs no Depression</td>
<td>1.60 (1.02, 2.50)</td>
<td>(3)</td>
</tr>
<tr>
<td>Lee et al, 2015</td>
<td>105822</td>
<td>Depression vs no Depression</td>
<td>1.38 (1.09, 1.73)</td>
<td>(5)</td>
</tr>
<tr>
<td>Parkin et al, 2017</td>
<td>734092</td>
<td>Depression vs no Depression</td>
<td>1.19 (0.95, 1.49)</td>
<td>(7)</td>
</tr>
<tr>
<td>Ray et al, 2002</td>
<td>75649</td>
<td>Antidepressants vs no Antidepressants</td>
<td>1.04 (0.94, 1.15)</td>
<td>(9)</td>
</tr>
<tr>
<td>Parkin et al, 2003</td>
<td>263</td>
<td>Antidepressants vs no Antidepressants</td>
<td>4.90 (1.10, 22.50)</td>
<td>(12)</td>
</tr>
<tr>
<td>Lacut et al, 2007</td>
<td>1354</td>
<td>Antidepressants vs no Antidepressants</td>
<td>1.10 (0.90, 1.50)</td>
<td>(10)</td>
</tr>
<tr>
<td>Jick et al, 2008</td>
<td>3867</td>
<td>Antidepressants vs no Antidepressants</td>
<td>1.20 (0.90, 1.40)</td>
<td>(8)</td>
</tr>
<tr>
<td>Wu et al, 2013</td>
<td>13102</td>
<td>Antidepressants vs no Antidepressants</td>
<td>1.59 (1.27, 2.00)</td>
<td>(6)</td>
</tr>
<tr>
<td>Parkin et al, 2017</td>
<td>734092</td>
<td>Antidepressants vs no Antidepressants</td>
<td>1.39 (1.23, 1.56)</td>
<td>(7)</td>
</tr>
</tbody>
</table>

Abbreviation: CI: Confidence Interval, RR: Relative Risk
link between antidepressants and thromboembolic risk in order to have a definite conclusion.

Collectively, depression represents a disorder with a gradually increasing incidence and antidepressants are increasingly being prescribed\(^1\).\(^2\). Consequently, the last years have seen an increase in the interest for the impact of depression and antidepressants in patients’ quality of life. Epidemiological studies provided evidence that depression and use of antidepressants were associated with increased risk for VTE. It is still unclear whether statistical significance means also causality. Furthermore, it remains to be addressed whether the key driver for the thromboembolic event is the depression itself or the drug. Towards this direction, there is amenable need for large, long term, well-designed studies including highly characterized participants and recording the exact type of the antidepressant used, as well as the time point of the thromboembolic event in association with the start of the drug.

Before definite conclusion is drawn, it will be important for the prescribers of such compounds to consider the increased VTE risk reported. Similarly to the prescription of estrogen-containing hormone modulating therapy, providers may ask about VTE, bleeding history and family history before prescribing antidepressants in such an easy way. Applying a personalized medicine approach and weighting the benefits and risks of such a prescription would be an important step, while the results of well-designed studies are anticipated.

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22. Chung KH, Chiou HY, Chen YH. Associations between serum homocysteine levels and anxiety and depression among children and adolescents in Taiwan. Scientific Reports 2017;
Water-pipe Smoking among young healthy smokers: Immediate effects on breathing pattern, respiratory drive and mechanics of tidal breathing

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Key Words:
- Carbon Monoxide
- Respiratory Center
- Respiratory Mechanics
- Respiratory Rate
- Smoking Water Pipes

INTRODUCTION

Water-pipe smoking (WPS), typically practiced in Middle Eastern countries and perceived as less harmful than other tobacco products,1,2 has become a global trend. Increased popularity and use of the water-pipe, has been associated with increased reported cases of Carbon Monoxide (CO) poisoning,3 especially among adolescents and young adults.4 During the sessions of WPS, the high quantities of CO produced by the burning charcoal are inhaled by the user and consequently lead to increased exhaled CO.

SUMMARY

BACKGROUND: The present study assessed the immediate respiratory effects of water-pipe smoking (WPS) specifically focusing on tidal breathing examining Impulse Oscillometry (IOS), Control of Breathing (CoB) and exhaled CO (eCO) among young healthy adults.

METHODS: A cross-over study design with sample size of 50 young healthy smokers was used. All measurements were taken immediately pre and post a Control and Experimental session. Repeated analysis of variance (ANOVA) and log-transformations were used for comparisons between pre-post and sessions. Significance was set to p<0.05. RESULTS: During the Experimental session, T/TTot, T/TTtot (p<0.001), P0.1 (p=0.005) and P0.1/(VT/TI) (p=0.021) increased significantly while T/E/TTot decreased (p=0.003) post WPS. IOS parameters Z5, R5, R10, R20 and fdr all increased significantly immediately post WPS (p<0.001) as did eCO and COHb (p<0.001). CONCLUSION: A 30-minute session of WPS altered respiratory mechanics expressed by the increased large and peripheral airways resistance, control of breathing expressed by increased P0.1 and modified the tidal breathing pattern.

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Previous studies on WPS have shown it is associated with adverse respiratory and cardio-vascular outcomes. More specifically, studies on lung function, using the forced respiratory maneuvers of Spirometry and flow-volume loops, have shown respiratory mechanics alterations expressed as decreased forced expiratory flows and volumes (FEV1, FVC, PEF, FEF25-75), while WPS studies on cardiopulmonary exercise testing have shown decreased exercise capacity. Furthermore, a consistent finding among the majority of studies conducted on WPS has been increased respiratory rate (f) and increased exhaled CO (eCO).

Respiratory rate and tidal volume are determinants of minute ventilation (V'E = VT x f), while increased CO inhalation and the consequent Carboxyhaemoglobin (COHb) formation leads to hypoxia and compensatory increase in ventilation. Therefore, the above-mentioned findings are indicative of an immediate effect of WPS on the control and pattern of tidal breathing. This effect however, has not yet been systematically explored by the classical non-invasive techniques available for the study of control of breathing (CoB). While the study of tidal breathing can provide more insight into respiratory pathophysiology and clinical symptomatology by detecting subtle alterations which are not evident by conventional forced techniques, the possible impact of WPS on the mechanics of tidal breathing has not yet been addressed.

Considering the existing gap, the current study aimed for the first time, to assess the immediate effect of WPS on CoB and respiratory mechanics. Specifically targeting tidal breathing the present study examined breathing pattern analysis, mouth occlusion pressure, and Impulse Oscillometry (IOS) in young healthy smokers.

METHODS

Participants

50 young adult smokers living in Athens, Greece voluntarily participated in the study. All participants reported no significant medical history or medications. Exclusion criteria included ages under 18 or over 35 years old, any acute or chronic disease, recent infection (<4 weeks prior to study), any use of medication (<2 weeks prior to study), pregnancy/lactation, or body mass index >30 kg/m².

Study Design

An experimental, cross-over study design was applied on the aforementioned population. Each participant underwent three sessions that took place over three consecutive days in a lung function laboratory. Participants underwent each session one at a time. Participants were instructed to avoid consuming food, drinks and beverages for four hours prior to the sessions and smoking for 12 hours prior to sessions, which was confirmed with eCO measurement <7ppm. During the first visit, initial assessment including medical history and flow-volume loop were measured for inclusion. During the second day (Control) and the third day (Experimental) sessions, measurements of IOS, CoB and eCO were performed in the above-mentioned sequence, before (pre) and immediately after (post) 30 minutes of WPS.

During the Experimental session, all subjects were instructed to remain in a sitting position and smoke ad libitum for 30 minutes inside a devoted smoking area ~30 m³ using the same type of water-pipe device (16 inches), 10g of peach-flavored moasel of the same brand and the same instant-light charcoal disks (diameter=3.8cm; width=1.5cm).

For the Control session, all subjects mimicked smoking water-pipe for 30 minutes without it being lit under the above-mentioned conditions. Since there was no smoke production by the use of the water-pipe without tobacco and charcoal disks, blind control was not possible.

The ethics committee of the Hellenic Cancer Society in Athens, Greece provided ethics approval (protocol number: 561/28-1-14) for the current study. Each subject read and signed a consent form prior to study enrollment.

Measurements

Flow-volume loop

Flow-volume loop was obtained during initial assessment for inclusion criteria only and was performed in a sitting position with a nose-clip applied using a Jaeger Master Screen Spirometry system (Franklin Lake, NJ, USA) according to the American Thoracic Society/European Respiratory Society guidelines. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), Tiffeneau Index (FEV1/FVC%), peak expiratory flow (PEF) and mid-expiratory flows (FEF at 25%, 50% and 75% of exhaled FVC) were recorded.

IOS measurements

Total Impedance (Z5), Resistance at 5, 10 and 20 Hz (R5, R10, and R20, respectively), Reactance at 5, 10 and 20 Hz (X5, X10 and X20, respectively), Frequency Dependence
of Resistance ($f_{dr} = R_{5-20}$), Resonant Frequency ($f_{res}$) and Reactance Area ($AX$) were measured using the Viasys Jaeger Master Screen IOS system (Franklin Lake, NJ, USA). IOS was performed according to guidelines and included three reproducible trials with an intra-assay coefficient of variation <10%.18,19

**CoB measurements: P0.1 and Analysis of Tidal Breathing**

P0.1, $f$, VE, inspiratory time (TI), expiratory time (TE), period of the respiratory cycle (Ttot), duty cycle (TI/Ttot), tidal volume (VT), mean inspiratory and expiratory flow (VT/TI and VT/TE) were measured, while TI/TE, TE/Ttot were calculated using a Care Fusion (formerly VIASYS and Cardinal Health) body-box system (Yorba Linda, CA, USA) and according to manufacturer guidelines. In addition, respiratory impedance ($P_{0.1}/(VT/TI)$) was subsequently calculated during analysis. Each participant, in a sitting position with a nose-clip applied, was instructed to breathe quietly for ~30 seconds and then were instructed to inspire to total lung capacity. Mean values of four efforts were recorded for all above-mentioned measured parameters.20

**Exhaled Carbon Monoxide measurements**

eCO (ppm) measurements were performed using the Bedfont® Scientific Ltd. Micro+™ Smokerlyzer® (Harrietsham, Maidstone, Kent) equipment and according to manufacturer guidelines. The same device, also estimated COHb levels using the Jarvis equation21. With a nose-clip applied, participants were instructed to quietly inhale and hold their breath for approximately 15 seconds and consecutively quietly exhale for approximately 10 seconds.22

**Statistical analysis**

Continuous variables were presented with means and standard deviations (SD). Differences in the changes between pre and post in Experimental and Control sessions for all measured parameters, were evaluated using repeated measurements analysis of variance (ANOVA). Log-transformations were made for the analysis of variance in case of skewed distribution. All p-values reported were two-tailed. Statistical significance was set at 0.05 and analyses were conducted using SPSS statistical software (version 20.0)

**RESULTS**

The current sample consisted of 50 young smokers with a mean age of 23±4.2 years old, an average of 3.6 pack-year history (average smoking of 7 cigarettes per day) and had normal flow-volume loop (Table 1).

The Control session revealed no significant changes between pre and post measurements for all IOS parameters (Table 2). In the Experimental session, $Z_{5}$, $R_{5}$, $R_{10}$, $R_{20}$ and $f_{dr}$ increased significantly immediately post WPS ($p<0.001$). These mean changes were also significantly different between Experimental and Control sessions ($p<0.001$) (Table 2).

Mean changes of eCO during the Experimental session increased significantly from 3.54±2.29 ppm to 27.16±12.32 ppm ($p<0.001$) pre to post WPS and COHb also increased from 1.22±0.35 % to 4.98±1.97 % ($p<0.001$) (Table 3).

In the Control session, no significant differences were found between pre and post measurements for all CoB parameters (Table 4). In the Experimental session, TI/TE, TI/Ttot increased significantly from 0.71±0.16 to 0.77±0.17 ($p<0.001$) and 0.39±0.05 to 0.40±0.05 ($p<0.001$), respectively, and TE/Ttot decreased from 0.56±0.05 to 0.54±0.05 ($p<0.05$) post WPS. P0.1 and P0.1/(VT/TI) also increased significantly ($p<0.05$) from 0.35±0.01 to 0.39±0.15 kPa and 0.54±0.18 to 0.59±0.23 kPa s⁻¹ l⁻¹, respectively, in the Experimental session. The pre to post changes for TI/TE, TI/Ttot and P0.1/(VT/TI) in the Experimental session were found to be significantly different from those in the Control session ($p<0.05$) (Table 4).

**TABLE 1.** Mean and Standard Deviation (SD) for Demographics and Flow-volume Loop

<table>
<thead>
<tr>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/Females</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Pack-years</td>
</tr>
</tbody>
</table>

**Flow-volume loop**

| FVC | 103.3 (±10.6) |
| FEV1 | 102 (±11.9) |
| FEV1/FVC% | 84.5 (±7.5) |
| PEF | 97.5 (±12.9) |
| FEF 25%-75% | 93.7 (±27.5) |
| FEF 25% | 96.6 (±38.3) |
| FEF 50% | 95.3 (±25.5) |
| FEF75% | 99.3 (±21.8) |

Note: * – absolute frequency, BMI: body mass index, FVC: Forced vital capacity, FEV1: forced expiratory volume in the first second, FEV1/FVC%; Tiffeneau Index, PEF: peak expiratory flow, FEF at 25%, 50% and 75% of exhaled, FVC: mid-expiratory flows. All Spirometry parameters were against their % predicted values.
The current study examined for the first time, the immediate effects of a 30 minute WPS session on parameters of tidal breathing, among young healthy smokers. Evaluation of respiratory mechanics, control of breathing and eCO showed increased respiratory impedance and resistance, increased mouth occlusion pressure, modification of the tidal breathing pattern and increased exhaled CO.

<table>
<thead>
<tr>
<th>TABLE 2. Mean and Standard Deviation (SD) of changes pre to post water-pipe smoking for Impulse Oscillometry parameters in Control and Experimental sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Z5 [kPa/(L/s)]</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Experimental</td>
</tr>
<tr>
<td><strong>R5 [kPa/(L/s)]</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Experimental</td>
</tr>
<tr>
<td><strong>R10 [kPa/(L/s)]</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Experimental</td>
</tr>
<tr>
<td><strong>R20 [kPa/(L/s)]</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Experimental</td>
</tr>
<tr>
<td>fdr (R5-R20)</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Experimental</td>
</tr>
<tr>
<td><strong>X5 [kPa/(L/s)]</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Experimental</td>
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<tr>
<td><strong>X10 [kPa/(L/s)]</strong></td>
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<tr>
<td>Control</td>
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<tr>
<td>Experimental</td>
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<tr>
<td><strong>X20 [kPa/(L/s)]</strong></td>
</tr>
<tr>
<td>Control</td>
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<tr>
<td>Experimental</td>
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<tr>
<td><strong>fres (Hz)</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Experimental</td>
</tr>
<tr>
<td><strong>AX [kPa/L]</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Experimental</td>
</tr>
</tbody>
</table>

Notes: * p-value for smoking effect,
** Effects reported include differences between the groups in the degree of change (repeated measurements ANOVA),
Z5: Total Impedance, R5: Resistance at 5Hz, R10: Resistance at 10Hz, R20: Resistance at 20Hz, X5: Reactance at 5Hz, X10: Reactance at 10Hz, X20: Reactance at 20Hz, fdr: Frequency Dependence of Resistance, fres: Resonant Frequency, AX: Reactance Area.
‡ p-value based on logarithmic transformations, significant p-values indicated in bold.

DISCUSSION

The current study examined for the first time, the immediate effects of a 30 minute WPS session on parameters of tidal breathing, among young healthy smokers. Evaluation of respiratory mechanics, control of breathing and eCO showed increased respiratory impedance and resistance, increased mouth occlusion pressure, modification of the tidal breathing pattern and increased exhaled CO.

WPS exhibits some particularities and differences from other tobacco products, as the water-pipe is a complex device consisting of a vase and a tubing circuit that adds an exogenous resistance to breathing. Furthermore, the charcoal, used for burning the tobacco, produces high concentrations of CO in addition to the conventional tobacco smoke constituents.23

Current IOS findings showed increased Total Impedance and Resistance post WPS and are in line with previous stud-
ies that have examined the health effects of active and passive smoking of various other tobacco products.\textsuperscript{15,16,24–27} IOS, using an effort independent, tidal breathing manoeuvre, is considered more sensitive for the evaluation of lung mechanics compared to Spirometry.\textsuperscript{28} An increase in Z5, R5, R20 and \( f_{dr} \) is correlated with acute bronchoconstriction and reduction of airway calibre in healthy and individuals with asthma.\textsuperscript{29–31} Therefore, current IOS findings of increased total impedance and resistance, indicate that WPS irritated both large (R20) and peripheral airways (R5-R20) and led to a degree of bronchoconstriction.\textsuperscript{19}

The current study found that P0.1 was significantly increased post the Experimental session, as was the effective Inspiratory Impedance (P0.1/VT/TI), denoting an increased inspiratory load, which is in agreement with the current IOS findings of increased total respiratory impedance and resistance. The addition of inspiratory resistance to normal subjects leads to the increase of their P0.1, denoting an increased respiratory drive\textsuperscript{32} as was the case in the current study.

V.E, \( f \) and VT/TI remained unchanged after the Experimental session. However, an acute, mild modification of the breathing pattern was observed, expressed by a tendency for TE and Ttot to decrease, that became more obvious in the significantly decreased ratio TE/Ttot and the increased ratio VT/TE. Further analysis of the breathing cycle structure, showed an effect of WPS on the Timing component, expressed by the significantly increased inspiratory duty cycle (TI/Ttot), while the mean inspiratory flow (VT/TI) did not change.

Since the exogenous resistance added by the water-pipe tubing circuit did not account for any pre to post changes in the control session measurements, the increased P0.1 found in the current study could be interpreted as the respiratory system’s response to either the direct effect of CO on CoB;\textsuperscript{33} the inhalation of the mixture of irritative constituents of WPS, the direct nicotine effect on the Central Nervous System, or to a combination of the above-mentioned factors.

Regarding the eCO, the significant increase observed post WPS in the current study is in agreement with previous studies on WPS.\textsuperscript{4,23,34} CO inhalation during WPS has been shown to be ten times higher as compared to cigarette smoking.\textsuperscript{35} Moreover, the burning charcoal releases increased concentrations of CO into the environment to which both smokers and bystanders are exposed and consequently at risk for CO intoxication.\textsuperscript{35}

The underlying mechanism for CO toxicity is based on the intense chemical affinity of CO to haemoglobin (240 times higher than that of oxygen),\textsuperscript{36} that leads to the inability for cells to use oxygen, the end-result being tissue and cellular hypoxia.\textsuperscript{33} The consequent brain hypoxia has been shown to activate the central chemoreceptors, initially leading to hyperventilation that is followed by delayed hypoventilation.\textsuperscript{33} This response however, usually occurs at higher levels of COHb (>60%),\textsuperscript{33} while at concentrations <20%, only the more sensitive higher centers of the central nervous system respond presenting as cognitive and psychomotor impairment.\textsuperscript{37}

As mean eCO measurements found post WPS were 27 ppm with the estimated COHb levels in the range of 3-7%, the present study results indicate that even low COHb concentrations in the range of 5-20% are possibly associated with detectable alterations of the respiratory center output and lung mechanics. Furthermore, it highlights the advantage of examining tidal breathing and increases our understanding of how WPS affects the respiratory function, not only at the airway level by increasing airway resistance, but also and more importantly, at the level of its central regulation leading to a modification of the breathing pattern and increased respiratory drive.

### Table 3: Mean and Standard Deviation (SD) of changes pre to post water-pipe smoking for Exhaled Carbon Monoxide (eCO) and Carboxyhaemoglobin (COHb) in Control and Experimental sessions

<table>
<thead>
<tr>
<th></th>
<th>Pre Mean (SD)</th>
<th>Post Mean (SD)</th>
<th>Change Mean (SD)</th>
<th>( p^* )</th>
<th>( p^{**} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>eCO (ppm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.32 (2.41)</td>
<td>4.18 (2.38)</td>
<td>-0.14 (1.54)</td>
<td>0.909</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Experimental</td>
<td>3.54 (2.29)</td>
<td>27.16 (12.32)</td>
<td>23.62 (12.17)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>COHb (%Hb)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1.50 (0.67)</td>
<td>1.43 (0.55)</td>
<td>-0.07 (0.58)</td>
<td>0.716</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Experimental</td>
<td>1.22 (0.35)</td>
<td>4.98 (1.97)</td>
<td>3.76 (1.94)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Notes: SD – Standard deviation, \( * \) p-value for difference between pre and post; \( ** \) p-value for differences between sessions in the degree of change. All p-values reported are derived from repeated measurements ANOVA. Significant p-values indicated in bold.
### Table 4. Mean and Standard Deviation (SD) of changes pre to post water-pipe smoking for Control of breathing parameters in Control and Experimental sessions

<table>
<thead>
<tr>
<th></th>
<th>Pre Mean (SD)</th>
<th>Post Mean (SD)</th>
<th>Change Mean (SD)</th>
<th>P*</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>( f ) (breaths/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>15.30 (5.00)</td>
<td>15.48 (4.60)</td>
<td>0.18 (2.70)</td>
<td>0.665</td>
<td>0.564</td>
</tr>
<tr>
<td>Experimental</td>
<td>15.70 (4.30)</td>
<td>16.26 (4.67)</td>
<td>0.52 (3.10)</td>
<td>0.213</td>
<td></td>
</tr>
<tr>
<td>( VE ) (l/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>15.25 (4.19)</td>
<td>14.95 (3.90)</td>
<td>-0.30 (2.90)</td>
<td>0.479</td>
<td>0.147</td>
</tr>
<tr>
<td>Experimental</td>
<td>15.57 (3.87)</td>
<td>16.15 (4.19)</td>
<td>0.58 (3.10)</td>
<td>0.179</td>
<td></td>
</tr>
<tr>
<td>( TI ) (s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1.66 (0.53)</td>
<td>1.67 (0.52)</td>
<td>0.01 (0.32)</td>
<td>0.839</td>
<td>0.707</td>
</tr>
<tr>
<td>Experimental</td>
<td>1.62 (0.53)</td>
<td>1.66 (0.55)</td>
<td>0.04 (0.40)</td>
<td>0.463</td>
<td></td>
</tr>
<tr>
<td>( TE ) (s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.40 (0.91)</td>
<td>2.43 (0.92)</td>
<td>0.03 (0.41)</td>
<td>0.654</td>
<td>0.109</td>
</tr>
<tr>
<td>Experimental</td>
<td>2.34 (0.80)</td>
<td>2.22 (0.72)</td>
<td>-0.12 (0.52)</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td>( T_{tot} ) (s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.27 (1.41)</td>
<td>4.29 (1.36)</td>
<td>0.02 (0.66)</td>
<td>0.860</td>
<td>0.488</td>
</tr>
<tr>
<td>Experimental</td>
<td>4.17 (1.28)</td>
<td>4.08 (1.20)</td>
<td>-0.09 (0.88)</td>
<td>0.421</td>
<td></td>
</tr>
<tr>
<td>( TI/TE )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.72 (0.14)</td>
<td>0.72 (0.17)</td>
<td>0.00 (0.10)</td>
<td>0.888</td>
<td>0.017</td>
</tr>
<tr>
<td>Experimental</td>
<td>0.71 (0.16)</td>
<td>0.77 (0.17)</td>
<td>0.06 (0.11)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( TI/T_{tot} )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.39 (0.04)</td>
<td>0.39 (0.05)</td>
<td>0.00 (0.03)</td>
<td>1.00</td>
<td>0.012</td>
</tr>
<tr>
<td>Experimental</td>
<td>0.39 (0.05)</td>
<td>0.40 (0.05)</td>
<td>0.01 (0.03)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( TE/T_{tot} )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.55 (0.05)</td>
<td>0.56 (0.06)</td>
<td>0.01 (0.04)</td>
<td>0.525</td>
<td>0.011</td>
</tr>
<tr>
<td>Experimental</td>
<td>0.56 (0.05)</td>
<td>0.54 (0.05)</td>
<td>-0.02 (0.03)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>( VT ) (l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.97 (0.28)</td>
<td>0.99 (0.26)</td>
<td>0.02 (0.15)</td>
<td>0.605</td>
<td>0.805</td>
</tr>
<tr>
<td>Experimental</td>
<td>1.03 (0.22)</td>
<td>1.05 (0.27)</td>
<td>0.02 (0.21)</td>
<td>0.387</td>
<td></td>
</tr>
<tr>
<td>( VT/TI ) (l/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.61 (0.18)</td>
<td>0.62 (0.17)</td>
<td>0.01 (0.11)</td>
<td>0.756</td>
<td>0.715</td>
</tr>
<tr>
<td>Experimental</td>
<td>0.67 (0.17)</td>
<td>0.67 (0.17)</td>
<td>0.00 (0.13)</td>
<td>0.836</td>
<td></td>
</tr>
<tr>
<td>( VT/TE ) (l/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.44 (0.16)</td>
<td>0.45 (0.17)</td>
<td>0.01 (0.12)</td>
<td>0.670</td>
<td>0.253</td>
</tr>
<tr>
<td>Experimental</td>
<td>0.47 (0.15)</td>
<td>0.5 (0.16)</td>
<td>0.03 (0.11)</td>
<td>0.043</td>
<td></td>
</tr>
<tr>
<td>( P_{0.1} ) (kPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.32 (0.09)</td>
<td>0.33 (0.10)</td>
<td>0.01 (0.12)</td>
<td>0.763</td>
<td>0.153</td>
</tr>
<tr>
<td>Experimental</td>
<td>0.35 (0.1)</td>
<td>0.39 (0.15)</td>
<td>0.04 (0.10)</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>( P_{0.1}/(VT/TI) ) (kPa s^-1l^-1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.66 (0.17)</td>
<td>0.64 (0.17)</td>
<td>-0.02 (0.11)</td>
<td>0.469</td>
<td>0.013</td>
</tr>
<tr>
<td>Experimental</td>
<td>0.54 (0.18)</td>
<td>0.59 (0.23)</td>
<td>0.05 (0.15)</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

Note: SD: Standard Deviation,
* P-value for difference between pre and post;
** P-value for differences between sessions in the degree of change; \( f \) – Respiratory frequency,
VE: Ventilation, TI: Inspiratory time, TE: Expiratory time, T_{tot}: Period of the respiratory cycle, TI/TE: Duty cycle, VT: Tidal volume, VT/ TI: Mean inspiratory flow, VT/TE: Mean Expiratory flow, P_{0.1}: Mouth occlusion pressure, P_{0.1}/VT/TI: Inspiratory Impedance.
All p-values reported are derived from repeated measurements ANOVA. Significant p-values indicated in bold.
Study limitations included non-blind control, non-standardized puffing topography and not having addressed the possible role of nicotine on current findings.

CONCLUSION

A 30-minute session of WPS had significant immediate effects on tidal breathing mechanics and control of breathing expressed by increased respiratory impedance and resistance of central and peripheral airways, increased mouth occlusion pressure and a modification of the breathing pattern. Given the rising global trend of water-pipe smoking, these findings add to the growing amount of evidence on the harmful effects of water-pipe smoking.

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Lung cancer screening trials: 
Review of literature

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Key words: 
- Lung cancer 
- Screening 
- LDCT 
- Mortality

SUMMARY
Lung cancer is considered one of the most common causes of morbidity and mortality globally. Survival depends mainly on clinical stage of the disease, histological type of lung cancer and patient’s performance status. Implementation of a screening program among high-risk subjects might increase overall survival by increasing detection of lung cancers in early stages. In general an ideal screening program should be highly sensitive and specific, based on simple and safe examinations, cost effective and easily implemented. Low-dose computed tomography (LDCT) is currently the only proposed screening method for lung cancer. Based on the results of the National Lung Screening Trial (NLST), which was conducted in the USA and proved a 20% reduction in lung cancer specific related mortality, U.S. Preventive Services Task Force proposed official guidelines since 2014. In Europe there are no lung cancer screening recommendations/guidelines as the final results of the NELSON trial are still pending. The aim of this paper is to review the most important published trials on lung cancer screening.

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INTRODUCTION
Lung cancer is considered one of the most common causes of morbidity and mortality globally. Even though improvement has been achieved in treatment modalities (targeted agents, anti-angiogenetic factors and surgical approach with minimally invasive techniques), it remains the leading cause of cancer related death for both sexes worldwide. It is estimated that 214,000 new lung cancer cases were diagnosed in Europe in 2012, while it is anticipated that new cases would be 222,500 in the USA during 2017.

Survival depends mainly on clinical stage of the disease, histological type of lung cancer and patient’s performance status. The 5-year survival rate for non small lung cancer (NSCLC) is about 92% for stage IA, 36% for those with IIIA and is almost zero for stage IVB. On the other hand, the 5-year survival rate for small cell lung cancer (SCLC) is about 31% for localized disease,
8-19% in case of regional lymph nodes involvement and is only 2% for extended disease.4

Implementation of a screening program among high-risk subjects might increase overall survival by increasing detection of lung cancers in early stages. In general an ideal screening program should be highly sensitive and specific, based on simple and safe examinations, cost effective and easily implemented. The primary endpoint of a cancer screening program is the reduction of cancer-related mortality. Important parameters that should be carefully evaluated are: a) the number of participants needed to screen in order to prevent a lung cancer death, b) incidence and management of false positive results, c) the surgical-related morbidity/mortality of the detected cases, d) overdiagnosis (cases of early stage lung cancer that probably would not reduce survival especially among the elderly), e) anxiety and stress due to false positives and f) accessibility and cost.

In Europe there are no official lung cancer screening recommendations/guidelines. On the contrary, guidelines were published in the USA in 2014.5-12 Low-dose computed tomography (LDCT) is currently the only proposed screening method for lung cancer. Undoubtedly the most important studies are the National Lung Screening Trial (NLST), which was conducted in the USA and its results affected nearly all guidelines, and the NELSON trial in Europe. The aim of this paper is to review the most important published trials on lung cancer screening.

We searched PubMed and Medline using the keywords: “Lung cancer” AND “screening” AND “mortality” as an initial criterion and mainly randomized studies were included in the present review.

SCREENING WITH CHEST X-RAY AND SPUTUM CYTOLOGY

Mayo Lung Project: It was a randomized controlled trial (1971-76) with prolonged follow up after the end of the trial. The study population included 9,211 males who underwent: chest x-rays and sputum cytology every 4 months for 6 consecutive years (intervention group) or advised to perform annual chest x-ray and sputum cytology in local healthcare units one (control).13 After thirteen years of follow up there was no difference in lung cancer and all-cause mortality between groups.13

Memorial Sloan-Kettering study: This was also a randomized controlled trial (1974-78, USA).13 All participants were men, current smokers, >45 years, who were randomly assigned to annual chest x-ray plus sputum cytology every 4 months vs annual chest x-ray. There was no significant difference for mortality rates between groups.14

Prostate, Lung, Colorectal, Ovarian cancer screening trial (PLCO): The PLCO trial was a randomized controlled multicentred study in the USA (1993-2001).15,16 This was the largest (n=154,901) clinical trial that evaluated the role of chest x-ray as a screening tool. After thirteen years of follow up, there was no statistically significant difference for lung cancer related mortality (RR: 0.99, 95% CI: 0.91-1.07).15,16

A recent Cochrane meta-analysis exploring the role of chest x-ray showed that frequent screening with chest x-ray is accompanied with a trend for increased lung cancer related mortality (RR: 1.11).12

SCREENING WITH LDCT

National Lung Screening Trial (NLST): This was the largest, randomized, controlled clinical study that evaluated the usefulness of LDCT as a screening tool and accomplished in 33 centers in the USA.17 In this study, 53,454 participants (both sexes, age: 55-74 years, current/former smokers, ≥30 pack-years and quitted <15 years) were enrolled (8/2002 – 4/2004) and were followed up until 31/12/2009. Participants underwent annual LDCT for 3 years, whereas the control group was screened with chest x-ray. Any non-calcified nodule of ≥4mm on LDCT scans was considered positive/suspicious but no specific diagnostic/follow-up algorithm was used.17

Lung cancer related mortality was reduced by 20% in the intervention group (247 vs 309 deaths/100,000 person/year, relative reduction 20%, 95% CI: 6.8-26.7%, p=0.004). All-cause mortality decreased by 6.7% (95% CI: 1.2-13.6, p=0.02) and this was exclusively attributed to reduction of lung cancer mortality.17 Nevertheless we should mention that the main disadvantage of this trial was the high rate of positive screening tests (false positive results: 96.4% intervention and 94.5% control group). The number needed to screen in order to prevent one lung cancer related death was 320. As the initial inclusion criteria were quite arbitrary a risk-model analysis was performed. The intervention group was divided into 5 quantities according to a validated prediction model for a 5-year risk of death because of lung cancer (Q1: 0.15-0.55%, Q5:>2%).18 Parameters that were incorporated in this prediction model were: age, body-mass index, pack-years of smoking, years since smoking cessation,
### TABLE 1. Large RCTs investigating lung cancer screening with LDCT

<table>
<thead>
<tr>
<th>RCT</th>
<th>Sample size</th>
<th>Inclusion criteria</th>
<th>Control group</th>
<th>Screening interval</th>
<th>Follow up</th>
<th>Positive result for LDCT</th>
<th>Lung cancer related mortality</th>
<th>Main limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLST (2002)</td>
<td>53,454</td>
<td>both sexes, 55-74 years old, current/ former smokers ≥30 pack-years and quitted &lt;15 years</td>
<td>Chest X-ray Annual</td>
<td>5 years</td>
<td>non-calcified ≥4mm, no specific diagnostic algorithm</td>
<td>20% reduction in the LDCT group</td>
<td>High rate of false positive tests</td>
<td></td>
</tr>
<tr>
<td>I-ELCAP (1993)</td>
<td>31,567</td>
<td>both sexes, &gt;40 year-old, current/former smokers, second-hand smokers history of occupational exposure, asymptomatic</td>
<td>no comparison 7-18 months</td>
<td>40 months</td>
<td>at least 1 non-calcified solid/ partly solid nodule ≥5mm or a non-solid, non-calcified nodule ≥8mm</td>
<td>no difference between baseline and annual screening</td>
<td>no specific follow up program</td>
<td></td>
</tr>
<tr>
<td>DANTE (2001)</td>
<td>2,472</td>
<td>males, 60-75 years old, current/former smokers, ≥20 pack-years</td>
<td>Chest X-ray and sputum cytology at baseline Annual clinical review</td>
<td>4 years</td>
<td>-</td>
<td>no significant difference</td>
<td>small sample size</td>
<td></td>
</tr>
<tr>
<td>DLCST (2004)</td>
<td>4,104</td>
<td>both sexes, 50-70 year old, current/former smokers Usual care (no intervention)</td>
<td>Annual</td>
<td>10 years</td>
<td>&gt;15mm or those with rapid growth</td>
<td>No significant difference</td>
<td>overdiagnosis</td>
<td></td>
</tr>
<tr>
<td>MILD (2005)</td>
<td>4,099</td>
<td>both sexes, ≥50 year old, current/former smokers, ≥20 pack-years</td>
<td>Usual care (no intervention) Annual vs biennial</td>
<td>10 years</td>
<td>-</td>
<td>no significant difference</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>ITALUNG (2003)</td>
<td>3,206</td>
<td>both sexes, 55-69 year old, current/ ex-smokers, asymptomatic</td>
<td>Usual care (no intervention)</td>
<td>Annual</td>
<td>solid ≥8mm, significant growth, new 3-5mm</td>
<td>-</td>
<td>overdiagnosis</td>
<td></td>
</tr>
<tr>
<td>LUSI (2007)</td>
<td>4,052</td>
<td>both sexes, 50-69 year old, current/ ex-smokers, ≥25 of 15 cigarettes/day</td>
<td>Usual care (no intervention)</td>
<td>Annual</td>
<td>suspicious: ≥5mm, significant growth</td>
<td>no significant difference</td>
<td>early recall rates</td>
<td></td>
</tr>
<tr>
<td>UKLS (2011)</td>
<td>4,055</td>
<td>both sexes, 50-75 year old, &gt;5% risk according to LLP risk model usual care (no intervention) LDCT at baseline</td>
<td>10 years</td>
<td>-</td>
<td>suspicious: &gt;500mm³, part solid &gt;100 mm³</td>
<td>-</td>
<td>no mortality rate investigation</td>
<td></td>
</tr>
<tr>
<td>NELSON (2003)</td>
<td>15,822</td>
<td>both sexes, 50-75 year old, current/former smokers, &gt;15 cig./d for &gt;25 years or &gt;10 cig./d for &gt;30 years</td>
<td>Usual care (no intervention) PFTs and LDCT at baseline, LDCT after 1, 2 and 2.5 years</td>
<td>-</td>
<td>a standard protocol was developed</td>
<td>-</td>
<td>“healthy user bias”</td>
<td></td>
</tr>
</tbody>
</table>
the presence of emphysema and first-degree relative with lung cancer. It was concluded that 88% of the CT-prevented lung cancer deaths were included in the 60% of participants who constituted the high risk quintiles (Q3-Q5) and only 1% of the CT-prevented lung cancer deaths were detected within the lowest risk quintile (Q1). Concerning the cost-effectiveness, the quality-adjusted life-year gained was $81,000. However the anticipated health care cost in Europe would be considerably lower.

International Early Lung Cancer Action Program (I-ELCAP): The I-ELCAP program was a large scale (n=31,567), multi-centered, international, uncontrolled study. All participants were asymptomatic, of both sexes, >40 year-old, current/former smokers (83%), second-hand smokers (11%), and/or had history of occupational exposure to asbestos, beryllium, uranium or radon (5%). A baseline positive result was defined as either the presence of at least one non-calcified solid/partly solid nodule ≥5mm or a non-solid, non-calcified nodule ≥8mm. Thirteen percent had positive LDCT scan at baseline evaluation (1993-2005) and 405 of them (9.7%) were diagnosed with lung cancer. The number of participants with stage I was 412 (85%), while 375 underwent surgical resection with an estimated 10-year survival rate of 92% in case of resection during the first month after diagnosis. It was actually the precursor for design and implementation of NLST.

Detection And Screening Of Early Lung Cancer By Novel Imaging Technology And Molecular Essays (Dante Trial): This was a randomized controlled trial that performed in Italy among 2,472 males (60-75 year old), current/former smokers with ≥20 pack-years. Until January 2008 there was a median follow-up of 33.7 months. Even though the number of clinical stage I cases was significantly higher in the LDCT group (33 vs 12, p=0.004), there was no difference in lung cancer-specific mortality between the two groups (1.6 versus 1.7%, p=0.84). Undoubtedly an important limitation was the small sample size. A more recent publication of this trial (8.35 years median follow-up) showed no significant difference in lung cancer related mortality.

Danish Lung Cancer Screening Trial (DLCST): The DLCST trial was a randomized, multicenter, national, government funded trial. A total number of 4,104 individuals (2,267 men) were enrolled in the clinical trial (10/2004-3/2006). They were current/former (abstinence <10 years, quit after the age of 50) smokers aged 50-70 years. Nodules >15mm or those with rapid growth (volume increase >25% during a 3 months period or/and volume doubling time <400 days) were subjected to further diagnostic workup. After an average follow-up of 9.5 years lung cancer-related mortality (HR: 1.03, 95% CI: 0.66–1.6; p = 0.888) as well as overall mortality had no significant difference between the two groups. Lung cancer incidence was higher in the LDCT group which was attributed to higher number of early stage cases (stage I and II: 54 versus 10, p<0.001). An interesting finding was that smoking prevalence was reduced in both groups whereas psycho-social consequences were noted to be increased (better psycho-social profile in the LDCT group).

Multi-Centric Italian Lung Detection Trial (MILD): This was a randomized, controlled, multicentered trial that included 3,206 asymptomatic subjects. Participants were randomized into: annual screening, biennial and a control group. There was no difference in lung cancer related mortality rates among groups. There was also no difference between annual and biennial LDCT screening regarding specificity, sensitivity, positive and negative predictive values for lung cancer diagnosis after 7 years of follow-up.

Italian Lung Cancer CT Screening Trial (ITALUNG): It was a randomized controlled, multicentered trial that included 3,005 asymptomatic subjects. Lung nodules were detected among 30.3% at baseline and after 4 annual screening rounds 23 out of 35 lung cancers were diagnosed at clinical stage I.

German Lung Cancer Screening Interventional Study (LUSI): This is an ongoing randomized, controlled trial with 4,052 participants. Until 4/2014 fifty-eight lung cancer cases have been diagnosed after 4 completed rounds of LDCT. There was no difference between groups regarding overall mortality 3 years after randomization.

United Kingdom Lung Cancer Screening Trial (UKLS): It is a randomized controlled trial planning to assess 30,000 individuals in order to evaluate LDCT effectiveness in a high-risk population. In total, 4,055 individuals were randomized in the pilot trial. The recruitment criteria were: age: 50-75 years and >5% risk of developing lung cancer according to a risk prediction model (Liverpool Lung Project (LLP) risk model v2, available on http://www.MylungRisk.org/). In addition, a nodule management protocol was developed for the classification of CT findings (size, composition and VDT of nodules).

Eventually 42 participants (2.1%) were diagnosed with lung cancer (34 at baseline and 8 at the 12-month scan), 85.7% were classified as clinical stage I or II and 83.3% underwent surgical resection. Moreover, the baseline estimate for the incremental cost-effectiveness ratio rela-
tive to symptomatic presentation was £8,466 per quality adjusted life year (QALY).

**Dutch Belgian Randomized Lung Cancer Screening Trial (NELSON):** It is the largest European randomized controlled trial. The primary endpoint is the reduction in lung cancer mortality and its final results are expected within the next few years.\(^\text{40}\) With a statistical power of 80% to prove a reduction in lung cancer related mortality of 20-25% after 10 years of follow-up, 17,300-27,900 participants should be enrolled.\(^\text{40}\) During the recruitment phase (12/2003-7/2006) 15,822 people of both sexes aged 50-75 years, current/former smokers (≤10 years of cessation, >15 cig./d for >25 years or >10 cig./d for >30 years) were randomized. Subjects of the intervention group underwent LDCT at baseline (first round), after 1 year (2nd), 2 years (3rd) and 2.5 years (4th, 5.5 years after baseline). PFTs were offered to the intervention group. All participants also received a quality of life questionnaire.\(^\text{40-49}\)

A standard protocol was developed for the evaluation of the nodules detected in CT scan based its volume, composition and growth rate.\(^\text{41}\) Results from the first three screening rounds showed that 209 participants were diagnosed with lung cancer: 70.8% of them were at clinical stage I and 51.2% of them were adenocarcinomas.\(^\text{42}\) After the first three rounds plus an additional 2 years of follow-up the sensitivity was 84.6% with a negative predictive value of 99.8% (196 screen-detected and 35 interval cancers).\(^\text{43}\) Interval cancers were generally at a more advanced stage and most of them were SCLC.\(^\text{43}\) Recent results reported that the interval cancers between the 3rd and 4th screenings were significantly more than those in the intervals of previous rounds (28 versus 5 and 28 versus 19).\(^\text{44}\)

New solid nodules were detected among 11% of the participants after two screening rounds, 4% of these were malignant and correlated with nodule’s volume (<27 mm³: low risk, 27-206 mm³: medium, >206 mm³: high).\(^\text{45}\)

Even though the “healthy user bias” was noted (eligible non responders were younger, more often former smokers and had higher level of physical exercise and education) it seems unlikely that these small differences will influence the generalizability of the NELSON trial.\(^\text{46}\) Importantly smoking abstinence was more common among controls even though they had a longer prolonged abstinence rate compared to intervention (LDCT) group.\(^\text{47}\) Even though increase in lung cancer specific distress was noted in participants who received an indeterminate baseline result there was no long term impact on health-related quality of life.\(^\text{48,49}\)

**CRITICAL ANALYSIS**

During the year 2014 the U.S. Preventive Services Task Force (USPSTF) used modeling studies to predict the benefits and harms of screening programs that use different screening intervals, age groups and smoking histories.\(^\text{5,6,11}\) According to their recommendation statement, LDCT lung cancer screening should be annually performed by adults between the age of 55 and 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued if a person has not smoked for 15 years or develops a health problem that significantly limits life’s expectancy or the ability to undergo treatment or is unwilling to receive cancer treatment. Centers of Medicare and Medicaid Services organisation (CMS) cover the expenses of lung cancer screening with LDCT once per year for people aged 55-77 years, who are current or former smokers (≥30 pack-years) who have quit smoking within the last 15 years.\(^\text{7}\)

Furthermore every organization affiliated with diagnosis and treatment of lung cancer in the USA (American Association for Thoracic Surgery\(^\text{10}\), American Cancer Society\(^\text{9,11}\), National Comprehensive Cancer Network\(^\text{50}\)) have incorporated the results of NLST trial in their recommendations. The same criteria are suggested from the Canadian Task Force on Preventive Health Care.\(^\text{51}\) Recently the European Society of Radiology in cooperation with the European Respiratory Society recommend that lung cancer screening should take place within a clinical trial or in routine clinical practice at certified multidisciplinary medical centres.\(^\text{52,53}\)

In 2017, a European Union position statement on lung cancer screening was published.\(^\text{54}\) It presented the current status of lung cancer screening, emphasizing on the outcomes of several lung cancer screening trials. According to the statement, It is crucial that a number of specific actions need to be adopted before the implementation of low-dose CT screening (eg risk stratification approach, detailed offer of information on the benefits and harms of screening, a smoking cessation program, use of semi-automatically measured volume and volume-doubling time for solid nodules, different protocols and multidisciplinary approach to nodules’ management).

**CONCLUSION**

Lung cancer is a major public health problem worldwide. As the survival rates at earlier stages are higher,
the implementation of a screening program is highly necessary in order to reduce mortality rate.

The largest and most longstanding trials are the NLST trial for the United States, which showed a reduction of 20% in lung cancer related mortality and the NELSON trial for the European Union. Results of the NELSON trial are still pending in order to provide the scientific basis for the development of a lung cancer screening program across Europe. An effective screening program should be easily accessible, sensitive, specific, cost-effective, with low percentages of false positive and false negative results.

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Logical Fallacies in the ICU

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SUMMARY
Medical reasoning, the method of solving clinical problems, is the foundation of all the decisions physicians make, aiming to understand the illness and arrive at the appropriate therapeutic decisions. Interaction among different physicians and exchange of opinions may often lead to disagreement with respect to the diagnostic or treatment priorities. The quality of the arguments presented comes in focus, making it necessary to be aware of and familiar with the logical fallacies, i.e. flawed ways of reasoning. Some of the more commonly encountered types of fallacies are described, along with examples to help clarify their substance. Logical fallacies can have a toxic effect, leading to improper medical decisions. Safeguarding medical reasoning is of paramount importance; adopting a critical method, actively seeking to identify erroneous arguments by asking appropriate questions is presented. Awareness of the presence and the features of flawed reasoning is a profoundly important skill for all physicians, an integral part of our ability to process clinical information efficiently and correctly. Pneumon 2018, 31(3):167-173.

INTRODUCTION
Routine medical practice is based mainly on intellectual procedures, including the search for facts and clues, in order to arrive at correct decisions regarding the management of our patients' clinical problems. This process comprises the collection of data from the patient's medical history, physical examination and the appropriate laboratory and imaging examinations. Understanding the pathophysiology, reaching the correct diagnosis and developing a treatment plan are the ultimate goals of this endeavour.

The method of approaching and solving clinical problems is what we call medical reasoning. This term signifies a qualitative investigation that studies the cognitive and mental procedures leading to therapeutic decisions¹.

Additionally, the significance of the interaction among the different physicians involved in a given medical case should not be disregarded, for it plays a major role in the shaping of diagnostic and therapeutic decisions,
since each of them brings to the case his/her own particular medical experiences, knowledge (especially when different medical specialties are involved), judgment, philosophy and mentality. Consequently, the investigation and related discussion of a given medical case may lead to disagreement with respect to both the most probable working hypothesis and the diagnostic or treatment priorities. The resolution of such conflicting situations inevitably includes the use of arguments and comparisons aiming to draw valid, reasonable conclusions upon which to base the medical decisions.

At this point, attention should be focused on the quality of the arguments presented in order to ensure the correctness and validity of the ensuing conclusions. And this is the main reason why one should be aware of and familiar with what are known as logical fallacies.

But what is a logical fallacy? In short, it is a flawed argument, a false, erroneous way of reasoning. Why is recognizing logical fallacies important? Because they are dangerous. They are often difficult to detect in the course of a discussion, subtly infecting the process of argumentation, with misleading results. Their persuasiveness, their success, is due to failure to recognize and understand the structural flaws, unsound quality or inaccuracies that characterize them. Logical fallacies have been aptly likened to magic tricks or visual illusions.

A list of all the logical fallacies that have been described would be quite lengthy, numbering in the hundreds. For this presentation, we shall settle for describing some of the more commonly encountered types, along with some realistic examples that might come up in routine medical discussions to help illustrate and further clarify the nature of the fallacy described.

**LOGICAL FALLACIES: TYPES, DEFINITIONS, EXAMPLES**

**Ad hoc fallacy:**
Latin phrase meaning “for this (purpose)”. This refers to an argument invoked when the facts appear to reject a hypothesis. The result is an explanation that lacks coherence and appears to be valid solely for a specific case, so that generalization of the argument’s validity is impossible.

*Example:*
- In the end, it was the inhaled amikacin that cured the patient from the respiratory infection caused by a multi-drug-resistant Acinetobacter.
- But its use in other patients with the same strain was not as effective.
- Surely that has nothing to do with the antibiotic; the drug must have been incorrectly nebulized.
- An ad hoc hypothesis is not necessarily false, but one must be wary when such arguments arise in a discussion.

**Ad hominem fallacy:**
This is essentially a verbal assault on the person making the argument, in order to undermine that person’s credibility and, as a consequence, his arguments. In effect it is an attempt to reject a hypothesis on the basis of presumed shortcomings or weaknesses in the character, motives or capabilities of the person who supports the hypothesis facts rather than of facts disproving it.

*Example:*
- Doctor X maintains that we should administer corticosteroids to all patients in severe septic shock under high doses of vasopressors.
- Our colleague, Doctor X, is too young and inexperienced; we could do without his advice.

**Appeal to authority:**
This describes using a person’s position, office or general standing to automatically validate and admit a proposition.

*Example:*
- Professor X holds that the use of non-invasive ventilation has no place in the management of ARDS; this, therefore, is the approach we should adopt.
- Any reasonable scientist should accept a conclusion when it is sufficiently supported by evidence. The appeal to authority fallacy, however, leads to the opposite result; that is, considering a proposition to be true simply on the grounds of its being endorsed by an authority. One should always bear in mind that even authorities may be misled.

**Appeal to fear:**
With this logical fallacy there is an attempt to exploit the emotion of fear, not rooted in reason, as a means of influencing the judgement of others, forcing them towards a certain decision regardless of the evidence.

*Example:*
- If you choose not to administer triple antibiotic coverage for this patient with severe and extensive burns, you will be held responsible for any infectious complications that might eventually arise.
- In this example, the use of triple antibiotic coverage might be considered to be a valid choice. Nevertheless, fear of possible complications and – particularly – of the risk of being held accountable for those complications,
should not form the rational basis of acceptance of our choice.

**Appeal to possibility:**

This is the fallacy of adopting a conclusion, relying not on the existing evidence but on the possibility that something is true. The trap to be avoided here, which requires special attention, is to not confuse the possibility of a phenomenon's happening with the probability that it will happen.

*Example:*

- We have decided not to place central venous catheters in the subclavian veins of our ICU patients, because we want to avoid the risk of causing iatrogenic pneumothorax. In this case, it must be stressed that causing iatrogenic pneumothorax is certainly possible, but the probability of its occurring depends on various factors, including experience, anatomical abnormalities, etc.

**Appeal to tradition (argumentum ad antiquitatem):**

This describes misleading reasoning that arises from the acceptance that appealing to the ancient origin or historical pedigree of a proposition (that has been established as “tradition”), automatically justifies and validates the correctness of the proposition in question. Put more simply: “this is true, because we have always believed it to be true”.

*Example:*

- I have no intention of stopping the use of somatostatin on patients suffering from acute pancreatitis. I consider it to be a very reasonable choice. After all, it has been standard practice in our department for many years and we’ve been quite satisfied with the results we’ve had.

The fallacy illustrated above contains two errors. On the one hand it presumes that the “traditional” premise is correctly established, having been adequately supported by evidence since it was first accepted – without considering the possibility of methodological errors or inaccuracies. On the other, it considers that the conditions justifying the adoption of the “traditional” proposition are eternal and unchanging, an assumption that could very well be wrong.

**Appeal to common belief:**

Also known as ‘appeal to the masses’, ‘appeal to the majority’ or ‘social conformance’. Appealing to common belief is nothing more than an attempt to validate the correctness of a claim based on the fact that it is held to be true by many, or even most, people.

*Example:*

- In the hospital where I worked before, most colleagues considered measuring CVP as a necessary parameter to assess for guiding the administration of fluids in all our patients.

**Argument from ignorance:**

when it is asserted that a proposition is valid merely because it has not yet been proven false (or the person who supports the proposition has no knowledge of evidence disproving it).

*Example:*

- Measuring gastric residual volumes is indispensable in order to manage the administration of enteral feeding in critically ill patients. When these volumes exceed 200mL, the administration should be stopped.
- Are you sure? A gastroenterologist colleague of mine told me that even greater residual volumes can be well tolerated; he proposed that we carry on with the feeding, maybe with the addition of metoclopramide.
- To my knowledge, there are no studies supporting this approach. Therefore, I see no reason to change our routine.

In science, the validity of a proposition should be based on the positive evidence presented, not on the absence of facts that disprove it. A very useful quote by Carl Sagan comes to mind here: “Absence of evidence is not evidence of absence”.

**Begging the Question:**

Also known as a ‘vicious circle’, or ‘circular reasoning’, this fallacy is a form of tautology where the validity of the conclusion is already accepted in the premises of a proposition.

*Example:*

- I view any discussion concerning the limiting of therapy as morally wrong, that is why I do not accept it.

The tautology in our example may be schematized as follows:

  * The limitation of therapy is morally wrong (premise)
  * I reject this choice because it is wrong

"Begging the question" is an *informal fallacy*, which means that there is no problem with the rational validity of the argument; rather, the argument is unpersuasive because its content is ambiguous, poorly supported, or of bad quality. In this specific case the person simply concludes the correctness of what is posited to be true.
Post hoc ergo propter hoc (after this therefore because of this):
This is a logical fallacy similar to the one just described (cum hoc ergo propter hoc), but which presumes that if event A is followed by event B, then the only explanation is that A was the cause of B.
Example:
\[\text{\bullet The administration of echinocandins in this patient has been a very successful choice. Fever has subsided, along with the rest of the septic manifestations, in less than 48 hours.}\]
\[\text{\bullet Well, it seems so, but how can we be certain of it? I mean, there are no confirming cultures so far. Surely we should not dismiss other plausible explanations.}\]
\[\text{\bullet The chronological correlation suffices for me. I am convinced it was a fungal infection.}\]

With regard to both Post hoc and Cum hoc arguments, it must be stressed that correlation does not always imply causation.

False dilemma (false dichotomy):
This is a kind of informal fallacy, formulated in such a way as to present only two (or a limited number of) alternatives, thus obscuring the fact that there may be at least one more and possibly a wide spectrum of additional alternatives to be considered.
Example:
\[\text{\bullet Ogilvie's syndrome, also referred to as acute colonic pseudo-obstruction, is a very severe condition. If the administration of neostigmine is not effective in relieving the symptoms, then the only choice would be to immediately take the patient to the operating room. Otherwise, there is a very high risk of the patient's developing caecal perforation and peritonitis.}\]

This example fails to acknowledge the existence of alternative treatments to neostigmine and surgery, e.g. correcting electrolyte disturbances, withdrawal of drugs that may induce the syndrome, or colonoscopic decompression. It should be noted, however, that although more alternatives may exist in ideal conditions, these additional choices are in practice useless when they are not readily available in a given situation (non-applicable due for example to absence of gastroenterologist, lack of appropriate instruments, etc.), in which case the choices are indeed limited and the argument is not faulty.

Straw man:
In this kind of fallacy the opposing proposition is distorted, for example through exaggeration or misrepresentation of the facts or arguments supporting it.
Example:
\[\text{\bullet Prone positioning holds a very important place in managing hypoxemia and lung protection in ARDS patients.}\]
\[\text{\bullet So, if I understand the matter correctly, our colleague here wishes to persuade me that all patients suffering from ARDS should be managed with prone positioning, or else the outcome could be detrimental. Well, no, I do not accept this!}\]

The ‘straw man’ argument in this case is a distorted proposition that appears to state that all ARDS patients should be treated with prone positioning. Thus, the manipulated thesis aims to replace the original one, rendering it more vulnerable to criticism and rejection.

Special pleading:
This is the attempt to defend a hypothesis and neutralize the rival arguments by appealing to the need for very specialized information, or “superior” knowledge in order to comprehend the hypothesis presented. In this fallacy, the point is to maintain that there are exceptional facts, which are hard to verify, that justify a hypothesis.
Example:
\[\text{\bullet I am convinced that the development of multi-organ failure that complicates septic situations largely depends on microthrombosis. That is why I advocate the use of drotrecogin alfa in severe sepsis.}\]
\[\text{\bullet But, as you know, the Cochrane review looking into this matter concluded that there is hardly any benefit.}\]
\[\text{\bullet I question the way the review was designed and presented. I believe that we have not fully comprehended the way this substance operates. But it is still a valuable drug in many cases.}\]

It is evident from our example that ‘special pleading’ serves to mislead and avoid addressing the arguments opposing a hypothesis in a rational manner.

Equivocation:
This is a logical fallacy that is present when a word or a term with more than one meaning is used ambiguously, thus leading to incorrect or inaccurate conclusions.
Example:
\[\text{\bullet I think that the significance attributed to the so-called bacterial translocation and its importance in the emergence and progress of sepsis and multi-organ dysfunction is not convincing. Anyway, it’s merely}\]
a theory.

The error in the example above is due to the ambiguity of the word \textit{theory}. It is common in everyday conversation to use it as a synonym for the word \textit{hypothesis}. In science, though, the word \textit{theory} is defined as a well-substantiated explanation of a phenomenon of the natural, with evidence acquired through the scientific method (observation, experimentation, repetitiveness, ability to formulate predictions and confirmation of these predictions).

An interesting related fallacy that is also worth mentioning is the \textit{accent fallacy (fallacy of prosody)}, when the sense of a phrase depends on where in a sentence the stress or emphasis is placed.

\textbf{Example:}

1. Measuring the dimensions of the inferior vena cava is \textbf{considered} significant in assessing the adequacy of the intravascular volume.
2. Measuring the dimensions of the inferior vena cava is \textbf{considered} to be \textbf{significant} in assessing the adequacy of the intravascular volume.

\section*{DISCUSSION}

As can be seen, the term \textit{medical reasoning} refers to the cognitive procedure leading to medical decision-making.

Proper application of medical reasoning in order to draw correct conclusions as to the diagnosis and treatment of patients requires a combination of data (history, physical examination, laboratory results) and medical knowledge (bibliography, research), which physicians use to try to interpret the pathology and determine the proper course of action to manage the problem.

The spectrum of interest in this field is wide, extending even to artificial intelligence applications. It is well worth considering the theoretical model proposed by Ledley and Lusted (1959)\textsuperscript{4}, who describe two stages of medical reasoning: a) hypothesis generation and b) hypothesis assessment. More specifically, analysing the method of medical reasoning, the authors discern the following four components:

- Information and data collection from the patient's history, physical examination and laboratory results
- Filtration and evaluation of the information collected and arrangement in order of significance from major to minor importance
- Compiling a mental list containing probable diseases, the signs and symptoms of which can adequately explain the available data
- Systematic analytical effort to limit the spectrum of differential diagnoses by eliminating the less likely causes, aiming to establish the identity of the disorder

We all know that the diagnostic process is not a dry, impersonal affair, a matter of pure calculation. The “feeling” a physician gets during his evaluation of the information and the data is frequently mentioned. This medical “feeling” appears to be beyond typical logical analysis, referring largely to the physician's accumulated experience, as well as to assessment of the credibility, the particular impact, the “specific weight” of every aspect of the information received (be it from the patient, his/her environment or from the various medical examinations).

Medical experience plays no small role: Patel et al. (2002) have demonstrated the superiority of experienced physicians over their younger colleagues, particularly in regard to narrowing down the range of probable differential diagnoses; this advantage has been attributed to a more efficient, sophisticated approach deriving from a “sharper” evaluation of the information. The result is a more effective selection and highlighting of the most essential data, while simultaneously downplaying the less relevant facts.

Experience, the in-depth understanding of a subject, also influences the method of approaching and investigating clinical problems in another way. In their 1981 paper, Chi et al.\textsuperscript{6} showed that those less experienced in a field tend to focus on the more superficial aspects of a matter. Experienced individuals, by contrast, direct their attention to the deep structure, trying to perceive the fundamental architecture and principles behind a phenomenon (e.g. laws of physics, principles of physiology) and the changes or disorders that may explain both the onset and the course of a problem.

A detailed and comprehensive analysis of medical reasoning and the diagnostic process is an extensive and very interesting subject, but one which is beyond the scope of the present study. Our interest here is focused on a careful scrutiny of the structure of an argument or proposition in order to detect potential rational flaws or misleading elements.

Everyday medical practice involves, on the one hand, contact with the patient, gathering the relevant information and evaluating it. On the other hand, doctors routinely discuss the diagnostic challenges and various possible therapeutic choices with colleagues in the same or another medical field. This interaction between scientists of
different specialties, background knowledge, individual expertise and level of experience is extremely useful. It serves to enrich the conversation, analyse and re-evaluate the facts, distinguish the essential from the secondary. In this way, the spectrum of differential diagnoses may be narrowed down, more accurate hypotheses may be formulated, and physicians may be helped to find more appropriate (or cost-effective) means to confirm or reject the hypotheses; thus, there is a higher probability of arriving at correct medical decisions, to the ultimate benefit of the patient. In other words, the strategy and the medical plan are worked out through dialogue and exchange of views among physicians of varied knowledge and experience.

Discussion constitutes a valuable tool in the medical arsenal that, under the proper conditions, acts as a positive multiplier of the efficiency of medical reasoning. Not only does the patient benefit from it, but it is also in the interest of all participants in the discussion of a medical case, since knowledge is increased and new experience is gained through a process of cross-fertilisation that extends and deepens our understanding. And it is precisely for these reasons that the quality of this process must be safeguarded.

So, what threatens the integrity and quality of the medical dialogue? Danger lurks in the form of faulty reasoning, the so-called logical fallacies, those unsound, pernicious, poor quality arguments used to support a logical position, sophisms based on questionable or false convictions that can sneak unnoticed into a discussion. They have a toxic effect, since they act to divert the attention or mislead. As a consequence, this type of argument is unable to adequately and rationally justify the conclusions desired by the person introducing the sophism. This, in turn, results in false or essentially unsubstantiated conclusions, with a strong likelihood of leading to improper decisions.

There is a wealth of resources (books - both specialized and popularized - as well as internet sites) one can explore, with extensive, comprehensive lists of the various fallacies (definitions, descriptions, examples) compiled and catalogued in a variety of ways. Of course, the sheer number of types of fallacies in those lists makes them extremely difficult to memorise, but fortunately, this is not necessary.

The key to safeguarding rational thinking and, in this context, medical reasoning from the undesired intrusion of logical fallacies lies in the adoption of a critical attitude towards all arguments presented. Sober evaluation of all separate elements in support of a proposition is imperative.

A highly recommended strategy for dealing with this challenge is to examine the rationale of a proposition by asking basic questions, with the aim of detecting the presence of sophisms. More specifically, the issues that should be addressed and clarified are:

- What are the causes and the conclusions of the reasoning process?
- Which causes are really related to the conclusion?
- Do the causes (supposed to lead to the final conclusion) offer an obvious explanation to justify the conclusion?
- Assuming the causes are true, do they support the conclusion rationally?
- Are there false or unacceptable values or beliefs? (These are the – commonly unstated but implied – principles that are considered as generally accepted, which are indispensable in defining the very essence of a conclusion: for example, the desired conclusion for a given medical case is different depending on whether we choose aggressive management and full support of a patient or opt for palliative care.)
- Are there any emotionally loaded words or phrases that might mislead?

On the other hand, adopting a permanently suspicious attitude in one’s interaction with fellow physicians is by no means desirable or helpful. In the vast majority of cases, there is no malevolent intent to deceive when these sophisms are used in an argument; rather, it reflects a sincere wish to support a specific diagnostic or therapeutic decision, of the value and correctness of which one is genuinely convinced. The fundamental common ground fellow physicians ought to agree upon is the preservation and improvement of the quality of scientific exchange and the sharing of opinion and information for the benefit of both the patients and the physicians themselves.

**CONCLUSION**

The preservation of a good quality medical reasoning and discussion depends, to a great extent, on the toxic risk posed by the unrecognized intrusion of false or unsound arguments: logical fallacies. We regard awareness of the presence and the features of this flawed reasoning as a profoundly important skill for all physicians, an integral part of our ability to process clinical information. A list of every type of logical fallacy would be very extensive. Our aim has been to present some of the most commonly encountered fallacies in critical care routine. Additionally, we strived to illustrate the form the fallacies may assume through the use of simplified examples.
It is obviously impossible, from a practical point of view, to memorize all the different names of the fallacies; fortunately this is not necessary. It is far more useful to adopt a healthy, carefully critical stance. Seeking the answers to appropriately formulated questions may decisively assist doctors to filter the arguments, assess their relevance, quality and validity, and to detect the flaws in the fabric of a logically constructed proposition. Identification of the error allows for more accurate conclusions and safer decisions. It also enables us to reject misleading sophisms, even if we do not know their official name.

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IC, DL participated in the writing of the manuscript. VP, IP, drafted the final version of the manuscript. All authors read and approved the final manuscript.

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The Th2/Th17 pathway in asthma and the relevant clinical significance

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- Biomarkers
- Treatment

Summary
Asthma is a heterogeneous chronic disease of the airways, characterized by different phenotypes. The principal pathophysiological pathway appears to be Th2 dependent eosinophilic inflammation mainly produced by T helper 2 (Th2) cells. More recently epithelial innate lymphoid cells (ILC2) cell have been implicated as another source of Th2 cytokines leading to bronchial eosinophilia without previous allergen sensitization. Another pathogenic pathway is the non-Th2 type, mediated by Th1 and especially Th17 lymphocytes, responsible for neutrophilic inflammation. Furthermore, recent studies have associated Th-17 cells with allergic inflammation and eosinophilic asthma. Ongoing clinical trials are expected to further elucidate the role of different cells in the evolution of asthmatic inflammation and also the role of established or novel potential biomarkers in routine clinical practice aiming to maximize drug efficacy in asthmatics. In the present review, we summarize the above mentioned mechanisms focusing on T-helper cell subset plasticity which led to the identification of dual positive Th2/Th17 inflammation. Pneumon 2018, 31(3):174-182.

Introduction
Asthma is a heterogeneous disease of the airways characterized by airway inflammation and bronchial hyperresponsiveness (BHR) leading to reversible airway obstruction1. This chronic disease affects many people, men and women, young and old, worldwide. It is defined by a history of respiratory symptoms (such as wheeze, shortness of breath, chest tightness and cough), which vary over time and in intensity2. The majority of asthma patients are well controlled by conventional therapies such as inhaled corticosteroids. However, about 5-10% of asthma patients have a severe and complex condition, described as “fatal or near fatal asthma”, “severe asthma”, “steroid-dependent asthma”, “steroid-insensitive asthma”, “difficult to control asthma”, “poorly controlled asthma”, “brittle asthma”, or “irreversible asthma”3.
For over 20 years, asthma has been considered a Th2-type dependent allergic disease, characterized by Th2 cells producing high levels of type 2 interleukins (ILs), such as IL-4, IL-5 and IL-13. Besides, other studies suggested that Th-1 cells producing interferon (IFN)-γ display a regulatory function in allergic asthma. Although the Th-1/Th2 mechanism provided the initial framework for asthma management, the discovery of a distinct subpopulation of CD4+ T cells that produce IL-17A, IL-17F, IL-22, TNF-α, and IL-21 led to a major revision of the Th-1/Th2 hypothesis (Figure 1). Th17 cells are differentiated and activated by several cytokines such as transforming growth factor TGFβ, IL-6 together with IL-21 and IL-23.

In addition to Th2 and Th17 cells, the heterogeneity of asthmatic patients suggests that also other factors must be involved in regulating asthma inflammation. Indeed, recent studies have implicated innate lymphoid cells (ILCs) of non-T, non-B effector cells that are antigen-nonspecific, have conserved effector cell functions and play crucial roles in tissue homeostasis, repair and remodeling and in innate immunity to pathogenic and nonpathogenic microorganisms. ILCs are classified into three categories (Type 1, Type 2 and Type 3 ILCs) depending on their ability to produce Th1, Th2 and Th17 cell-associated cytokines. In specific, ILC type 2 (ILC2) have been associated with asthma by producing a broad array of cytokines, including IL-5, IL-13 and IL-17.

Asthma was initially categorized in terms of ‘allergic’ or “nonallergic” asthma. A distinction was then made when sputum became available between eosinophilic and non-eosinophilic asthma. The last decade, a global approach for the understanding of asthma pathogenesis has introduced the concept of phenotypes as a grouping of clinical/physiologic characteristics, triggering factors and inflammatory components. A new approach includes the addition of genetic or blood biomarker for the classification of disease entities within the asthma syndrome which led to the introduction of the term endotype. Indeed, asthma endotyping has shed light into key pathogenic mechanisms for this complex disorder.

Recent discoveries revealed possible subgroups of Th2 high asthma that differ in terms of both the presence of underlying allergy and the potential source of type 2 cytokines. The current concept involves Th2-high asthma, eosinophilic, characterized by high levels of type 2 interleukins (ILs), and involves type 2 helper T cells (Th2 cells), mast cells, basophils, B cells and ILC2s. The fact that ILC2 produce Th2 cytokines could explain severe eosinophilic inflammation, when classical Th2 mediated allergy is absent, which is further supported in other studies.

On the other hand lays Th2-low/Non-Type 2 as non eosinophilic asthma, where Th17 cells are involved (IL-17A, IL-23, IL-22, IL-6), mostly characterized by neutrophilic inflammation. An interesting issue for Th2 and Th17 cells is the qualitative difference concerning their response to glucocorticoid treatment, as IL-17 production was shown to be less susceptible to inhibition by glucocorticoids when compared to IL-4 and IL-5 production.

According to recent literature possible endotypes associated with eosinophilic phenotypes include, early onset allergic asthma with or without obesity, aspirin sensitive asthma and late onset eosinophilic asthma, exacerbation prone asthma, and exercise induced asthma, whereas those associated with non-eosinophilic asthma and for which the pathobiologic pathways are not yet defined, include those patients with obesity-related late onset asthma, asthma with fixed airflow obstruction and very little inflammation (paucigranulocytic), and asthma associated with neutrophilia.

**BIOMARKERS IN ASTHMA**

A biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator of...
normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention\textsuperscript{9}. Cytokines play a significant role in the pathogenesis and chronic inflammation of the airways in asthma and therefore, interleukins as biomarkers could identify endotypes and subtypes of asthma, reflecting the predominant pathophysiological mechanism\textsuperscript{10}. The use of biomarkers can potentially help avoid unnecessary morbidity from high-dose corticosteroid therapy, and allow the most appropriate and cost-effective use of targeted therapies\textsuperscript{14}. As cytokines include markers of inflammation, several studies have been trying to identify molecular endotypes based on serum cytokine profile\textsuperscript{15}. However, the persistent airway inflammation in asthma is caused by a large variety of cytokines that recruit, activate and perpetuate the inflammatory cells in the asthmatic airways. As a result, several attempts to inhibit inflammatory cytokines in asthma with blocking antibodies have shown poor results so far and besides studies of targeted therapy in non-phenotyped asthma did not show profound or even any efficacy\textsuperscript{16}. Furthermore, it is a fact that there is no consensus how to best identify asthma endotypes and what therapy to use for a given endotype. Apart from cytokine profile, the use of blood eosinophils can facilitate individualized treatment and management of asthma.

Th2-specific biomarkers identified so far include sputum/blood eosinophils, total serum IgE, the fraction of exhaled nitric oxide (FeNO) and bronchial epithelium-derived proteins such as periostin and DPP4\textsuperscript{11}. The first biomarker proposed to predict corticosteroid response was the eosinophil count in sputum and blood\textsuperscript{17}. Furthermore, total serum IgE is used specifically to identify allergic asthma phenotype\textsuperscript{2}. However, IgE has a low sensitivity and correlates poorly with eosinophilic inflammation\textsuperscript{18}. FeNO is also a biomarker of Th2 inflammation\textsuperscript{19} and is suggested to be used as a predictor of steroid responsiveness more consistently than other parameters\textsuperscript{20}. According to recent literature, in patients with mild to severe asthma, blood eosinophils have the highest accuracy in the identification of sputum eosinophilia when compared to serum periostin and exhaled nitric oxide (FeNO)\textsuperscript{11}. Indeed, serum periostin, exhaled nitric oxide and blood eosinophil counts are the most promising biomarkers until now that could identify patients most likely to derive benefit from biologic agents targeting IgE, IL-5 and IL-4/13\textsuperscript{22}.

The combined evaluation of FeNO and peripheral blood eosinophil counts represent two significant biomarkers of asthma, comparable to sputum eosinophil count and are often used to distinguish asthma phenotypes and even identify responders to inhaled corticosteroid treatment\textsuperscript{23}. An count of >400 eosinophils/μL is associated with more severe asthma\textsuperscript{24}. Concerning the non Th2 pathway biomarkers, data are limited compared to Th2 type. Sputum neutrophils, mixed granulocytic and paucigranulocytic patterns include the most commonly used biomarkers\textsuperscript{25}.

Th2 cytokines

Th2 cytokines (IL-4, IL-5, IL-9, IL-10, and IL-13) have a substantial effect on the pathogenesis of atopic diseases\textsuperscript{26}. It is currently suggested that apart from Th2 cells, ILC2s are also responsible for the production of the majority of Th2 cytokines in the airway\textsuperscript{27}.

IL-4/IL-13

Th2 cytokines IL-4 and IL-13 share significant pathways and many biological activities concerning asthma. In specific, they play an important role in the identification of the presence of eosinophilic inflammation and also are key factors in IgE synthesis by B cells, mucus production, bronchial fibrosis and airway hyperresponsiveness in asthma\textsuperscript{28,29}. There is a plethora of studies associating IL-4, IL-13 and asthma. When comparison was made between asthmatics and healthy controls, levels of IL-mRNA, protein levels in serum, bronchoalveolar lavage fluid (BAL), bronchial biopsies and exhaled breath condensate were found higher in asthmatics\textsuperscript{30-34}. Similarly in other studies, increased IL-13 mRNA and protein levels are also found in sputum, BAL and bronchial biopsies of patients with asthma when compared to controls\textsuperscript{35-37}.

Furthermore, it is well-known that single-nucleotide polymorphisms (SNP) can be used to assess genetic disorders. A recent meta-analysis showed that IL-4 C-589T and C-33T were associated with asthma in Europeans\textsuperscript{38}. As for IL-13, two SNPs, positioned at regions +2044G/A and +1923C/T have been suggested to play critical role in the development of asthma\textsuperscript{39-41}.

Anti-IL-13 and anti-IL-13/anti-IL-4 receptors targeted therapies with humanized monoclonal antibodies are currently used as add-on therapy in patients with Th2-high inflammation with uncontrolled asthma despite maximum therapy. Specific studies have shown that Th2-high and especially periostin-high groups of asthmatics with moderate-to-severe uncontrolled asthma are suggested to compose the group that could benefit from anti-IL-13 therapy\textsuperscript{42}. Anti-IL-13 biologic agents (anrukizumab, lebrikizumab and tralokinumab), are currently under clinical
evaluation to further elucidate the use of predictive Th-2 biomarkers43.

Besides, IL-4 and IL-13 share some structural similarities and they bind the IL-4Ra/IL-13Ra1 receptor complex by which the transcription factor STAT-6 is activated44. Based on this concept, biologic agent such as dupilumab that target the dual cytokines IL-4/13 may be more encouraging approach for those patients suffering from refractive difficult-to-control eosinophilic asthma. Indeed, recently Wenzel et al reported that dupilumab increased lung function and reduced severe exacerbations in patients with uncontrolled persistent asthma irrespective of baseline eosinophil count and had a favourable safety profile45. More recently, another study reported that in patients with glucocorticoid-dependent severe asthma, dupilumab treatment reduced the rate of severe exacerbations and the use of oral steroids along with increasing the FEV146. Significantly lower rates of severe asthma exacerbations, as well as better lung function and asthma control were also reported in another study in patients treated with dupilumab47.

IL-5

IL-5 is produced by CD4 + Th2 lymphocytes and ILC2 cells and, to a lesser extent, also by natural killer T (NKT) cells, mast cells, and eosinophils themselves48. Multiple studies have demonstrated the link between IL-5 and asthma as higher IL-5 mRNA levels49 and IL-5 levels in sputum50 have been associated with increasing eosinophil production or acute asthmatic exacerbations51. As for genetics, IL-5 C-746T was found to influence atopic outcomes52. Based on the above, IL-5 has been considered a suitable target for add-on biological therapies of severe eosinophilic asthma53,54. In particular, the anti-IL-5 antibodies developed, include mepolizumab and reslizumab, and the IL-5 receptor antagonist benralizumab which are evaluated for the treatment of refractory eosinophilic asthma55-57. Apart from mepolizumab and reslizumab, already FDA approved55, benralizumab has also recently obtained the approval of FDA on the basis of several successful randomized controlled trials58.

IL-17A/IL-23

A distinct subpopulation of CD4+ T cells produce Th-17 cells that by secreting IL-17, orchestrate the recruitment of neutrophil granulocytes in the lungs59. Furthermore, IL-17 contribute to the development of airway fibrosis during asthma by enhancing the production of profibrotic cytokines, proangiogenic factors, and collagen60. Besides, in vitro studies investigating the role of epithelial-mesenchymal transition (EMT) in asthma have shown IL-17 synergization with IL-4 and TGF-β promotes EMT with the expression of mesenchymal markers61,62. Th17 cells produce IL-17A, IL-17F, IL-21 and IL-22 cytokines63. IL-17A has been involved in severe asthma characterized by airway intense neutrophil infiltration and less responsive to corticosteroids59,63. Furthermore, these steroid-insensitive patients could be classified as a Th2 low phenotype of asthma7. Clinical studies have shown that levels of IL-17A is sputum, bronchoalveolar lavage fluid (BALF) and serum of asthmatic patients are significant higher in asthmatics than in healthy subjects and that these are correlated with the severity of disease64. Additionally, in a study on pre-school children with history and physical exam in favor of asthma which cannot be tested by spirometry, they concluded that IL-23 serum levels might be an auxiliary biomarker for the diagnosis of asthma65.

Recently, Fattahi et al showed that atopy is associated with lower numbers of IL-17 cells in asthmatic airways66. Current data suggest that IL-17 has also been implicated in Th2 cell-mediated eosinophilic airway inflammation in mouse models of asthma67 along with increased levels of IL-2368 or in asthmatic patients with allergy after a challenge with house dust mite69. Furthermore, recently Camargo et al reported that inhibition of IL-17 even in exacerbated asthmatic patients significantly contributed to the control of Th1/Th2/Th17 inflammation, chemokine expression, extracellular matrix remodeling, and oxidative stress in a murine experimental asthma model exacerbated by Lipopolysaccharide (LPS)70. As for genetics, a recent meta-analysis concerning the association between IL-17A polymorphisms and asthma risk suggested that the IL-17A -737C/T polymorphism provides protection against the disease, whereas the IL-17A -197G/A polymorphism does not contribute to asthma risk71. However, so far, results from clinical trials targeting IL-17 Receptor (Brodalumab) including moderate to severe asthmatics, showed no improvement in asthma outcomes. This fact could be apparently attributed to inadequate selection of patients with asthma72. More specifically, although there was no effect of brodalumab on the primary outcome (the Asthma Control Questionnaire score), researchers, based on a subgroup analysis, suggested a new phenotype including patients with high reversibility of FEV1 in response to albuterol and a new
endotype which is IL-17R-dependent. In future trials targeting IL-17 pathway, the selection of patients based on sputum neutrophilia could exclude Th2 high asthematics that are less likely to respond to an IL-17-targeted therapy.

**Dual positive Th2/Th17 cells**

Although T-helper cells were thought to be fully differentiated, expressing a master regulatory transcription factor and their development from naive CD4 cells was considered to be lineage specific, Cosmi et al demonstrated that there is great plasticity in human Th17 cells even toward the Th2 phenotype, suggesting the existence of CD4+ T cells able to produce both Th17 related (IL-17A) and Th2 (IL-4) related cytokines. Besides, several in vitro studies and animal studies suggest that T-helper cell subsets display plasticity by changing their transcription factor or by expressing multiple transcription factors.

Asthmatic patients can suffer from a predominant eosinophilic inflammation usually seen in mild-to-moderate disease, from neutrophilic inflammation in more severe disease or even mixed eosinophilic/neutrophilic inflammatory response. The underlying T cell response is predominated by Th2, Th17, or a mixed Th2/Th17 cell immune response.

A recent study showed that asthma is associated with a higher frequency of dual-positive Th2/Th17 cells in BAL fluid. They concluded that Th2/Th17 (predominant) subgroup of asthmatic patients manifested glucocorticoid resistance in vitro and also had the greatest airway obstruction and hyperreactivity compared with the Th2 (predominant) and Th2/Th17 (low) subgroups. Moreover, in experimental animal models, IL-17 has not only been involved to produce airway intense neutrophil infiltration but to exacerbate Th2 cell mediated eosinophilic airway inflammation and hyperresponsiveness.

However, in another study, Choy et al investigated the potential of Th2 cytokine suppression in promoting TH17 responses in a preclinical model of allergen-induced asthma and concluded that IL-13 and IL-17A reciprocally regulate the expression of their target pathways in the lung. In specific, IL-13 stimulation repressed the expression of the Th17 genes, with a trend for a similar repressive effect of IL-17A stimulation on Th2 genes.

Furthermore, in an effort to discover the possible mechanism of severe late-onset hypereosinophilic phenotype, ILC2 activation along with dual positive Th2/Th17 inflammation has been proposed. Besides, recent data suggest that combination therapies targeting both pathways may maximize therapeutic efficacy across a patient population comprising both Th2 and Th17 endotypes.

**CONCLUSIONS AND FUTURE PERSPECTIVES**

As new research data concerning the different T helper lymphocyte pathogenic pathways are being developed in the asthmatic inflammation cascade, new effective individualized therapies in severe asthma are urgently needed to block specific inflammatory pathways using monoclonal antibodies. The only approved therapies so far include anti-IL-5 IgG (Mepolizumab, Reslizumab, Benralizumab) for severe eosinophilic asthma and anti-IgE (Omalizumab) for the treatment of severe allergic asthma. There is none approved biomarker for Non-Type 2/Th2 low asthma. One could possibly further suggest that combination therapies targeting both pathways might maximize therapeutic efficacy across a patient population comprising both Th2 and Th17 endotypes. Clinically, the ability to identify a Th2 or Th17 high or a mixed asthma phenotype on the basis of testing blood eosinophils may facilitate the use of effective biologically targeted approaches in asthmatic patients. The fact that analyzing the cytokine pattern in serum samples does not give us information on the source of the assessed cytokine may reflect the significance of local environment like lung tissues or intracellular molecular methods in analyzing the cytokine levels. But meanwhile, the feasibility of serum sampling as a noninvasive method to analyze cytokine levels has directed the interests toward noninvasive methods rather than invasive ones.
ΠΕΡΙΛΗΨΗ
Το μονοπάτι Th2/Th17 στο άσθμα και η κλινική του σημασία
Καλλιόπη Δόμβρη1, Γεώργιος Τζημαγιώργης2, Δέσποινα Παπακώστα1
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Θεσσαλονίκης
Το άσθμα είναι μια ετερογενής χρόνια νόσος των αεραγωγών, που χαρακτηρίζεται από διαφορετικούς
φαινοτύπους. Η κύρια παθοφυσιολογική οδός είναι εξαρτώμενη από την Th2 ηωσινοφιλική φλεγμονή που
παράγεται κυρίως από βοηθητικά Τ2 λεμφοκύτταρα (Th2). Πρόσφατες βιβλιογραφικές αναφορές προτεί-
νουν τα μη ευαισθητοποιημένα λεμφοκύτταρα του βρογχικού επιθηλίου (innate lymphoid cells, ILC2) ως
μία άλλη πηγή ηωσινοφιλών, με αποτέλεσμα την παραγωγή ηωσινοφίλων χωρίς προηγούμενη αντι-
γονική ευαισθητοποίηση. Άλλο παθοφυσιολογικό μονοπάτι είναι η μη Th2 φλεγμονή που εξελίσσεται μέσω
των Th1 λεμφοκυττάρων και των Th17 που εμπλέκονται στην ουδετεροφιλική φλεγμονή. Όμως, πρόσφα-
τες μελέτες έχουν συνδέσει και τα Th17 κύτταρα με την αλλεργική φλεγμονή και το ηωσινοφιλικό άσθμα.
Οι τρέχουσες κλινικές μελέτες αναμένεται να διευκρινίσουν περαιτέρω τον ρόλο των διαφόρων κυττάρων
στην εξέλιξη της ασθματικής φλεγμονής και επίσης τον ρόλο των καθιερωμένων ή νέων πιθανών βιοδει-
κτών στην καθημερινή κλινική πράξη με στόχο τη μεγιστοποίηση της αποτελεσματικότητας των αντι-
ασθματικών φαρμάκων. Στην παρούσα επισκόπηση, συνοψίζουμε τους προαναφερθέντες μηχανισμούς,
επικεντρώνοντας στην πλαστικότητα κι ευελιξία των υποπληθυσμών των Τ-βοηθητικών κυττάρων και
στην αναγνώριση της διπλής Th2/Th17 θετικής φλεγμονής.
Λέξεις - Κλειδιά: Th2/Th17, Άσθμα, Φαινότυποι, Βιοδείκτες, Θεραπεία

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Dasatinib-induced chylothorax in a patient with chronic myeloid leukemia: A Case Report

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Key words: - Chylothorax - Dasatinib - Chronic Myeloid Leukemia

INTRODUCTION

Chylothorax typically results from disruption of the normal lymphatic flow, such as insult to the thoracic duct, causing leakage of lymphatic fluid into the thoracic cavity. The etiology of chylothorax can be classified into two main categories, non-traumatic and traumatic chylothorax. Traumatic chylothorax, particularly postoperative chylothorax, accounts for more than 50% of all cases described in the literature. Malignancy-induced thoracic duct obstruction is the leading cause of non-traumatic chylothorax, with most malignancies being lymphomas (70% of which are Hodgkin lymphomas). Treatment for chylothorax includes conservative measures (total parenteral nutrition, pleural drainage, and pleurodesis) and surgery (thoracic duct ligation). Conservative treatment aims to reduce chyle flow and to drain the pleural cavity in an effective manner.
CASE PRESENTATION

A 51-year-old man arrived at the Emergency Department complaining of a gradually worsening dry cough and shortness of breath for the past 2 weeks. The patient also reported anorexia, malaise and myalgia. He used to walk 2 to 3 km per day without any difficulty, however nowadays he would get short of breath walking less than 300m. He had been hospitalized for 7 days in a district hospital due to dry cough 3 days prior to this day. He had been diagnosed there with a lower respiratory tract infection and treated with antibiotics (2g ceftriaxone twice a day and 300 mg clindamycin once daily) and bronchodilators (500μg ipratropium bromide four times a day and 0.5 mg budesonide twice a day). The patient had been diagnosed with chronic myeloid leukemia (CML) 20 years ago. He has been on 70 mg dasatinib twice a day for the last 7 years, which he has tolerated well so far. He claimed to be a non-smoker.

During the physical examination, the patient was haemodynamically stable and his oxygen saturation was good (94% on breathing ambient air). He had a pulse rate of 80 beats per minute with a sinus rhythm on ECG, blood pressure of 110/60 mm Hg, temperature of 37° C and respiratory rate of about 28 breaths per minute. The findings of the lung auscultation were decreased breath sounds in the left base and diminished lung sounds in the right lower lobes. Physical examination on the other systems did not reveal any further problems.

The laboratory results showed white blood count of 12,350 cells/mm³ (neutrophils=76.1%, lymphocytes=14.6%, monocytes=7.9%). CRP level was 1.6 mg/dl and ESR was 36mm. A chest X-ray was performed and revealed bilateral pleural effusion, more prominent on his right side. A subsequent chest Computed Tomography (CT) confirmed a large right pleural effusion and a small amount of pleural effusion at the left side, both causing atelectasis in the lower lobes. Physical examination on the other systems did not reveal any further problems.

The cultures of the fluid bilateral were negative for bacteria and fungus as well as the gram stain; tuberculosis was excluded. In addition, the cytology test of the pleural effusion found a small number of lymphocytes, macrophage and mesothelial cells. There was no evidence of malignancy.

Based on the clinical features, the pleural fluid’s milky appearance and its high level of triglycerides, the diagnosis of chylothorax was reached. Following the patient’s admission to the pulmonary department, a large bore catheter was placed in the right side for fluid drainage. Moreover, due to the advantages of reduced dietary intake on our patient’s condition, parenteral nutrition was solely given. Finally, based on the suspicion that the cause of chylothorax was in fact dasatinib, it was immediately discontinued in consultation with the patient’s leukemia treating physician.

The catheter’s placement resulted in improvement of the patient’s dyspnea. About 1.5 L of milky chylous pleural fluid was drained and the chest drain could be removed after 3 days. In the meantime, he developed large pleural effusion on the left side as well. The patient remained under observation for 7 days, without perceiving any medication till a repeat chest X-ray showed a significant improvement in his pleural effusion bilaterally. Therefore, he was dismissed from the pulmonary department and

![FIGURE 1. Initial chest X-ray demonstrates bilateral pleural effusion, more prominent at the right side.](image)
was advised to follow a low-fat diet program. A fast-complete remission of the pleural effusion bilaterally was noted at follow up (1 month and 2 months after hospitalization). The patient was also evaluated from his leukemia treating physician. Dasatinib was permanently discontinued and replaced by nilotinib. Currently, the patient continues to follow up with our pulmonary and oncology departments and reports no symptoms regarding his therapy.

**DISCUSSION**

Here we present a rare case of dasatinib-induced chylothorax in a patient with CML. The patient’s history and thorough workup, including a CT scan of the chest, did not suggest any other possible etiology. The chronic treatment with dasatinib was immediately interrupted after agreement with the patient’s leukemia treating physician. A large bore catheter was inserted in the pleural cavity in order to drain the chylous effusion. In the meantime, special dietary modifications including fasting and systematically parenteral nutrition were applied. The patient was dismissed from our department clinically improved and went home with instructions to avoid oral food lipids intake. The reevaluation of the patient with a chest X-ray 1 and 2 months later revealed a fast complete remission of the effusion. To our knowledge, dasatinib is the only pharmaceutical agent that is associated with the induction of a chylothorax\(^5\)\(^6\). Dasatinib is a second-generation potent and efficacious oral tyrosine kinase inhibitor, frequently used for BCR-ABL-positive chronic myeloid leukemia (CML) and for Philadelphia chromosome-positive acute lymphocytic leukemia\(^6\). Pulmonary

**FIGURE 2.** Chest X-ray at follow-up one month later reveals complete remission of the pleural effusion at the left side and a small amount of pleural effusion at the right side.

**FIGURE 3.** Chest CT demonstrates a large right pleural effusion and a small amount of pleural effusion at the left side, both causing atelectasis in the lower lobes.
adverse events are reported in about 35% of patients. The most common pulmonary abnormalities associated with dasatinib include pleural effusion, pulmonary hypertension, and parenchymal opacities. Dasatinib-related chylothorax is an uncommon pulmonary adverse event and the mechanism via which chylothorax is provoked is not fully understood. Various factors have been associated with the appearance of dasatinib-associated chylothorax. The prescription of a single dose (140 mg) per day is associated with a significantly lower number of chylothoraces and pleural effusions generally than those who receive 70 mg twice a day. Initial efforts should be focused on treating the chylothorax by attempting dose reduction as opposed to discontinuing dasatinib altogether. In addition, the use of short-term steroids and diuretics has also been shown to be helpful. There are no firm guidelines to establish when to switch from one kind of treatment to another.

**ΠΕΡΙΛΗΨΗ**

Χυλοθώρακας οφειλόμενος στη λήψη dasatinib σε ασθενή με Χρόνια Μυελογενή Λευχαιμία: Παρουσίαση περιστατικού

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Πνευμονολογικό Τμήμα, Γ.Ν.Θ. “Γ. Παπανικολάου”, Ιατρική Σχολή, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Θεσσαλονίκη

Παρουσιάζουμε την περίπτωση ενός 51χρονου άνδρα που πάσχει από χρόνια μυελογενή λευχαιμία κατά τα τελευταία 20 χρόνια και προσήλθε στο τμήμα μας λόγω βήχα και αισθήματος δύσπνοιας από ημερών. Η ακτινογραφία θώρακα ανέδειξε υπεζωκοτική συλλογή αμφοτερόπλευρα. Διεξήχθη διαγνωστική παρακέντηση του υπεζωκοτικού υγρού με υπερηχογραφική καθοδήγηση και η βιοχημική ανάλυση του πλευριτικού υγρού αποκάλυψε υψηλή συγκέντρωση τριγλυκεριδίων τόσο δεξιά (927 mg/dl) όσο και αριστερά (1232 mg/dl). Με βάση τα κριτήρια του Light το υγρό ταξινομήθηκε ως εξίδρωμα λεμφοκυτταρικού τύπου αμφοτερόπλευρα. Κατά τα τελευταία 7 χρόνια ο ασθενής λάμβανε θεραπεία με dasatinib, έναν από του στόματος αναστολέα της τυροσινικής κινάσης που έχει συσχετιστεί με μεγάλο αριθμό περιπτώσεων χυλοθώρακα. Η λήψη dasatinib διακόπηκε και ο ασθενής τέθηκε σε αυστηρούς διαιτητικούς περιορισμούς με διακοπή σίτισης per os και παρεντερική διατροφή. Μια νέα ακτινογραφία θώρακα 2 μήνες αργότερα ανέδειξε ταχεία πλήρη υποχώρηση των πλευριτικών συλλογών.


Λέξεις - Κλειδιά: Χυλοθώρακας, dasatinib, Χρόνια Μυελογενής Λευχαιμία

**REFERENCES**

Leukonychia

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A 72-year old smoker being evaluated for idiopathic pulmonary fibrosis is also complaining for leukonychia observed first 10 years ago. He doesn't recall any injuries to his hands and he hasn't any known nutritional or physiological deficiency.

Leukonychia (or leuconychia) is a medical term for white discoloration appearing on nails. It is derived from the Greek words leuko («white») and onyx («nail»). The most common cause is injury to the base of the nail (the matrix) where the nail is formed.

It is harmless and most commonly caused by minor injuries, occurs most commonly in healthy individuals, and is unrelated to any known nutritional or physiological deficiency.

Illnesses that can lead to white nails include:
Iron deficiency anemia, liver cirrhosis, kidney disease, heart failure, diabetes, zinc deficiency, hyperthyroidism, psoriasis, eczema.
Adult-form scimitar syndrome in a 64-year old woman

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A 64-year old female, current smoker of approximately 44 pack-years, was referred to us due to fever, dry cough, and shortness of breath on exertion. Physical examination revealed fever, tachypnea, tachycardia, and an oxygen saturation of 90% on room air (SpO₂: 90%, FiO₂: 21%). Laboratory evaluation showed a mild elevation of the white blood cell count (14,000/mm³) and C-reactive protein (9mg/dl). A chest radiograph demonstrated consolidation of the left lung base, as well as an anomalous pulmonary vein on the right side (Figure 1). Based on these radiographic findings, the Scimitar syndrome was suspected.

The patient underwent a CT-angiography (CTPA) in order to confirm the suggested diagnosis, which demonstrated a right-sided volume loss of the lung parenchyma, a shift of the heart and mediastinum to the right, and also anomalous ejection of the right lower pulmonary vein (which was dilated, Figure 2) to inferior vena cava. Increased cardiothoracic index and severe dilation of the azygos vein terminating in the superior vena cava were also noted.

Scimitar syndrome is a rare congenital malformation of the right lung characterized by an abnormal right sided pulmonary drainage into the inferior vena cava, hypoplasia of the right lung, with cardiac malformation (dextroposition of the heart or dextrocardia) as well as abnormal artery supply. It usually presents as recurrent lung infection, exertional dyspnea, whereas pulmonary artery hypertension and hemoptysis are uncommon symptoms of the syndrome in adult life. Scimitar syndrome in infants includes cyanosis, pulmonary artery hypertension, and cardiac defects often requiring surgical intervention with a rather high mortality risk. Diagnosis of Scimitar syndrome is confirmed with chest radiography, CT-angiography and echocardiography.

REFERENCES
Sarcoid granuloma:
An Ultra Sound visible Lesion!

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Sarcoidosis is a multisystemic inflammatory disease of unknown etiology that manifests as noncaseating granulomas, predominantly in the lungs and intrathoracic lymph nodes. The age-adjusted incidence is 11 cases per 100,000 population in whites but 34 cases per 100,000 population in African Americans. In Greece the incidence of the disease is estimated as 1,07 cases /100,000 population.

A 73 – years old female patient with a history of 25 years of sarcoidosis (stage II of the disease, under chronic corticosteroid remission) was admitted to our outpatient clinic. After all the laboratory and serologic tests, we performed imaging testing (during the last four years the patient did not refer to a chest physician for the follow up).

HRCT was performed showing the typical findings of the disease (symmetric hilar lymphadenopathy, bronchovascular bundles including centrilobular nodules, perilymphatic irregular nodular thickening, features of small airways disease and few subpleural nodules, especially in the RLL).

Therefore we performed an Ultra Sound scan of the chest wall at the area of the RLL. An hypoechoic, subpleural sarcoid lesion was detected, measuring of 1,5 – 2,2 mm of dimension, which is located in the lateral basal segment of the RLL (corresponding to the CT image)!

The use of Ultra Sound is, to our knowledge, a very new diagnostic procedure for the detection of subpleural sarcoid lesions and can be a useful implement in the following up of the disease (or in recognizing areas for transthoracic biopsies).

REFERENCES

1. Imaging of Sarcoidosis; Clinical Reviews in Allergy & Immunology August 2015; 49:45–53.
Spontaneous expulsion of left endobronchial Foreign Body

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A 50 year old man came with a chief complaints of cough with hemoptysis and dysphagia since 4 days. Patient had no other comorbidities and addiction history. Chest X ray was done but was within normal limits. In view of hemoptysis, patient was evaluated with high resolution computed tomography (HRCT) thorax which showed the presence of mild mucoid debris in left main bronchus and the intermediate bronchus as shown in figure 1. However, patient had expectorated a foreign body as shown in figure 2 following a violent cough. Patient had a symptomatic relief following spontaneous expulsion. Hence history was reviewed. Patient admitted the intake of sea food 4 days back. However, he did not recollect any history of choking. HRCT was reviewed, that was suggestive of soft tissue with foci of air within likely represents a foreign body. Bronchoscopy was done to rule out any remnants and injuries. It showed contact hemorrhage at left main bronchus probably representing the site of impaction with no remnants. Hence the diagnosis of spontaneously expectorated foreign body was made.

Foreign body aspiration is more common in children of age 1-3 years when compared to adults1. As lodgement of foreign body in adult is usually in the more peripheral pathway, with spontaneous resolution in symptoms, causing diagnosis in adult difficult2. Based on the foreign body location and patients' general condition, rigid or flexible bronchoscopy can be used for foreign body removal. Spontaneous expulsion of foreign body is a very rare condition with the incidence of 2-4%3.

CONFLICTS OF INTEREST
None.

REFERENCES
Pneumomediastinum associated with interstitial lung disease

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Key words:
- Pneumomediastinum
- Interstitial lung disease

A 79 year old female with a history of interstitial lung disease was referred from her family doctor due to escalating dyspnea and cervical swelling, over 2 weeks. Physical examination revealed bilateral crackles on auscultation, crepitus over the anterior chest and low saturation, 85% on 2L/min supplemental oxygen via nasal cannula. Blood work showed white cell count of 12.5×10⁹ L⁻¹ (normal range: 4–11×10⁹ L⁻¹) and a C-reactive protein of 10mg·L⁻¹ (normal range: <5mg·L⁻¹). A chest CT was performed and confirmed the diagnosis of secondary pneumomediastinum and pneumothorax. Further CT findings included subcutaneous emphysema, bilateral ground glass opacities, interlobular septal thickening, calcified mediastinal lymph nodes and traction bronchiectasis (Fig. 1, 2, 3). Patient was treated with a course of antibiotics and high concentration of oxygen and was discharged clinically improved after a week.

Pneumomediastinum is the presence of air in the mediastinum. Louis Hamman first described it in 1939, hence the associated “Hamman crunch”, defined as crepitus synchronized with heartbeat, absent in this case. Pneumomediastinum is usually the result of rupture of the alveoli due to a marked increase in intralveolar pressure, and in case of severe ILD, the result of ruptured paracardiac blebs, due to the distortion of lung architecture. It may present with dyspnea, odynophagia, voice hoarseness, or retrosternal chest pain. Although not supported by abundant evidence, treatment with high flow oxygen, is usually applied. Studies suggest that the mechanism of resolution is that, by breathing 100% oxygen, nitrogen is dissipated from the blood, thus increasing gas absorption gradient. It is necessary to include pneumomediastinum in the differential diagnosis of dyspnea, especially in the presence of underlying interstitial lung disease.

COMPETING INTERESTS

All authors declare that they do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. No conflict of interest to declare.

REFERENCES

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