Scientific Report

April 2020

3rd Phase of execution/2020

I. Study Protocol

- **Patients:**

The inclusion criteria are:
1) age>18 years;
2) HF diagnosis regardless of cause as defined by the Framingham criteria and satisfying the European Society of Cardiology guidelines;
The exclusion criteria are:
1) metallic joint prostheses, cardiac stent or pacemakers, decompensated cirrhosis, pregnancy and limb amputations (due to bioimpedance technique limitations);
2) patients with known persistent pleurisy, pulmonary fibrosis or pneumectomy; (due to lung ultrasonography limitations);
3) end stage renal disease (due to difficulties in the interpretation of overhydration symptoms and signs and also to different biomarker kinetics in this type of patients);
3) absence of congenital heart disease.

- **Methods:**

We collected **blood** from all included patients (for biomarker analysis); all patients had also a complete **clinical evaluation**:
- Personal data (age, sex, height);
- Cardiovascular risk factors (smoking, weight, body mass index);
- Medication;
- The etiology, duration and classification (NYHA class) of heart failure;
- Comorbidities (diabetes, hypertension, stroke, coronary artery disease, chronic kidney disease etc);
- Physical examination (blood pressure, crackles, pedal edema etc);
- Renal function evaluation (serum urea and creatinine, serum electrolytes – K, Na, Cl)
- Nutrition status evaluation: serum protein, cholesterol, triglycerides;
- Inflammation evaluation: CRP;
- Serum glucose and uric acid;
- Hemoleucogram;
- Electrocardiogram.

Bioimpedance spectroscopy analysis

This analysis was performed at baseline using the portable whole-body multifrequency bioimpedance analysis device (BCM®Body Composition Monitor – Fresenius Medical Care D GmbH).

The technique involves attaching electrodes to the patient's forearm and ipsilateral ankle, with the patient in a supine position. The BCM® measures the body resistance and reactance to electrical currents of 50 discrete frequencies, ranging between 5 and 1000 kHz. Based on a fluid model using these resistances, the extracellular water (ECW), the intracellular water (ICW) and the total body water (TBW) are calculated. These volumes are then used to determine the amount of fluid overload. All calculations are automatically performed by the software of the BCM® device. Absolute fluid overload (AFO) is is defined as the difference between the expected patient's ECW under normal physiological conditions and the actual ECW, whereas the relative fluid overload (RFO) is defined as the absolute fluid overload AFO to ECW ratio. In addition, this analysis will provide the LTI and FTI for the included patients.

Echocardiography
Echocardiographic evaluations were performed in each patient at baseline. All echocardiographic measurements were carried out according to the recommendations of the American Society of Echocardiography by an observer unaware of the lung ultrasound and bioimpedance results.

Lung ultrasonography
Examinations were performed in the supine position. Scanning of the anterior and lateral chest was performed on both sides of the chest, from the second to the fourth (on the right side to the fifth) intercostal spaces, at parasternal to mid-axillary lines. B-lines were recorded in each intercostal space and were defined as a hyperechoic, coherent US bundle at narrow basis going from the transducer to the limit of the screen.
B-lines starting from the pleural line can be either localized or scattered to the whole lung and be present as isolated or multiple artifacts. The sum of B-lines produces a score reflecting the extent of lung water accumulation (0 being no detectable B-line).

II. The proposed/achieved objectives

For the third and final stage of the project the following objectives have been accomplished:

1. We finalized patients' enrollment, biomarkers assessment, data acquisition and statistical analysis.

2. We have monitored closely patients' clinical evolution.

3. Dissemination:

<u>During the entire period of the project:</u>

a. Oral presentations

- Extravascular Lung Water Assessment Using Pulmonary Ultrasonography – WorkShop during the 15th edition of the International Congress for Medical Students and Young Doctors – Congressis 2018;

- Cardiac Failure – Oral Presentation during the CardioRenal Course – 28 September 2019, Hotel Bavaria Blu, Constanța (https://www.cardioportal.ro/cardiorenal/).

b. Posters

- Fluid overload is associated with all-cause and cardiovascular mortality in hemodialysis patients: a time-varying survival analysis – Poster during the 55th edition of the European Renal Association – European Dialysis and Transplant Association Congress – Copenhagen 2018
- Pulmonary congestion, as assessed by lung ultrasonography, is dependent on renal function and fluid overload in patients with heart failure – Prize winner Poster during the 56th edition of the European Renal Association – European Dialysis and Transplant Association Congress – Budapest 2019

c. Manuscripts published in ISI journals

- An analysis of the impact of fluid overload and fluid depletion for all-cause and cardiovascular mortality – Manuscript in Nephrology Dialysis Transplantation Journal (IF 4.198)

<u>During the last phase:</u>

a. Posters

- The effect of serum C-reactive protein and ferritin levels on all-cause and cardiovascular mortality in haemodialysis patients – Accepted at the 57th edition of the European Renal Association – European Dialysis and Transplant Association Congress – Milan 2020

b. Manuscripts published in ISI journals

- Prognostic value of lung ultrasonography and bioimpedance spectroscopy in patients with heart failure and reduced ejection fraction – Manuscript in Archives of Medical Sciences Journal (IF 2.380)
- Assessment and management of volume overload among patients on chronic dialysis – Manuscript in Current Vascular Pharmacology Journal (IF 2.455)

4. We are also preparing another manuscript intitled: “Pathways leading to pulmonary congestion: A Structural Equation Modelling Approach in Patients with Cardiac Failure and Reduced Left Ventricular Ejection Fraction”.