Pleural effusion (PE) is a common clinical condition that affects approximately 1.5 million patients per year in the United States with the annual number of thoracenteses (pleural taps) reported between 127,000 and 173,000. The underlying cause may be either an acute disease e.g. pneumonia, pulmonary embolism, or chronic conditions as heart failure, liver cirrhosis or malignancy. Irrespective of the cause of PE accumulation, its large volume may compress the lung, heart and diaphragm, having a significant effect on cardiac and pulmonary function and gas exchange. These changes are manifested as dyspnea, cough or chest pain and serious impairment of the quality of life. The primary therapeutic intervention in patients with PE is therapeutic thoracentesis (TT), also known as pleural tap. Its goal is pleural fluid withdrawal and symptom alleviation. Introduction of novel technologies of pleural pressure monitoring (pleural manometry) during TT allows to follow the pattern of plural pressure fall during TT to optimize the course of the procedure and to predict its effects and potential complications. It also provides a great opportunity for studying the physiological changes associated with PE and thoracentesis. Our team has been working on these issues since 2010, when an early cooperation between clinicians and engineers yielded the development and validation of the own, original electronic pleural manometer. Our previous studies on the impact of TT on pulmonary and heart function resulted in some novel and intriguing research findings referring to the interactions between different intrathoracic structures. Thus, we are submitting a new research project aimed at better characterization and understanding of these phenomena and to face several new relevant questions. The first study objective is to verify if voluntary cough or application of continuous positive airway pressure (CPAP) via a face mask during TT facilitates a better aeration of the compressed lung. Second, we are planning to explore whether a decreased blood oxygenation during and after TT results from increased blood flow through the collapsed lung. The third aim is to assess the impact of mediastinum and diaphragm compression on blood oxygenation and lung expandability during TT. Also, the impact of PE on respiratory muscle function will be characterized using ultrasound (US) examination. Finally, we will study a new phenomenon observed by our team during previous studies and named “pleural pressure pulse” (small oscillation recorded on pleural pressure curve) and its relationship with heart function. The study is planned as a combined randomized, open label and observational study. Eighty one adult patients with pleural effusion who require TT will be enrolled. The patients will be randomly allocated to three arms: 1) large volume TT with pleural manometry and cough intervention, 2) large volume TT with manometry and CPAP intervention, 3) large volume TT with manometry and no other intervention. In each patient, pre-thoracentesis assessment will be performed including: medical history with dyspnea assessment, physical examination, chest imaging studies, routine blood tests, arterial blood gases and biomarkers of heart stretch, US assessment of respiratory muscles (including diaphragm) and mediastinum, pulmonary function tests, advanced echocardiography with three-dimension heart assessment. Then patients will undergo TT with continuous pleural pressure (P_{pl}) monitoring. Fluid will be withdrawn in portions and after each portion removal P_{pl} will be recorded. Temporal pleural elastance (ability of the lung to expand) determined by volume-pressure relationship will be followed during the procedure to attempt to gain new data on the relative expandability of lung, as well as diaphragm and mediastinum compliance. Simultaneously, continuous measurement and record of heart rate, blood pressure, pulse-oximetry, cardiac output (CO), stroke volume (SV), as along with noninvasive, transcutaneous measurement of oxygen and carbon dioxide tension will be performed to answer the specific questions which formed the base for the study objectives. After the withdrawal of 600 ml and 1100 ml, some patients will be asked for 3-4 series of vigorous cough (interventional ‘cough’ arm) or CPAP will be applied through a face mask with fixed expiratory pressure of 5 cm H_2O (CPAP) for 3 minutes (‘interventional CPAP’ group). The procedure will be terminated when: 1) there will be no more fluid in pleural cavity, 2) P_{pl} will decline below -25 cm H_2O or 3) symptoms of severe chest discomfort or uncontrolled cough will occur. To evaluate the impact of pleural fluid evacuation on blood oxygenation, post-thoracentesis heart function and respiratory muscle function assessment comprising of the same tests as prior TT, will be performed

It should be emphasized that all research hypotheses to be evaluated in this project are based on the results of our previous studies, as well as recent data published by other groups involved in pleural research. The project will be the first study comparing the effect of cough and passive CPAP on the course of TT and on P_{pl} changes. We may suppose that the positive results may be a prerequisite for changing the recommendations on TT in the future (e.g. encouragement to cough or CPAP application during and after the procedure). An important part of the project will be an advanced assessment of cardiovascular function. Application of 3D echocardiography and continuous estimation of CO and SV together with pleural fluid volume and P_{pl} monitoring will help to better characterize cardiovascular response to pleural effusion and pleural fluid withdrawal. To our knowledge, our project will be the first which will apply advanced transthoracic ultrasound to assess the functional status of inspiratory muscles and mediastinum. In case of encouraging results, it might become a new application for functional assessment of patients with pleural effusion.

To sum up, we believe that the scope of this project may allow to make further progress in our understanding of the changes related to pleural effusion and therapeutic thoracentesis.