GRIGORE T. POPA UNIVERSITY OF MEDICINE AND PHARMACY IASI

An etiopathogenic perspective on heart failure

Habilitation Thesis

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Contents

ABREVIATION LIST

ACS - Acute Coronary Syndromes

AF - Atrial Fibrillation

AHA - American Heart Association

ALT - Alanine Aminotransferase

AMI - Acute Myocardial Infarction

APHRS - Asia Pacific Heart Rhythm Society

AR - Aortic Regurgitation

AS - Aortic Stenosis

AST - Aspartate Amino Transaminase

BMI - Body Mass Index

CAD - Coronary Artery Disease

CCS - Chronic Coronary Syndromes

CHD - Coronary Heart Disease

CHF - Congestive Heart Failure

CK-MB - Creatine Kinase MB

CRP - C Reactive Protein

CS - Cardiogenic Shock

EHRA - European Heart Rhythm Association

ESC - European Society of Cardiology

ESR - Erythrocyte Sedimentation Rate

HDL-col - High Density Lipoprotein cholesterol

HF - Heart Failure

HRS - Heart Rhythm Society

LA - Left Atrium

LAHRS - Latin American Heart Rhythm Society

LDL-col - Low Density Lipoprotein Cholesterol

LV - Left Ventricle

LVEF - Left Ventricular Ejection Fraction

LVH - Left Ventricular Hypertrophy

MAU - Microalbuminuria

MI - Myocardial Infarction

MR - Mitral Regurgitation

MS - Metabolic Syndrome

MS - Mitral Stenosis

NSTEMI - no persistent ST-segment elevation

PA - Pulmonary Artery

PASP - Systolic Pulmonary Artery Pressure

PCI - Percutaneous Coronary Intervention

PGI - Patient Generated Index

PH - Pulmonary Hypertension

RCT - Randomized Clinical Trial

RV - Right Ventricular

RV-FAC - Right Ventricular Fractional Area Change

RVMI - Right Ventricle Myocardial Infarct

STEMI - ST-segment elevation myocardial infarction

TAPSE - Tricuspid Annular Plane Systolic Excursion

TDI -Tissue Doppler Imaging

TSH - Thyroid Stimulating Hormone

VEGF - Vascular Endothelial Growth Factor

REZUMATUL TEZEI

Profesia didactică necesită dobândirea permanentă a cunoștințelor, abilităților și competențelor specifice din trei domenii fundamentale: educație, sănătate și cercetare. În zilele noastre, realizările profesionale sunt diverse, dar necesită o formare continuă multidisciplinară pentru a îndeplini cerințele actuale din fiecare dintre aceste domenii. Mediul academic oferă o multitudine de oportunități, dar și de responsabilități și, prin urmare, atât perfecționarea profesională, cât și dezvoltarea personală sunt obligatorii.Această teză de abilitare trece în revistă activitatea mea profesională, academică și științifică din perioada postdoctorală (2012-2021), în cadrul Universității de Medicină și Farmacie „Grigore T. Popa" din Iași. Conform recomandărilor Consiliul Național pentru Atestarea Titlurilor, Diplomelor și Certificatelor (CNATDCU), prezenta teză este structurată în patru secțiuni, după cum urmează:

Secțiunea I oferă un sumar al realizărilor mele profesionale, academice și științifice din ultimii 9 ani, după obținerea titlului de doctor în medicină.

Secțiunea II prezintă una dintre cele mai importante direcții ale activității mele de cercetare postdoctorală, centrată pe insuficiența cardiacă (IC), o afecțiune cardiacă considerată epidemică și în prezent. Etiopatogenia insuficienței cardiace este multifactorială și variază în cadrul fiecărei zone geografice, precum și între diferite zone geografice. Diferite patologii cardiovasculare și non-cardiovasculare contribuie la apariția insuficienței cardiace. Prin urmare, identificarea corectă a acestor afecțiuni este o etapă esențială a procesului de diagnosticare, cu implementarea ulterioară a diverse metode terapeutice. Această secțiune este structurată metodic în 4 capitole ce ilustrează principala mea arie de interes, din perioada postdoctorală și până la poziția actuală de conferențiar universitar.

Capitolul 1 abordează relația dintre sindromul coronarian acut/cronic și insuficiența cardiacă. Este cunoscut faptul că boala coronariană aterosclerotică (BCA) este etiologia primară la 70% dintre pacienții cu insuficiență cardiacă. Progresia BCA are ca rezultat diferite prezentări clinice, clasificate fie ca sindroame coronariene acute (ACS), fie ca sindroame coronariene cronice (CCS), în conformitate cu ghidurile Societății Europene de Cardiologie. Pacienții cu IC și boală cardiacă ischemică au de obicei un istoric de infarct miocardic sau de revascularizare miocardică, însă o angiografie coronariană normală nu exclude prezența fibrozei miocardice extinse sau a unei microcirculații coronariene compromise.

Capitolul 2 se referă la bolile cardiace valvulare - afecțiuni care pot provoca sau promova progresia IC. Astfel, pacienții cu IC și boli cardiace valvulare concomitente reprezintă o populație cu risc înalt. În bolile cardiace valvulare acute, supraîncărcarea de volum sau de presiune contribuie la apariția insuficienței cardiace acute (ICA). În valvulopatiile cronice însă, este dificil să se facă diferența între efectele condițiilor hemodinamice anormale și debutul disfuncției miocardice ca sursă a insuficienței cardiace congestive (ICC).

Capitolul 3 prezintă studii privind rolul tulburărilor de respirație din timpul somnului în progresia IC, cele mai frecvente tipuri fiind apneea în somn centrală, apneea în somn obstructivă (OSA) și un model mixt al celor două. Diagnosticul acestor afecțiuni necesită în mod curent

polisomnografie. Cu toate acestea, instrumente inovatoare de testare la domiciliu, care pot diferenția între tipurile de apnee în somn, au fost introduse recent în practica clinică. Tratamentul OSA cuprinde suplimentarea nocturnă cu oxigen, terapia CPAP (Continuous Positive Airway Pressure - presiune pozitivă continuă în căile aeriene), terapia BiPAP (Bilevel Positive Airway Pressure - presiunea pozitivă a căilor respiratorii pe două niveluri) și servo-ventilația adaptivă (ASV- Adaptive Servo Ventilation), conform recomandărilor ghidurilor actuale.

Capitolul 4 se referă la predictori ai mortalității cardiovasculare la pacienții cu insuficiență cardiacă. Datele epidemiologice acutuale sunt limitate de lipsa raportării cazurilor în țările subdezvoltate, precum și de inconsecvența metodelor de evaluare a ratei de apariție a insuficienței cardiace la nivel populațional. În plus, în insuficiența cardiacă există un curs imprevizibil de exacerbare-remisie asociat cu progresia bolii și datele cu privire la prognostic sunt dificil de obținut. La acești pacienți au fost recunoscuți mai mulți markeri prognostici (de deces și/sau spitalizare pentru IC), dar aplicabilitatea lor în practica clinică este limitată. Prin urmare, identificarea unor predictori valoroși, clinici, biologici și imagistici și și realizarea unei stratificări exacte a riscului în IC sunt încă impedimente majore în practica clinică.

Secțiunea III trece în revistă obiectivele viitoare, concrete, de perfecționare profesională, academică și științifică. În ceea ce privește activitatea didactică, intenționez să dezvolt în permanență un parteneriat cu studenții și medicii rezidenți. Activitatea mea medicală se va concentra pe acumularea de noi cunoștințe și dezvoltarea de noi abilități și competențe în domeniul cardiologiei.

În ceea ce privește activitatea științifică, îmi propun să continui proiectele pe care le-am inițiat până la momentul actual și să dezvolt altele noi. În prezent, cercetarea mea clinică este direcționată către:

- evaluarea prevalenței cardiomiopatiei induse de pacing prin intermediul imagisticii prin rezonanță magnetică cardiacă; în ciuda progreselor semnificative în înțelegerea fiziopatologiei cardiomiopatiei induse de pacing și în implementarea unui tratament adecvat, există încă o mulțime de întrebări fără răspuns și, de asemenea, puterea imagisticii prin rezonanță magnetică cardiacă de a prezice dezvoltarea cardiomiopatiei induse de pacing și valoarea predictivă a acestei tehnici imagistice comparativ cu cea a ecocardiografiei transtoracice nu au fost încă analizate;

- evaluarea capacității de predicție a unor noi biomarkeri în dezvoltarea insuficienței cardiace cronice după un infarct miocardic acut; cele mai multe analize s-au concentrat asupra puterii predictive a biomarkerilor cardiaci în IC cronică și, prin urmare, utilitatea acestora în context acut nu a fost încă evaluată prin studii observaționale largi;

- evaluarea impactului deficitului de fier asupra ratei de răspuns la terapia de resincronizare cardiacă (CRT); datele acumulate până în prezent susțin faptul că deficiența de fier are un impact negativ asupra eficacității CRT și că substituția de fier ar putea crește rata de răspuns; cu toate acestea, magnitudinea remodelării inverse a VS și gradul de reducere a nivelului peptidelor natriuretice la un an după CRT nu a fost evaluată la subiecții cu deficit de fier care beneficiază de o repleție adecvată.

Secțiunea IV include o listă de referințe bibliografice citate în prezenta teză de abilitare.

THESIS SUMMARY

The teaching profession demands the permanent acquisition of specific knowledge, skills, and competencies in three fundamental areas: education, health, and research. Nowadays, the professional fulfillments are numerous but they demand continuous multidisciplinary training in order to meet the current requirements in each of these fields. The academic environment offers a multitude of opportunities, but also responsibilities, and therefore, both professional and personal improvements are mandatory.

This habilitation thesis reviews my professional, academic and scientific activity in the postdoctoral period (2012-2021) at the "Grigore T. Popa" University of Medicine and Pharmacy from Iași.

As recommended and approved by the National Council for Attestation of Titles, Diplomas, and Certificates (CNATDCU), the present thesis is structured in four sections, as follows:

Section I offers a summary of my professional, academic, and scientific achievements over the past 9 years after I attained the Ph.D. title.

Section II presents one of the most significant component of my postdoctoral research activity, with a special focus on heart failure, an epidemic heart disease even today. The etiology of heart failure is multifactorial and varies within and among different geographic areas. Cardiovascular and non-cardiovascular pathologies contribute to the advent of heart failure. Therefore, the proper identification of these conditions is an essential part of the diagnostic workup, with further implementation of specific therapeutic methods. This section is structured into 4 chapters and emphasize my major research interest, beginning with the post-doctoral period, up to the current possition of associate professor.

Chapter 1 addresses the relationship between acute/chronic coronary syndrome and heart failure. It is known that coronary artery disease (CAD) is the underlying pathology in 70% of heart failure patients. The CAD progression results in various clinical presentations, classified as either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS), according to the European Society of Cardiology 2019 guideline. While patients with HF and ischemic heart disease typically have a history of myocardial infarction or revascularization, a normal coronary angiogram does not exclude myocardial scar or compromised coronary microcirculation.

Chapter 2 refers to valvular heart disease – a condition that may cause or promote HF progression. Thus, patients with HF and concomitant valvular heart disease represent a high-risk population. In acute valvular heart disease, the deleterious effects of volume or pressure overloading contribute to the onset of congestive heart failure (CHF). Nevertheless, in chronic valvular heart disease, it is challenging to make the difference between the effects of abnormal loading conditions and the onset of myocardial dysfunction as the source of CHF.

Chapter 3 presents studies regarding the role of sleep breathing disorders in HF progression, the most common types being central sleep apnoea (CSA), obstructive sleep apnoea (OSA), and a mixed pattern of the two. Diagnosis commonly necessitates overnight polysomnography.

However, innovative home testing tools that can distinguish the type of sleep apnoea have recently been settled. The treatment of OSA comprises nocturnal oxygen supplementation, continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP), and adaptive servo-ventilation (ASV), as recommended in current guidelines.

Chapter 4 refers to the predictors of cardiovascular outcomes in patients with heart failure. Data regarding heart failure (HF) are not entirely reliable due to the lack of case reports in underdeveloped countries and the inconsistency of methods in evaluating the occurrence rate of this disorder.

Several prognostic markers of death and/or HF hospitalization have been recognized in patients with HF, but their applicability in clinical practice is limited. In HF there is an unpredictable exacerbating-remitting course associated with disease progression and data regarding the prognosis are difficult to be given.

Therefore, identifying valuable predictors and attaining an accurate risk stratification in HF are still challenging issues.

Section III emphasizes my approach to further improvement in professional, academic, and scientific areas. Concerning the teaching activity, I intend to develop a partnership with students and training physicians. My medical activity will be focused on the accumulation of new knowledge and the development of new skills and competencies in the field of cardiology. With regard to scientific activity, I aim to continue the projects I have already started, as well as to design new ones. Currently, my clinical research consideration aims to address the following topics:

- the assessment of the prevalence of pacing-induced cardiomyopathy through cardiac magnetic resonance imaging; despite significant progress in understanding the pathophysiology of pacing-induced cardiomyopathy and in implementing proper medical care, there are still a lot of unanswered questions and additionally CMR imaging's potency to predict PICM development and its predictive value in comparison to that of transthoracic echocardiography have not been reviewed ever before;

- the evaluation of the potency of novel biomarkers to predict chronic heart failure development following an acute myocardial infarction; most research has focused on the predictive power of cardiac biomarkers in chronic HF, and thus their suitability in acute presentations has yet to be assessed through the aid of observational studies;

- the appraisal of the impact of iron deficiency on the response rate to cardiac resynchronization therapy; emerging data indicate that iron deficiency negatively impacts CRT efficacy, that iron substitution might enhance LV contractility in subjects with incomplete LV reverse remodeling following CRT, and that serially persistent reductions in natriuretic peptides concentrations are related to the extent of LV reverse remodeling; however, the magnitude of LV reverse remodeling and brain natriuretic peptides levels reduction at one year after CRT has not been evaluated in subjects with baseline iron deficiency that benefit from proper iron repletion.

Section IV includes a list of bibliographic references cited in the present habilitation thesis.

SECTION I. Summary of personal professional, academic and scientific activities

The perspective of an academic career is fascinating and can tempt any young person, from the first days as a student. I am privileged to be able to carry out my professional activity both as a doctor and as a teacher, two of the most beautiful and noble professions. This expertise involves however long-term commitment, work, satisfaction, sacrifice, and responsibility.

I have the privilege of being part of the university where Professor Leon Scully held his first anatomy course 141 years ago. History legitimizes us but also obliges us. We are part of a dynamic society, marked out by profound transformations towards modernity, also reflected by the alignment of university education with the European standards and norms. The performances of the University of Medicine and Pharmacy "Grigore T. Popa" Iasi were recognized by ranking it the first in the country and the 42nd among the universities analyzed in the Times Higher Education Emerging Economies University Rankings.

I.1. EVOLUTION AND TRAINING AS A DOCTOR

The first information about the complexity of the cardiology residency was obtained from Mrs. Prof. Dr. Cătălina Arsenescu Georgescu, who later became my coordinator.

Right from the first year of residency, I went to the Cardiac Electrophysiology and Pacing Laboratory, where I learned to perform both temporary and permanent cardiac pacing, a revolutionary therapeutic method for patients with atrioventricular conduction disorder, but also with sinus node dysfunction or vasovagal syncope. Here, I instantaneously developed my passion for this cutting-edge field of modern cardiology which later proved to be a source of inspiration for scientific publications and the path to follow for my doctoral research.

Once I began my residency, I started attending numerous medical conferences, both in the country and abroad. In March 2009 I completed my training in cardiology, obtaining the title of specialist cardiologist, with clinical integration within the Cardiac Electrophysiology and Pacing Department of the Institute of Cardiovascular Diseases "Prof. Dr. George IM Georgescu" of Iași.

The year 2009 ended with special recognition and appreciation, being awarded by the Romanian Society of Internal Medicine with the "Daniel Danielopolu Award". That moment proved to me once again that relentless effort brings much satisfaction.

I constantly had the desire for self-improvement, which is why I regularly attended postgraduate courses and international workshops where I had the opportunity to learn from masters of cardiology and especially of arrhythmology and electrophysiology. I would like to mention only one of these international fellowship training programs "Meet the Masters - a program for Heart Rhythm Management Fellows" coordinated by Prof. Pedro BRUGADA, held during a year, with numerous meetings on a theoretical and practical basis. Throughout the course, I have managed to integrate myself into a working group, premised on the basic-science-guided arrhythmias management.

In June 2013, following the board certification exam, I obtained the title of Senior Cardiologist, as a crowning achievement of my entire medical activity.

In 2018, with the foundation of a Postgraduate Training Program in Romania, I obtained the Certificate of Complementary Studies Stimulators and Implantable Cardiac Defibrillators, and also became the Program Manager within the University Centre Iasi.

I. 2. TEACHING ACTIVITY

I started my academic career with the residency in Cardiology, at the University of Medicine and Pharmacy "Gr.T.Popa" of Iași in February 2003, being admitted by contest as a teaching assistant at Medical Cardiology Discipline, Cardiology Center of Iași, under the guidance of Prof. Dr. George I.M. Georgescu and Mrs. Prof. Dr. Cătălina Arsenescu Georgescu. The high level of proficiency that I have encountered as a newcomer in this discipline has determined me to adapt my conduct and working practices to that of my new colleagues and also to learn from their experience. At the same time, I have come to believe that the evolution of my performance as an educator later depends on the success of my professional debut.

My academic career continued so that in 2009 I was promoted by contest as Assistant Professor. The complexity of the teaching activity stimulated me and made me want to reach a level of performance that would give me comfort and prestige as a young educator in front of a group of students.

Gradually I went from the status of a person who attends a course as part of the auditorium, to that of a Lecturer. I actively got involved in numerous medical conferences and projects, both locally and nationally, held under the auspices of the Romanian Society of Cardiology, especially of the Hypertension Working Group, but also of other working groups. Of course, the transition from a learner to a lecturer involved several responsibilities: professional behavior, the ability to convey information, to communicate easily with others, to adapt my vocabulary to that of the audience, to respond accurately and clearly to questions, the honesty to recognize my limits and the permanent struggle to overcome them.

Following the directions of the University of Medicine and Pharmacy "Grigore T. Popa" Iasi, I also tutored at the College of Nurses, Botosani, and Iasi divisions, when I had the highest teaching load via hourly payments. During this period, I guided students in the elaboration of undergraduate theses. From the beginning of my teaching activity, I have actively participated in the development of various teaching materials for both students and residents: diagrams, graphics, clinical cases, tests for partial and final evaluations.

In 2014, I have been appointed as Senior lecturer, by contest. I have continued with the advancement of my previous projects but I have also implemented new ones. Thus, in 2015 I was the Training Manager from the University of Medicine and Pharmacy ”Grigore T. Popa” of Iași within the POSDRU project 179/3.2/S/151363, entitled “Training specialists in the field of pediatric cardiology for a quality medical act in order to improve the quality of life”, the acronym “100 HEARTS for 100 CHILDREN” developed in collaboration with the Institute of

Cardiovascular Diseases "Prof. George Georgescu" of Iasi and the University of Medicine and Pharmacy "Carol Davila" of Bucharest.

Moreover, in 2015 I have participated in the elaboration of the new Residency Manual, edited by Prof. Dr. Viorel Scripcariu. In 2019 I had the honor to be one of the Editors of the Treaty of Internal Medicine, together and under the coordination of Prof. Dr. Laurențiu Șorodoc which today is the reference book for all students entering the 4th year of medical school, but also for residents during their first years of training, where solid initial benchmarks shall remain the basis of future profession.

I have considered an engaging occasion the project "Integrative module for the study of the heart", designed by the University of Medicine and Pharmacy "Grigore T. Popa" of Iasi, which proposed a new, cross-over didactic approach. I was a Guest Lecturer at numerous Courses, Workshops, Summer Schools, National Congresses, organized either by our University or by National Scientific Societies or by the Romanian College of Physicians.

Another component of my teaching activity is related to resident physicians, either from cardiology or from other related specialties, whom I guide in their daily activity. I believe that the academic environment is directly responsible for delivering qualified healthcare providers. Practically, the health system depends on the way we train future specialists, professionally but also humanly.

In 2020, I was promoted by contest from the position of Senior Lecturer to that of Associate Professor.

I have positively responded to the challenges launched by the Dean of the Faculty of Medicine and participated in committees of undergraduate thesis examination, residency admission exam, teaching position promotion, and specialty certificate examination. The privilege of being appointed as Vice-Dean, an honor granted in 2015 by Prof. Dr. Lăcrămioara Șerban, Dean of the Faculty of Medicine, came at a moment when my personal development needed new perspectives. Entering the large, administrative family of the University was an accomplishment, whereas the active participation in organizational and decision-making activities at the level of the Faculty of Medicine triggered large enthusiasm.

I.3. RESEARCH ACTIVITY

In the academic year 2005 - 2006, I attended the courses of a Master in Epidemiology and Methodology of Clinical Research at the University of Medicine and Pharmacy "Gr.T.Popa" of Iași, which further broadened my horizons in outlining and executing research projects.

Ever since 2003, I was entrained as co-investigator, study coordinator, and finally as principal investigator, for a series of 17 research grants, international clinical studies of phase II or III, or registers, in the research team of the Institute of Cardiovascular Diseases "Prof George IM Georgescu". My active involvement in these research projects was useful for the development of teamwork skills and the establishment of individual goals. The final results were communicated via publications in prestigious journals, within the team of investigators.

In 2006, I was admitted by a contest to the Doctoral School within the University of Medicine and Pharmacy "Gr. T. Popa" of Iași, at the end of which, in October 2007 I submitted the project of the Doctoral Thesis with the topic "Methods of Optimizing Results in Permanent Electrical Cardiac Stimulation", under the guidance of Prof. Dr. Cătălina Arsenescu Georgescu. The main objective was to define the approach of cardiac pacing that improves clinical outcomes, on a 12-month post-procedural follow-up in patients who have undergone pacemaker implantation. As an element of originality, the second main objective of my study was to imagine a simple method of programming the AV interval in bicameral pacemakers, based on the evaluation of the surface electrocardiogram and pacemaker interrogation, which would provide adequate hemodynamic improvement, validated by echocardiographic parameters of left ventricle systolic and diastolic function.

During the doctoral school, I held presentations both in the country and abroad and I have published in extenso the data obtained. The Ph.D. thesis was finalized in 2012, obtaining the Ph.D. degree in medicine.

My research activity is also highlighted by the collaborations I had, both nationally and internationally. Starting with 2014, as a Senior lecturer, I developed new partnerships in academic teams and research projects, of which I would like to mention: internal medicine led by Prof. Dr. Laurențiu ȘORODOC, nephrology led by Prof. Dr. Adrian COVIC, neurology led by Prof. Dr. Adrian CUCIUREANU, pharmacology led by Mrs. Prof. Dr. Cătălina LUPUȘORU, but also anatomy.

These collaborations were materialized through more than 20 articles in prestigious journals, with ISI Thomson indexing (reaching so far a Hirsch index of 7), and over 40 articles in other journals indexed in international databases. Moreover, I was a member of the research team of 2 national grants won by competition, as well as a training manager within the POSDRU project "100 hearts for 100 children".

As a cardiologist, I tried to go beyond the boundaries of this specialty, being attracted by interventional and surgical techniques, and thus addressing a leading field of modern cardiology - Arrhythmology and Cardiac Implantable Electronic Devices. My constant concentration on improvement, participation in courses and workshops, both locally and abroad, and collaborative efforts within the Laboratory of Electrophysiology and Cardiac Pacing of the Institute of Cardiovascular Diseases "Prof. George I.M. GEORGESCU "from Iași allowed me a complete professional development in this area, perpetuating the prestige of the institution where I have trained.

Throughout this period, I performed a number of over 6,500 interventions, including pacemaker and defibrillator insertions and cardiac resynchronization therapy procedures. In June 2009, following a competition held in Berlin, organized by the European Heart Rhythm Association, under the auspices of the European Society of Cardiology, I obtained the European Accreditation for Cardiac Pacing and Implantable Defibrillators, fully completed in 2012, with the Diploma handing at its headquarter in Sophia Antipolis.

Section II. Scientific accomplishments

Introduction: Heart failure - a constantly changing paradigm

The European Society of Cardiology (ESC) defines heart failure (HF) as "a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress" [Ponikowski et al., 2016]. Consequently, in HF the left ventricle is unable to satisfy tissue oxygen demand.

The diagnosis of HF requires the identification of the primary cardiac cause, which is usually represented by myocardial disease resulting in systolic and/or diastolic dysfunction. Injuries of the valves, pericardium, and endocardium, as well as heart rhythm and conduction disorders, can cause the emergence of HF. Knowing the etiology is crucial in choosing the appropriate treatment [Ponikowski et al., 2016]. It has been shown that coronary artery disease is the underlying pathology of HF in 70% of cases [Ambrose et al., 2015].

Epidemiological studies showed that HF is the most common cause of hospital admission in patients aged > 65 years; moreover, the incidence of HF equalizes the collective incidence of lung, breast, bowel, and prostate cancer together [Conrad et al., 2018; Beattie et al., 2020]. It seems that HF incidence increases two times during each decade between 65 and 85 years, while for women triples over the same age groups [Lloyd-Jones et al., 2002; Beattie et al., 2020].

Based on the assessment of left ventricular ejection fraction (EF), the Heart Failure Association (HFA) defines three HF phenotypes: HF with a reduced EF (HFrEF), when the EF is <40%, HF with a mid-range or mildly reduced EF (HFmrEF) [EF 40–49%], and HF with preserved EF (HFpEF) [EF ≥ 50%][Ponikowski et al., 2016].

All these phenotypes portray a similar clinical appearance. The diagnosis is usually considered in people presenting with exertional dyspnea or orthopnea and fatigue, that exhibit a collection of stereotypical clinical features.

Heart failure can manifest insidiously or as acute HF (AHF), the latter being characterized by rapidly progressive symptoms. By analyzing all the subjects admitted with HF, it seems that only one-third are addressed for AHF, the majority of the cases being related to acute decompensation of chronic HF (ADCHF) [Greene et al., 2017]. A study conducted in 2019 by Nielsen et al., comprising 370 consecutive patients hospitalized for dyspnea, with echocardiographic evidence of left ventricular dysfunction, and elevated NT-proBNP, illustrated that acute decompensation of chronic HF was diagnosed in 80%, 62%, and 28% subjects with HFrEF, HFmrEF, and HFpEF [Nielsen et al., 2019].

In HF, acute ventricular dysfunction should be managed according to the underlying cause, to attain the so-called myocardial remission; however, most of the survivors of the acute phase will develop chronic heart failure (CHF).

The etiopathogenesis of acute heart failure (AHF) is not very well understood. Usually, the patients have a fast onset of illness, frequently on the grounds of preexisting cardiomyopathy. The

prognosis is commonly poor with a high risk of readmission and death post-discharge. The mortality rates during the index admission, as stated by the UK National Heart Failure Audit account for approximately 10% with a post-discharge 30-day and 1-year mortality of 6.5% and 30%, respectively [Donkor et al., 2016; Kurmani, Squire, 2017].

In CHF, both mechanical failure and autonomic nervous system dysfunction can determine sudden cardiac death (SCD). The diagnosis of HF remains a challenge for the clinician even after hospital admission. It is based on a complex integration of symptoms, sustained by objective evidence of heart structural anomalies on electrocardiography, echocardiography, or chest X-ray [Ciampi et al., 2007; Ponikowski et al., 2016]. Early detection is crucial in order to restrain disease progression.

Morbidity and mortality in chronic heart failure remain high, despite major therapeutic advances [Clark et al., 2004]. In patients with mild symptoms, the mortality rate per year is ranging between 5% to 10%, increasing to 30% to 40% in those with more advanced symptoms [Bui et al., 2011].

As outlined by recent clinical guidelines, the treatment should primarily approach congestion and hypoperfusion [Ponikowski et al., 2016; Beattie et al., 2020]. Comorbidities may interfere with HF treatment. Sometimes pharmacological therapy may worsen HF clinical course. Consequently, proper management of associated pathologies is fundamental in the general care of patients with HF. As proved by several trials, HFpEF exhibits a higher prevalence of comorbidities when compared to HFrEF, and many of these coexisting conditions may contribute to the progression of the disease [Ponikowski et al., 2016].

Several markers of death and/or HF hospitalization have been identified and analyzed in patients with HF, but their clinical utility is only partially exploited. Accurate risk stratification in HF is still in the attention of researchers. In the last years, multivariable prognostic risk scores have been imagined for patients with HF [Pocock et al., 2013; Rahimi et al., 2014; Ouwerkerk et al., 2014; Ponikowski et al., 2016] as they may help predict death. However, these scores remain less valuable for the estimation of HF hospitalizations [Rahimi et al., 2014; Ouwerkerk et al., 2014; Ponikowski et al., 2016].

The goal of HF therapy is to provide both community and in-hospital support. More and more data suggest that significant cost saving may be accomplished by using cardiac rehabilitation and secondary prevention programs as they reduce subsequent hospital admissions and total expense of medical care.

Although studies of cost benefit and effectiveness are not widely reported, it seems that cardiac rehabilitation programs have benefits and effectiveness similar to other successful interventions in the treatment of cardiac and vascular diseases.

In HF, multidisciplinary management is essential for improving outcomes through planned follow-up with patient education, optimization of medical treatment, psychosocial support, and improved access to care. All these measures are necessary to reduce HF hospitalization and mortality in patients discharged from the hospital [Madamanchi et al., 2014; Ponikowski et al., 2016].

Chapter 1. The relationship between acute/chronic coronary syndrome and heart failure

1.1. Scientific context

Coronary artery disease (CAD) represents a pathological process characterized by obstructive or non-obstructive lipid accumulation in the epicardial arteries. Disease evolution may be influenced by lifestyle adjustments, pharmacological therapies, and invasive interventions. The disease can evolve as a longtime stable lesion, but can also become unstable at any time, usually in the context of an acute thrombotic event produced by plaque erosion or rupture. The CAD progression results in various clinical presentations, classified according to the 2019 ESC guidelines as either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS)[Knuuti et al., 2020].

According to 2020 European Society of Cardiology (ESC) guidelines, the presentation of patients with acute coronary syndromes varies from cardiac arrest, electrical or hemodynamic instability with cardiogenic shock (CS), to patients who are pain-free at the time of presentation [Roffi et al., 2016; Collet et al., 2020]. Acute chest discomfort represents the most common symptom in patients with suspected ACS and it is described by the patient as pain, pressure, tightness, and burning. Moreover, chest pain-equivalent symptoms may be represented by dyspnea, epigastric pain, and pain in the left arm. Electrocardiogram results allow the identification of two groups of individuals. The first group includes patients with acute chest pain and persistent ST-segment elevation reflecting an acute total or subtotal coronary occlusion. This category will finally progress to an ST-segment elevation myocardial infarction (STEMI). The reperfusion by primary percutaneous coronary intervention (PCI) or, if not available in a short time, by fibrinolytic therapy, is indicated in this situation. The second group contains patients with acute chest discomfort but no persistent ST-segment elevation which is expressed on a microscopic level by necrosis of myocytes (NSTEMI) or by solely ischemia without necrosis (unstable angina) [Ibanez et al., 2018; Collet et al., 2020]. Immediate coronary angiography and, if applicable, revascularization, are indicated, taking into account the risk of developing CS and/or malignant ventricular arrhythmias.

The definition of acute myocardial infarction (AMI) refers to coagulative necrosis of cardiac cells related to acute myocardial ischemia [Collet et al., 2020]. The diagnostic criteria of AMI require an increase and/or decrease of a cardiac biomarker level along with one of the following elements: (1) symptoms of myocardial ischemia; (2) new ischemic ECG changes; (3) development of pathological Q waves on ECG; (4) imaging evidence of loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; (5) intracoronary thrombus detected on angiography or autopsy [Collet et al., 2020].

Unstable angina is defined by ESC as myocardial ischemia at rest or on minimal exertion without myocyte injury/necrosis. The hs-cTn measurements instead of standard troponin analyses resulted in increased detection of MI (4% absolute and 20% relative increases) and a mutual

decrease in the diagnosis of unstable angina [Reichlin et al., 2012; Braunwald and Morrow, 2013; Reichlin et al., 2013; Shah et al., 2014; Shah et al., 2018]. It was shown that compared with NSTEMI patients, subjects with unstable angina have no acute cardiomyocyte injury/necrosis, present a significantly lower risk of death, and seem to derive less benefit from increased antiplatelet therapy, as well as an invasive strategy within 72 h [Roe et al., 2000; Reynolds et al., 2011; Thygesen et al., 2019; Puelacher et al., 2019; Collet et al., 2020].

Acute heart failure is a common complication of NSTE-ACS. According to previous data, these patients present a two to four-fold higher risk of in-hospital mortality compared with NSTE-ACS without acute heart failure [Bahit et al., 2013; Chioncel et al., 2017; Arrigo et al., 2017]. Sometimes, the diagnosis of NSTE-ACS in the context of acute heart failure can be difficult since patients with acute heart failure may have chest discomfort; moreover, myocardial injury with troponin elevation can occur in the absence of obstructive CAD and the ECG may not be interpretable [Harjola et al., 2020]. In these cases, coronary angiography may be necessary for the NSTE-ACS diagnosis.

The current recommendations for the management of acute heart failure are very accurate [Mebazaa et al., 2015; Ponikowski et al., 2016]. All data regarding LVEF, regional wall motion abnormalities, right ventricular function, presence of valvular heart disease, and volume loading can be obtained by performing an emergency echocardiography [Ponikowski et al., 2016; Neumann et al., 2019]. The revascularization approach should consider LV function, the coronary anatomy, comorbidities,and the functional relevance of stenosis [Neumann et al., 2019].

Cardiogenic shock (CS) represents one of the most important causes of mortality worldwide [Berg et al., 2019; Vahdatpour et al., 2019], being a major challenge in acute cardiovascular care [Kolte et al., 2014; van Diepen et al., 2017]. Almost 5% to 10% of acute myocardial infarction (AMI) are complicated with CS [Hochman et al., 1999; Hartley et al., 2016; van Diepen et al., 2017; Vrints, 2018; Ibanez et al., 2018; Vahdatpour et al., 2019]. In 2019, the Society of Cardiovascular Angiography and Interventions (SCAI) has proposed a new classification of cardiogenic shock, dividing patients into five subgroups: patients at risk of developing CS (A), patients with beginning CS (B), classic CS (C), deteriorating patients (D) or patients presenting in extremis (E)[Baran et al., 2019]. In 2020, Schrage et al. applied this classification in a broad real-world cohort of patients with cardiogenic shock and demonstrated that higher SCAI class was significantly associated with lower 30-day survival (Schrage et al., 2020).

One-third to one-half of patients with inferior myocardial infarction develop right ventricular myocardial infarction (RVMI) [Albulushi et al., 2018; Liao et al., 2010] and less than 10% of those with anterior myocardial infarction. Isolated RVMI is rare (< 3% of all cases of fatal infarction) [Kakouros et al., 2010; Harnett et al., 2016; Kosuge et al., 2016; Alhamshari et al., 2017; Marin et al., 2019]. RVMI has a reserved short term prognosis due to hemodynamic and electrophysiological complications [Nadziakiewicz et al., 2017]. Appropriate identification and

treatment of these patients is very important in order to decrease mortality [Lewicki et al., 2015; Namana et al., 2018].

Other studies proved that almost 4% of patients with NSTE-ACS may develop CS [Holmes et al., 1999; Kolte et al., 2016] in the context of ischemia-related heart failure, acute severe mitral regurgitation, and mechanical complications. In this situation, immediate coronary angiography is indicated and PCI should be realized. Approximately 80% of such patients have CAD with multivessel involvement. According to Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial [Thiele et al., 2017], non-culprit lesions should not be usually treated immediately, and PCI strategy should be limited to the culprit lesion only. The results of CULPRIT-SHOCK proved that in culprit-lesion only PCI led to a significant reduction in all-cause death or renal replacement therapy at 30-day follow-up, favoring culprit-lesion only PCI with possible staged revascularization [RR 0.83, (95% CI 0.710.96)][Thiele et al., 2017]. Emergency CABG should be performed only in patients with a coronary anatomy not suitable for PCI.

It is known that CAD is the most common cause of HF in Europe. Management recommendations are based on clinical trials including patients with ischemic cardiomyopathy. Myocardial injury and ischemia are the main factors involved in the pathophysiologic mechanism of systolic dysfunction. Patients with symptomatic HF have a reduced ejection fraction (<50%) and they should be treated according to the 2016 ESC HF guidelines [Ponikowski et al., 2016]. Randomized clinical trials that sustain the use of drugs and devices in patients with chronic heart failure are founded on cohorts with stable ischemic heart disease and reduced LV function. Though, patients with CCS necessitating acute or chronic mechanical support are basically excluded from clinical trials. Consequently, the optimal management of such patients with drugs and devices during episodes of acute decompensation has not been sufficiently approached [Knuuti et al., 2020].

Clinical practice proved that hypertension is associated with an increased risk of developing HF and that antihypertensive treatment significantly reduces the incidence of HF. As a previous cohort study performed in 2015 by Lip et al showed, in a population with incident HF, higher baseline systolic, diastolic, and pulse pressure levels were linked with an increased rate of adverse events [Lip et al., 2015]. Consequently, blood pressure control is a key component of the general management of patients with HF.

This direction of research is reflected in the following published articles and projects:

Şalaru DL, Macovei L, **Stătescu C**, Arsenescu-Georgescu C. Assessment of microalbuminuria in hypertensive patients with established coronary artery disease. *Rev Romana Med Lab* 2013; 21(4):407-14. **IF: 0.171**
http://www.rrml.ro/articole/articol.php?year=2013&vol=4&poz=5

Anghel L, Prisacariu C**,** Sascău R, Macovei L, Cristea EC, Prisacariu G, **Stătescu C.** Particularities of acute Myocardial Infarction in Young Adults. *Journal of Cardiovascular Emergencies* 2019; 5(1):25-31.
https://www.jce.ro/wp-content/uploads/2019/04/jce-2019-0005-1.pdf

Zavalichi MA, Nistor I, Nedelcu AE, et al. Extracorporeal Membrane Oxygenation in Cardiogenic Shock due to Acute Myocardial Infarction: A Systematic Review. *Biomed Res Int* 2020; 2020:6126534. **IF:2.276**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7193268/pdf/BMRI2020-6126534.pdf
Research projects

„SIGNifY" – study with ivabradine in patients with coronary heart disease, 2010 - 2014; international contract, sub-investigator.
„CLARifY" – international register, regarding the diagnosis, evaluation, and treatment, evolution of the patient with coronary heart disease, 2010-2015; coinvestigator.
„SOLID – TIMI 52" – A Clinical Outcomes Study of Darapladib Versus Placebo in Subjects Following Acute Coronary Syndrome to Compare the Incidence of Major Adverse Cardiovascular Events (MACE) - international contract, phase III, multicenter, randomized, double-blind, placebo-controlled, in dyslipidemic patients after acute coronary accident, 2009 - 2014; study coordinator.
"AEGIS-II" - international phase 3 contract, double-blind, multicenter, randomized, placebo-controlled – aimed to investigate the efficacy and safety of CSL-112 in patients with Acute Coronary Syndrome; ongoing from 2019; principal investigator

1.2. Microalbuminuria in hypertensive patients with coronary artery disease

1.2.1. Introduction

Microalbuminuria (MAU) defines an abnormal increase in the rate of urinary excretion of albumin. This condition represents an early indicator of diabetic kidney disease and a marker of endothelial dysfunction and atherosclerotic disease.

Numerous studies describe microalbuminuria as a powerful independent predictor of small blood vessel lesions, cardiovascular disease [Borch-Johnsen et al., 1999], cardiovascular mortality, and kidney disease, including end-stage renal failure [Wada et al., 2012; Fox et al., 2012].

MAU levels emerged as a valuable tool for risk stratification of hypertensive patients [Böhm et al., 2007], since several trials displayed evidence that early determination and treatment of microalbuminuria, as well as blood pressure control, can delay the onset and the complications of cardiovascular disease [Parving et al., 2001; Ibsen et al., 2005].

MAU has often been related to atherosclerotic cardiovascular disease burden [Agrawal et al., 1996; Jensen et al., 1996], and to an increased level of atherosclerotic risk markers in hypertensive patients [Pontremoli et al., 1997].

The link between MAU and the development of the vascular disease is supported by its presence in acute ischemic heart disease [Jensen et al., 2000], stroke [Yuyun et al., 2004], congestive heart failure [Vaur et al., 2003], peripheral arterial disease, and carotid atherosclerosis [Lakka et al., 1999].

Consequently, MAU might aid as a 'diagnostic window' for blood vessels, being a marker of endothelial dysfunction [Schmieder et al., 2007; Fox et al., 2012].

1.2.2. Aim

The objective of our research was to investigate the clinical significance of MAU in high-risk hypertensive patients with known coronary heart disease and to emphasize important correlations with traditional cardiovascular risk factors.

1.2.3. Material and methods

The *study group* included 94 patients with arterial hypertension and known coronary artery disease, admitted to the Institute of Cardiovascular Diseases from January 2012 to April 2013. All subjects were screened for MAU.

The exclusion criteria were fever (> 38ºC), renal disease (eGFR <60 ml/min/1,73 m^2, Cockroft-Gault formula), urinary tract infection, or patients having practiced extensive physical effort 24 h before the measurement.

The study was in accordance with the ethical principles of the Declaration of Helsinki and written informed consent was obtained from all patients. Data about medical history, demographics, biometric data, urine and blood collections, and laboratory analysis were noted within the study.

For the diagnosis of microalbuminuria, a first-morning urine sample was analyzed by immunoturbidimetry (MAU range: 20-200 mg/l, the microalbuminuric group) (subjects with urinary albumin excretion >200 mg/l were excluded, and those with values <20 mg/l were considered the normoalbuminuric group).

According to the guidelines, we defined hypertension as systolic blood pressure >140 mm Hg, diastolic blood pressure > 90 mm Hg, and/or use of antihypertensive drugs; dyslipidemia was defined as cholesterol > 180 mg/dl and/or HDL < 40 mg/dl in male patients and < 50 mg/dl in female patients and/or LDL > 160 mg/dl and/or triglycerides > 150 mg/dl and/or use of lipid-lowering treatment; obesity was defined as BMI ≥ 30 kg/m^2; diabetes was defined as fasting plasma glucose levels > 126 mg/dl and/or use of antidiabetic therapy.

We echocardiographically assessed left ventricular hypertrophy (LVH) and left ventricular ejection fraction (LVEF). LVH was defined as posterior wall thickness or/and interventricular septum thickness > 12 mm). LVEF was determined via the Sympson method.

Statistical analysis was performed with SPSS 21.0 (SPSS Inc., Chicago, IL, USA). All data were presented as mean ± SD for continuous variables and as percentages of the total number of patients for categorical variables.

Correlation analysis was conducted using Pearson (r) or Spearman (ρ) tests. The data were also logarithmically transformed to achieve normal distribution, whenever possible.

A univariate analysis was performed using a *t*-test for normally distributed continuous variables and Mann-Whitney test if variables were not normally distributed.

For comparisons of categorical variables, Chi-square test was used. A P value ≤ 0,05 was considered significant.

1.2.4. Results

The main characteristics of the study population are presented in Table I. 53.2% of our study group was represented by high-risk hypertensives showing evidence of MAU, while 80% were dyslipidemic. Subjects having microalbuminuria were older, mostly male, with a longer duration of hypertension, and with a higher prevalence of left ventricular hypertrophy. Our results showed that LVEF values did not display a statistical significance in relationship with microalbuminuria (p=0.824).

In order to assess the relationship of microalbuminuria with traditional risk factors, a correlation analysis was performed: male gender (p=0.48), age (p=0.07), smoking (p=0.139), diabetes mellitus (p=0.75), dyslipidemia (p=0.406), obesity (p=0.837) but none of them showed a statistical significance.

Also, MAU and serum levels of glucose and lipids didn't exhibit any correlation (ρ = -0.002 and 0.041, respectively); moreover, MAU was not influenced by eGFR (p=0.249). Still, a strong correlation was achieved with the presence of left ventricular hypertrophy (p=0.005, Figure 1) and duration of hypertension (p=0.046).

Table I. Clinical and biological characteristics of the study population

	Normoalbuminuric group n = 44	**Microalbuminuric group n=50**	**p-value**
Age, y	60 (50-72)	62.5 (55-75)	p=0.29
Male, %	54.50%	60%	p=0.67
Smokers, %	56.80%	46%	p=0.31
Hypertension, y	5 (2-9)	6 (3-10.25)	p=0.26
Dyslipidemia, %	77.30%	80%	p=0.8
Diabetes mellitus, %	52.30%	44%	p=0.53
Obesity, %	36.40%	46%	p=0.4
LVH, %	50%	66%	p=0.144
EF (%)	45 (35-50)	45 (40-50)	p=0.676
Laboratory data			
Glucose (mg/dl)	117 (105-180)	108 (100.25-173)	p=0.179
HDL-C (mg/dl)	50 (32-59)	48 (38.75-54)	p=0.964
LDL-C (mg/dl)	113 (95-164)	119 (93-139)	p=0.578
Cholesterol (mg/dl)	185 (159-221)	193 (163.5-215.25)	p=0.894
Triglycerides (mg/l)	154 (108-200)	118(73-212.25)	p=0.1
eGFR (ml/min/1.73m2)	89.6 (64.3-117.97)	84.65 (68.64-99.75)	p=0.74
Microalbuminuria (mg/l)	10.12 (6.21-15.77)	48.65 (30.62-87.06)	
logmicroalbuminuria	1 (0.78-1.19)	1.68 (1.48-1.93)	

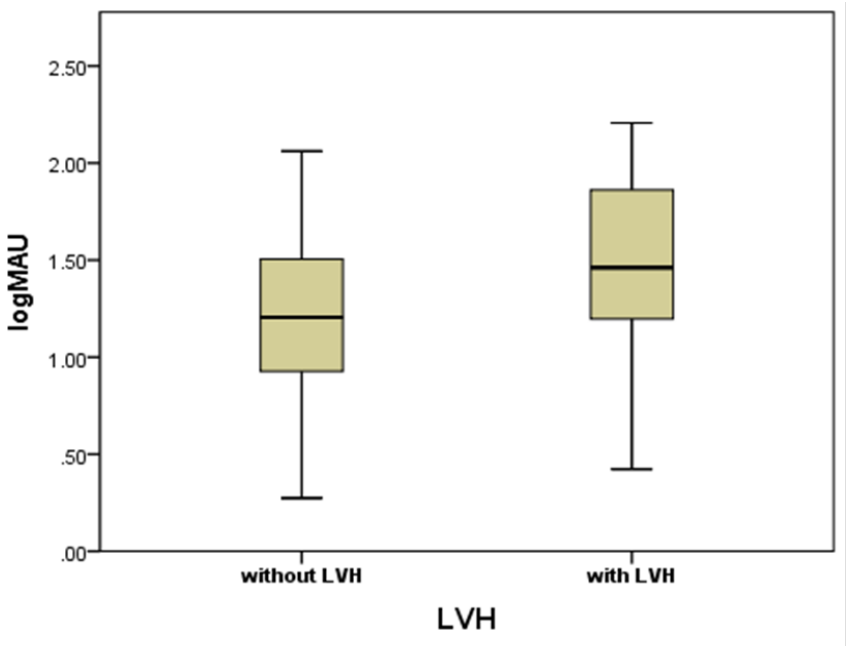

Figure 1. Relationship between level of MAU (logMAU) and the presence of LVH

1.2.5. Discussion

Our results proved a high prevalence of MAU among patients with coronary artery disease. The prevalence of MAU in patients with hypertension and diabetes varied between 10% to 15% and 15% to 20%, respectively, in previous reports; the value is higher than the prevalence in individuals from the general population in whom values of 6% to 8% have been described [Garg et al., 2002; Hillege et al., 2001].

It is known that hypertensive patients have an increased cardiovascular risk and a higher mortality rate than the general population. Mahfoud et al showed in the I-SEARCH study, that MAU values are related with the number of associated morbid disorders [Mahfoud et al., 2012]. Copenhagen City Heart study proved a solid correlation between MAU and the metabolic syndrome [Klausen et al., 2007]; the results highlighted the association between MAU and an increased risk of death and cardiovascular disease. Our study cohort had a high prevalence of the elements of metabolic syndrome, but we did not measure its effect individually. I-SEARCH study showed that, similar to our results, patients with LVH presented microalbuminuria in 68% of the cases [Mahfoud et al., 2012]. Previous reports showed that LVH is a strong and independent predictor of both cardiovascular events and all-cause mortality in patients with hypertension [de Simone et al., 2008]. Consequently, those patients with electrocardiographically or echocardiographically proven LVH should be systematically examined.

HOPE study results indicated that coronary heart disease in individuals with or without diabetes may be predicted by any level of MAU [Gerstein et al., 2001] and that MAU is a strong determinant of coronary artery disease and death independently of age, sex, hypertension, diabetes

mellitus, renal function, and lipids [Klausen et al., 2004]. It is essential to identify and treat hypertension as early as possible [Kannel et al., 2000].

The presence of MAU reveals vascular injury and is connected with a negative risk score and target organ damage. Though, the relation between MAU and coronary artery disease is not clearly explained. The pathological changes causing MAU and those leading to premature atherosclerosis appear to be similar. Endothelial dysfunction, the initial stage of atherosclerosis with low grade inflammation, is documented in both MAU and cardiovascular disease [Deckert et al., 1992; Stehouwer et al., 2006]. Microalbuminuria is associated with inflammatory and prothrombotic changes and thus may represent a favorable condition for atherosclerosis [Deckert et al., 1989; Stehouwer et al., 1992; Stehouwer et al., 2002; Klausen et al 1999; Festa et al., 2000]. According to previous studies, MAU reflects a systemic transvascular outflow of albumin, which may be connected with the leakage of lipoproteins and other macromolecules [Jensen et al., 1995; Jensen et al., 2005]. As a result, the modified endothelial permeability allows lipid influx into the intima initiating atherosclerotic process [Garg et al., 2002]. With regard to small blood vessels injury, previous research [Ayerden Ebinç et al., 2008] proved that vascular endothelial growth factor (VEGF) levels are higher in hypertensive patients in the coexistence of MAU. It is known that VEGF controls the process of angiogenesis and additionally increases vascular permeability; as a result, it may also increase glomerular permeability and induce MAU in hypertension.

The European guidelines emphasize the significance of evaluating microalbuminuria as a routine measurement in every hypertensive patient [Mancia et al., 2009]. However, in 2010, American College of Cardiology and AHA [Greenland et al., 2010] underlined that novel risk factors or biomarkers, in addition to classical risk factors, should be considered in coronary heart disease risk prediction. Therefore, the MAU assessment is considered reasonable in adults with hypertension or diabetes; moreover, because of its relatively low cost and wide applicability, this test should be used in detecting patients at high risk for whom further preventive and therapeutic treatment are suitable [Viazzi et al., 2013].

Limitations of the study: Our study population does not allow predictions on a large-size effect because of the small number of subjects. Secondly, we used a single morning spot urine sample to assess microalbuminuria, as a substitute of timed urine collections, which would have been desirable. Thirdly, we did not use left ventricular mass index in order to appreciate LVH. Previous studies showed that the concordance between wall thickness and left ventricular mass index is only of 60% [Leibowitz et al., 2007]. However, echocardiography, if available, should be the test of choice to assess LVH, being much more sensitive than electrocardiography [Bauml and Underwood, 2010].

The lack of sustainable data about previous antihypertensive medication was another limitation. Results of ONTARGET trial have provided evidence for slowing the progression of renal disease demonstrated by level of microalbuminuria in at-risk patients, including those with diabetes, treated with telmisartan or ramipril [Mann et al., 2008; Mann et al., 2009]. Besides, ROADMAP trial showed that pharmacological blockade of angiotensin II receptors by olmesartan is effective in reducing the risk of new-onset albuminuria in type 2 diabetic patients [Chatzikyrkou

and Menne, 2012]. In this context, it would have been of interest the assessment of ACEI/ARB medication.

1.2.6. Conclusions

MAU is often underdiagnosed in high-risk hypertensive patients. In addition, awareness of its importance as a marker of cardiovascular risk is still poor. MAU is known as a strong, early and independent marker of cardiovascular morbidity and mortality; consequently, our study underlines the significance of microalbuminuria assessment and the necessity for a proper management of hypertensive patients.

Anghel L, Prisacariu C**,** Sascău R, Macovei L, Cristea EC, Prisacariu G, **Stătescu C.** Particularities of acute Myocardial Infarction in Young Adults. *Journal of Cardiovascular Emergencies* 2019; 5(1):25-31. https://www.jce.ro/wp-content/uploads/2019/04/jce-2019-0005-1.pdf

1.3.Myocardial Infarction in Young Adults

1.3.1. Introduction

Coronary heart disease (CHD) represents the leading cause of death worldwide. The prevalence of the disease accounts for about 80% of all deaths attributable to cardiovascular disease in developing and underdeveloped countries [Fournier et al., 2004]. According to the National Institute of Statistics, in 2016 the death occurrence in the context of a cardiovascular pathology was approximately 60% in the Eastern Europe, including Romania [Piepoli et al., 2016]. There are few data related to premature CHD and myocardial infarction (MI) in the "young" patients, irrespective of the consequences on the patient's psychology, ability to work and socio-economic burden [Shah et al., 2016]. The age which defines a "young" or "young adult" varies in literature from 40 years [Gale et al., 2014; Yunyun et al., 2014] to 55 years [Hoit et al., 1986], growing over time due to an increase in life expectancy. In the current ESC Guidelines, the term "young" delineates patients under the age of 45 years [Ibanez et al., 2018], people under the age of 35 being considered "very young" [Akram et al., 2015].

1.3.2. Aim

The article aimed to present the particularities of acute myocardial infarction occurring at a young age, in comparison with the rest of the population with AMI.

1.3.3. Material and methods

Although young patients with acute myocardial infarction represent a relatively small proportion of subjects suffering from an acute ischemic event, they represent a subgroup that is

distinguished from elderly patients by different risk factors, frequently atypical clinical presentation, and different prognosis. Therefore, we revised medical database studies that address the particularities of acute myocardial infarction in young people.

1.3.4. Results

By conducting a literature search on several databases, as Medline, PubMed, Embase, CINAHL, PsycInfo, and Ageline and reviewing Clinical Evidence, UpToDate, and the websites of major guideline development organisations an updated information on the diagnostic and therapeutic approaches of myocardial infarction in young patients was attained.

1.3.5 Discussions

Few data are published in the medical literature with regard to acute myocardial infarction in young people. "Framingham Heart Study" carried out for a 10-year follow-up period, reports an incidence of myocardial infarction in young people (<55 years) of 51.1 / 1000 in men and 7.4 / 1000 for women [Kannel and Abbott, 1984], compared to older adults which ranges between for 8.45 % women and 23.4 % for men [Ibanez et al., 2018].

Generally, the patients suffering a MI at a "young" age have at least one identifiable cardiovascular risk factor [Ge et al., 2017; Goel et al., 2016]. A study performed in 1986 reported a higher prevalence of smoking, family history of premature CHD and male gender among "young" MI patients compared with their older counterparts [Hoit et al., 1986]. Numerous studies identified smoking as an important modifiable risk factors among "young" MI patients, with rates varying from 51 % to 89 % [Yusuf et al., 2004; Egiziano et al., 2013; McManus et al., 2011; Chan et al., 2012; Goliasch et al., 2012; Hosseini et al., 2009; Larsen et al., 2013]. Aggarwal et al. found that smoking was five times more prevalent in young AMI subjects than in age- and gender-matched patients presenting to hospital with non-cardiac complaints [Aggarwal et al., 2012]. "Young" MI patients seems to have a two-fold increase in the rate of family history of CHD or a family history of premature CHD compared to older individuals, usually defined as documented CHD in a first-degree relative before the age of 55-60 years [Hoit et al., 1986; Hosseini et al., 2009; Piepoli et al., 2016].

Analyzing the main causes of MI in "young" people, the literature discusses two categories: atherosclerotic and non-atherosclerotic underlying mechanisms.

Atherosclerosis is not only a disease of modern population linked to the lifestyle, but a process that initiates in early childhood; therefore, early detection can help prevent or delay the development of cardiovascular injuries. This condition starts silently and ends noisily [Calais et al., 2018]. Endothelial dysfunction has an essential role in the onset of atherosclerotic process. The increase of the vascular permeability with lipoprotein accumulation in the intima, adherence of the monocytes and platelets with increased endothelial aggregation activity and decreased vasodilatation are few processes linked to the pathogenesis of atherosclerosis [Chaudhary et al., 2016]. Previous reports showed that endothelial function can be genetically modulated, being

affected by insertion/deletion polymorphism in angiotensin-converting enzyme genes; moreover, the polymorphism of the gene encoding vascular endothelial growth factor impacts coronary artery disease severity [Calais et al., 2018]. In approximately 20% of young patients with myocardial infarction, angiography reveals normal coronary arteries, unlike those over the age of 45, with a prevalence of only 10%. The percentage is even higher, up to 53% for patients under 35 years old [Gostman et al., 2003; Hosseini et al., 2009].

Non-atherosclerotic causes of acute myocardial infarction include inflammatory disease, coronary artery trauma, metabolic or proliferative diseases, lumen stenosis of various causes, coronary embolism, congenital coronary anomalies, disproportion on the oxygen demand-supply in the myocardium, hematological causes [Hoit, 1986].

Classical cardiovascular risk factors

The risk factor profile of young people diagnosed with acute MI consist of smoking, dyslipidemia and a family history of coronary artery disease in young age (TableII) [Leifheit-Limson et al., 2015; Lu et al., 2017]. Table III summarizes literature data on the frequency of some characteristics and risk factors by gender (Table III) [Lu et al., 2017]. The relationship between the two sexes is in favor of men. Numerous studies show a male: female ratio which ranges between 5 : 2 to 9: 1 [Gostman et al., 2003; Goel at al., 2016; Chaudhary et al., 2016]. A 7-year study in America performed by Egiziano et al. also reported higher incidence in men than in women [Egiziano et al., 2013]; still, in-hospital mortality was significantly higher for women: 4.5% versus 3% [Kehera et al., 2015].

The most common risk factor identified in younger patients who have experienced a cardiovascular event is smoking, different studies reporting an incidence ranging from 55% [Goel et al., 2016] to 89% [Larsen et al., 2013; Shah et al., 2016].

Table II. Comparison between cardiovascular risk factors [Lu et al., 2017]

	Patients <45 years	**Patients >45 years**
Prevalence of myocardial infarction	-	+
Only one cardiovascular risk factor	-	+
Smoking	+	-
Family history	+	-
Dyslipidemia	+	-
Arterial hypertension	-	+
Diabetes mellitus	-	+
Coronary artery disease	+	-

Dyslipidemia has a higher incidence in subjects under 45 years who suffer of an acute coronary syndrome, while arterial hypertension is more common in patients over 45 years old. There was reported an incidence of arterial hypertension of 23% in a European study [Incalcaterra et al., 2013], compared with 25% in a study in India [Goel et al., 2016].

Diabetes mellitus, an independent risk factor in cardiovascular pathology, is reported in a smaller number of cases of younger patients suffering an AMI compared to elderly patients. The prevalence of diabetes mellitus, an independent risk factor in cardiovascular pathology, ranged from 14.7% in a study conducted in Australia [Shah et al., 2016] to 20% in a study performed in India [Goel et al., 2016]. Previous studies showed that the risk of myocardial infarction is six times higher in young women with diabetes compared to those without diabetes. Moreover, the risk is 4 times higher in women with hypertension, three times higher in those with dyslipidemia, compared to women where these risk factors are not present [Siegerink et al., 2015; Sreckovic et al., 2015].

In 2016, Shah et al. showed that young people diagnosed with acute myocardial infarction tend to have an increased body mass index, and more often, central obesity [Shah et al., 2016]. Another study conducted in India reported a 20% prevalence of obesity and 46% of sedentariness in a group of young patients with AMI hospitalized during a year [Goel et al., 2016].

Table III. Different characteristics between young men and women with cardiovascular events **[Lu et al., 2017]**

	Men <45 years	**Women <45 years**
Prevalence	+	-
Smoking	+	-
Dyslipidemia	+	-
Family history	+	-
Arterial hypertension	-	+
Diabetes mellitus	-	+
Associated pathologies	-	+
Coronary vasospasm	+	-
In-hospital mortality	-	+
Long term mortality	-	+

The major factor responsible for the increasing incidence of obesity is the urbanization process, which has changed the lifestyle of the young population [Shah et al., 2016] and the eating habits, with low consumption of vegetables and high ingestion of high-fat foods. However, obese people have displayed better outcomes and fewer complications following a coronary revascularization procedures, regardless of the high rates of CAD. This phenomenon has been

named the obesity paradox and basically refers to the observation that while the risk of developing coronary heart disease is greater in obese individuals, the clinical outcomes - including cardiovascular mortality, myocardial infarction [MI], and related complications - are less common in these individuals after a coronary revascularization procedure [Patel et al., 2017].

In addition to classical risk factors, the medical research focused on the level of homocysteinemia, lipoprotein(a), factor V Leiden, thrombophilia, antiphospholipid antibody syndrome (APS), contraceptive medication, or cocaine use.

Hyperhomocysteinemia influences the development of atherosclerosis, and subsequently of acute coronary and cerebrovascular events. Homocysteine is an amino acid resulting from the metabolization of methionine and cysteine under the influence of vitamins B6, B12 and folic acid [Sreckovic et al., 2017].

Abnormalities in homocysteine metabolism lead to increased serum and urine levels of this metabolic product. The direct toxic effect on vascular endothelium along with stimulation of vascular smooth muscle cells proliferation, platelet activation and alteration of fibrinolysis, explains the increasing risk of cardiovascular events.

Homocysteine undergoes oxidation and forms free radical in the blood serum which promotes the atherosclerotic process; thus, the vessels walls lose their elasticity and vasodilating properties [Gale et al., 2010].

Lipoprotein(a) represents another independent risk factor for ischemic cardiovascular disease [Sreckovic et al., 2017] which has a plasminogen-like structure. It is stored in the thickness of the arterial wall, mainly in the atherosclerotic plaques areas, together with fibrinogen [Wiesbauer et al., 2009].

Thrombophilia has been specifically studied in young patients who have had an AMI. Previous studies showed that AMI was usually linked with an increased procoagulant activity due to an increase in V and II factor concentrations in woman, while in men, it was mostly determined by homozygosity for MTHFR variants with hyperhomocisteinemia [Nazir et al., 2017].

In young people, thrombocytosis represents a cause of myocardial infarction being considered a precipitating factor for coronary artery obstruction when atheromatous lesions are present. However, myocardial infarction after splenectomy secondary to thrombocytosis has been reported in the absence of coronary atherothrombotic injuries [Varner et al., 2018].

Factor V Leiden defects - generally reported in smokers and in those who use oral contraceptives - are connected with a high risk of cardiovascular events via their procoagulant effect [Maino et al., 2016; Maor et al., 2015].

Atherosclerosis may emerge in connective tissue diseases, in the context of chronic systemic inflammation, and occasionally due to long-term therapy. AMI is a rarely reported entity in these cases, most often through coronary vasculitis and/or atherothrombotic occlusive lesions. Chaudhary et al. showed that women with systemic lupus erythematosus have a 50-fold greater risk of developing myocardial infarction than women without the disease [Chaudhary et al., 2016].

Antiphospholipid antibody syndrome (APS) is associated with AMI in approximately 2.8% of affected patients [Nazir et al., 2017], but in young patients with acute coronary syndromes

it was diagnosed in 13-21% of cases [Cervera et al., 2002]. APS presents as a thrombotic disorder of both arteries and veins. Acute thrombosis of coronary arteries produces myocardial ischemia in APS, requiring therefore therapeutic anticoagulation [Cervera et al., 2002].

Thus, in young patients with AMI, especially if previous thromboses, lower platelet counts, high partial thromboplastin times, and normal coronary arteries or coronary thromboses are identified, APS should be considered.

For these patients, life-time anticoagulation is required, even after a single first episode; though, the role of coronary stents in these patients is still under debate and needs further research [Nazir et al., 2017].

Contraceptive medication has been reported in 40% of women who have had an AMI [Maino et al., 2016], but information related to AMI in this group are contradictory, being influenced by the type of contraceptives, the presence or absence of smoking, high blood pressure or prothrombotic status, which may increase by 10 times the risk of myocardial infarction [Roach et al., 2015].

Cocaine use has been linked to acute myocardial infarction and other cardiovascular events [Ibanez et al., 2018; Vasilcu et al., 2018]. Yunyun et al noted the cocaine use in 48% of cases of patients younger than 30 years admitted with non-traumatic anterior chest pain [Yunyun et al., 2015; Shah et al., 2016].

Also, the use of marijuana and amphetamines was discussed in this context, without being certified [Velibey et al., 2015].

With regard to clinical presentation and management of AMI in "young" patients, several studies showed that almost one third will present with ST- segment elevation myocardial infarction (STEMI) and two-thirds will present with non-ST elevation myocardial infarction (NSTEMI)[McManus et al., 2011].

Generally, the incidence of STEMI is reduced among the "young" patients but the proportion of "young" patients diagnosed with AMI is increasing [McManus et al., 2011]. "Young" MI patients do not have a history of previous angina, MI or congestive heart failure as compared with the older patient demographic [Hoit et al., 1986; Doughty et al., 2002]. Egiziano et al. reported that only about 25% of "young" MI patients presented chest pain the month before their address for acute coronary event [Egiziano et al., 2013], and the rate was even lower among women.

In addition, younger patients with acute myocardial infarction have less extensive coronary artery disease. A study of Zimmerman et al. reported normal coronary arteries in 16% of men and 21% of women [Zimmerman et al., 1995]. Among "young" MI patients, a single coronary artery disease is more frequent [Chan et al., 2012] and the most commonly affected branch is the left anterior descending artery [Zimmerman et al., 1995; Chan et al., 2012].

Additionally, spontaneous coronary artery dissection is more frequent in young patients than their older counterparts. In this regard, Tweet et al. described the occurrence of this pathology in "young" patients with a mean age of 43 years, commonly women [Tweet et al., 2012].

The guidelines advocate for the same management of myocardial infarction in young patients as to their older counterpart [Ibanez et al., 2018]. Taking into account that "young" age is an independent predictor for favorable prognosis following thrombolysis [Moccetti et al., 1997], it should still be applied when primary angioplasty cannot be performed.

An improved control of risk factors is extremely important in the management of myocardial infarction in young patients. Smoking is one of the most important modifiable risk factor among "young" MI subjects.

Critchley et al. studied the benefit of smoking cessation in patients with CHD and reported a 36% reduction in basic relative risk of mortality for patients with CHD who quit smoking compared to those who continued to smoke (relative risk 0.64: 95% CI, 0.58-0.71)[Critchley et al., 2003]; coronary events also appear to be reduced by smoking cessation.

The prognosis is generally favorable in "young" MI patients. Previous studies showed that in-hospital and six-month mortality in young patients with AMI is 0.7% and 3.1%, respectively [Puymirat et al., 2012], compared with older counterparts whose mortality is 8.3% and 12% [Lichtman et al., 2018].

A left ventricular ejection fraction ≤ 45% seems to be the strongest independent risk factor for mortality (OR 4.4: 95% CI, 1.6-12.4)[Fournier et al., 2004]. Epidemiological studies showed a significant reduction of heart failure incidence from 20% in 1970s to below 6% in 2005 among "young" MI patients [Schmieder et al., 2007], probably due to a mixture of factors including the use of prophylactic implantable cardiac defibrillators. Heart failure, malignant ventricular arrhythmias, angina pectoris and re-infarction are other factors associated with higher mortality [Fournier et al., 2004].

An important issue is the significant reduction of health-related quality of life post MI in "young" MI patients. Depression and angina are the most frequent problems occurring post - MI [Ziegelstein et al., 2001], Denollet et al. reported depressive symptoms post MI occurring in approximately 47% of cases with a mean age of 54 years [Denollet et al., 1995]. Therefore, an appropriate management of depression and angina following MI in "young" patients determines an improvement in health-related quality of life [Longmore et al., 2011].

1.3.6. Conclusions

Young subjects with AMI represent a subgroup of patients that is distinguished by a specific risk factor profile, atypical clinical presentation and different prognosis when compared to elderly patients. Short-term outcome post-MI is positive, but longer-term prognosis is relatively poor, especially in patients with reduced left ventricular ejection fraction.

Zavalichi MA, Nistor I, Nedelcu AE, et al. Extracorporeal Membrane Oxygenation in Cardiogenic Shock due to Acute Myocardial Infarction: A Systematic Review. *Biomed Res Int* 2020; 2020:6126534. **IF:2.276**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7193268/pdf/BMRI2020-6126534.pdf

1.4. Extracorporeal Membrane Oxygenation in Cardiogenic Shock due to Acute Myocardial Infarction

1.4.1. Introduction

Epidemiological studies showed that myocardial infarction accounts for 5–10% of patients with cardiogenic shock [Goldberg et al., 1999; Goldberg et al., 2001]. Moreover, cardiogenic shock is the main cause of mortality in patients with acute myocardial infarction (AMI) [Noc, Radsel, 2008], the incidence of cardiogenic shock increasing from 6.5% in 2003 to 10.1% in 2010 [Kolte et al., 2014]. Patients having an AMI commonly undergo percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) in order to restore the blood flow, although success rate remains low, despite maximum therapy [Khalid, Dhakam, 2008]. With this regard, innovative strategies for reperfusion therapy have been linked with improvement in survival rates; yet, significant differences between trials are reported [van Diepen et al., 2017].

The 2017 European Society of Cardiology Guidelines suggest the use of short-term active mechanical support in cardiogenic shock based on a class IIb, level of evidence C [Ibanez et al., 2018].

The use of intra-aortic balloon counter pulsation (IABP) among patients with AMI and cardiogenic shock did not reduce early or late mortality, as demonstrated in the IABP-SHOCK II trial [Thiele et al., 2012], while ventricular assist devices (VAD) and ECMO are increasingly popular but have not been sufficiently evaluated in clinical trials [Ibanez et al., 2018].

The new extracorporeal membrane oxygenation (ECMO) machine offers support similar to the cardiopulmonary bypass by using a centrifugal pump and a membrane oxygenator with a drainage and return cannula.

Recent studies revealed that venoarterial ECMO has the benefit of preserving an optimal cardiac output, before or after coronary revascularization, allowing the use of lower doses of vasoactive drugs. ECMO was linked with high survival rates (up to 51% survival to discharge) in cardiogenic shock, being used as saving therapy in these patients [El Sibai et al., 2018], with short- and long-term survival benefits of cardiopulmonary resuscitation compared to standard care [Chen et al., 2008].

Extracorporeal Life Support Organization guidelines integrate special algorithms for using ECMO as a bridge-to-recovery approach for postacute myocardial infarction [ELSO, 2017]. Moreover, other mechanical devices are used after ECMO initiation, to offer optimal hemodynamic conditions and reducing time on ECMO, with beneficial impact on cardiogenic shock [Flaherty et al., 2017].

ECPELLA strategy, representing the combination of Impella and V-A ECMO has proved to be effective in several trials and to avoid increased left ventricular afterload during extracorporeal support [Patel et al., 2019]. Yet, survival benefits of ECMO therapy for cardiogenic shock are not consistent, showing a great variability of potential advantages versus disadvantages of this type of mechanical support [Meani et al., 2019].

1.4.2. Aim

Our report evaluates the impact on survival, potential benefits, and side effects of V-A ECMO in patients with cardiogenic shock due acute myocardial infarction (ST-segment elevation myocardial infarction and non-ST segment elevation myocardial infarction) in a systematic way.

1.4.3. Material and methods

The study protocol has been registered in the PROSPERO database of systematic review protocols, under registration number CRD42019123982. We have searched PubMed/MEDLINE (inception (1969) to January 10, 2019), ProQuest (inception (January 14, 1988) to January 10, 2019), and clinicaltrials.gov (inception (September 12, 2005) to January 10, 2019) without language restrictions.

Within our research, we paid attention to observational studies and randomized clinical trials for adults with myocardial infarction complicated by cardiogenic shock that were treated with ECMO for mechanical circulatory support. We analyzed information about the impact of V-A ECMO on survival, ECMO duration, ECMO complications, and the opportunity to switch to ventricular assist devices, using only studies performed on more than 10 patients.

Data extraction was done independently by 2 authors using standardized data extraction forms, including identifiable information, study outcomes, details of the study protocol, and demographic data, characteristics of each study, including type of ECMO; ECMO duration; survival rate at 1, 6, and 12 months; and whether ECMO has been used as a bridge to transplantation or not.

Disagreements were resolved by consultation between all authors. Methods used were similar to the methods of Bilha et al. [Bilha et al., 2018]. Quality of the selected studies was independently evaluated by 2 reviewers, using the Newcastle-Ottawa scale (NOS). Disagreements were resolved by consensus [Stang et al., 2010].

Statistical Analysis. We performed a narrative synthesis using data extraction tables, independently carried out by 2 authors.

1.4.4. Results

A flow diagram providing the selection process of the included studies is presented in Figure 2.

Our search resulted in 2,302 potentially appropriate articles, but a systematic analysis of the abstracts led to the exclusion of 219 articles with no interest for this review; moreover, 681 articles were excluded because the outcomes were not reported; 123 reported studies under 10 patients for analysis, case reports, editorials, and reviews (n = 1,095), and 5 duplicates were also excluded.

Therefore, a total of 179 full-text articles were methodically analyzed; 8 of these were excluded due to absence of survival data, 67 did not include the target population, 95 were excluded because they reported data about the use of intraaortic balloon counter-

pulsation/percutaneous ventricular assist device prior to ECMO. After an in-depth analysis, 9 observational studies involving 1,998 patients were included in this systematic review.

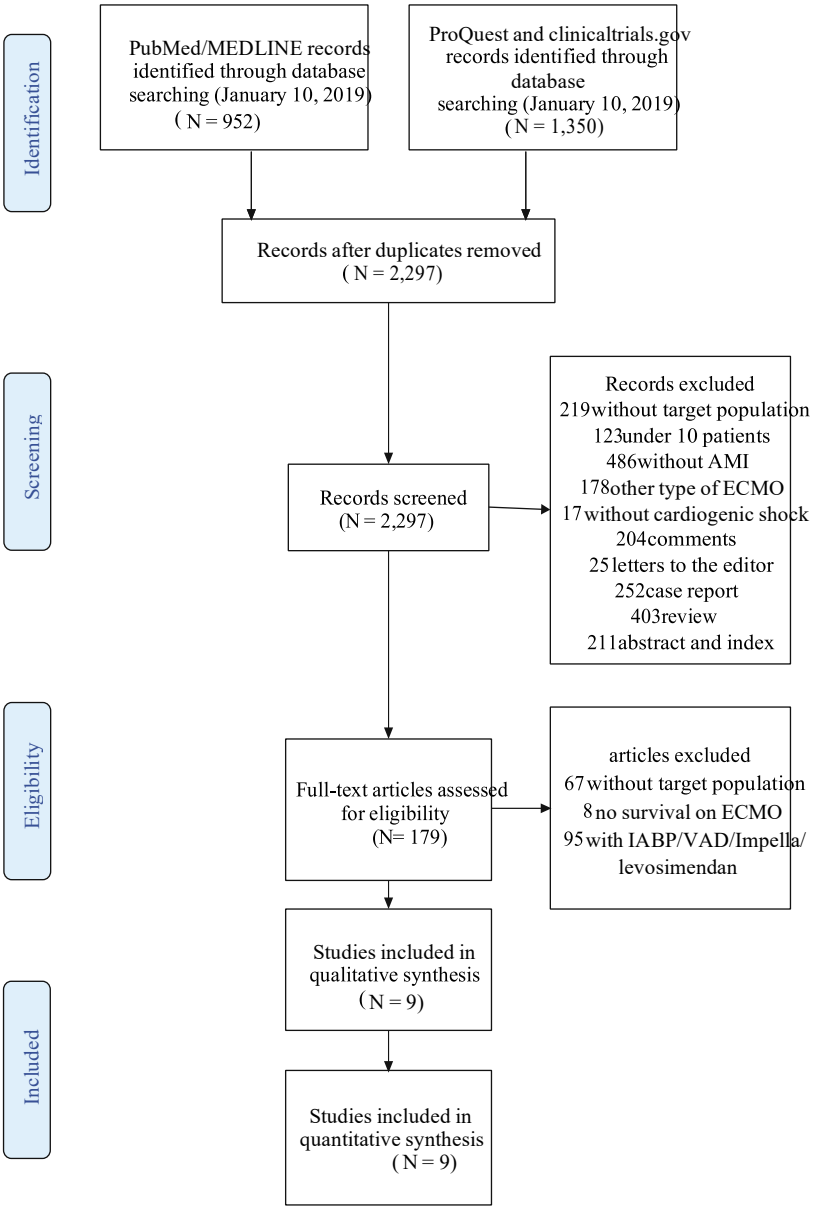

Figure 2. Selection process of the included studies

Baseline Study and Patient Characteristics. The median follow-up period generally varied between 1 and 12 months in the included studies; 3 studies in the People's Republic of China, 2 in Taiwan, 1 in Germany, 2 in the United States of America, and 1 in South Korea were performed. The mean age of the patients varied between 55 and 65 years; males accounted for 76.02% of the total number of patients.

The most frequent comorbidities were diabetes mellitus and stroke. A study conducted in 2015 [Negi et al., 2015] reported that 56.2% of the patients had diabetes. Stroke rates were similar, varying from 10.9% [Chang et al., 2016] to 14.2% [Wu et al., 2013].

Hypertension was present in 55.8% of the population included in the study by Chou et al. [Chou et al., 2014], in 46.6% of the patients by Chang et al. [Chang et al., 2016], and 45% by Huang et al. [Huang et al., 2017]. Several studies reported a history of previous heart disease [Wu et al., 2013; Chou et al., 2014; Sandoval et al., 2015; Chang et al., 2016; 22].

ECMO Duration varied from 1.96 days [Chang et al., 2016], to 2.75 days [Wu et al., 2013], 5.0 days [Guenther et al., 2014], 4.26 days [Huang et al., 2017], and 6 days. [Sandoval et al., 2015].

Survival on ECMO: Only 3 studies have reported the total number of patients weaned from ECMO and the number of those who did not survive to discharge after being weaned off [Guenther et al., 2014; Sandoval et al., 2015; Huang et al., 2017]. The data are summarized in Table IV.

Table IV. Patients weaned from ECMO.

Study	Number of patients weaned from V-A ECMO	Number of nonsurvivors after weaning
Negi et al. [17]	NA	NA
Chang et al. [18]	NA	NA
Wu et al. [19]	22	NA
Chou et al. [20]	15	NA
Huang et al. [21]	8	2
Sandoval et al. [22]	16	5
Guenther et al. [23]	15	3
Jeon et al. [24]	NA	NA
Fu et al. [26]	NA	NA

Study outcomes:

V-A ECMO Survival at Discharge at 1, 6, and 12 Months. Overall, survival at discharge was reported in 8 out of the 9 studies included, with the highest registered rate of 79.16% [Sandoval et al., 2015].

Regardless of this survival rate, the number of patients included was low, with only 21 subjects with no follow-up data being available. Survival at 1 month after extracorporeal life support varied between 34% [Chang et al., 2016], to 52% [Guenther et al., 2014], 39.8% [Jeon et al., 2018], and 58% [Negi et al., 2015].

Survival at 6 months ranged from 33.6% [Wu et al., 2013] to 37% [Jeon et al., 2018]. Survival at 12 months was reported as 73% [Wu et al., 2013], 23.2% [Chang et al., 2016], 34.9% [Chou et al., 2014], and 36.1% [Jeon et al., 2018].

Complications during Hospitalization of Patients with Cardiogenic Shock on ECMO Support. The most common adverse effect was acute kidney failure, seen from 45.7% of patients

[Wu et al., 2013] (25.7% were patients with chronic kidney disease), to 23% [Chang et al., 2016] (8.8% already had chronic kidney disease), and 58.3% [Sattler et al., 2014].

Nevertheless, only these 3 studies reported data for acute kidney injury. In view of peripheral complications, limb ischaemia was encountered in 8.5% of the study population [Wu et al., 2013].

In terms of cerebral complications, hypoxic ischaemic encephalopathy was the most common: 75% in Huang et al. [Huang et al., 2017], and 45.7% in Wu et al. [Wu et al., 2013]). Moreover, ischaemic stroke and intracerebral haemorrhage were also found (2.8% and 1.7%, respectively, in Chang et al. [Chang et al., 2016]). Gastrointestinal bleeding was reported in 63 patients, representing 3.6% (13.2% with previous gastric ulcer disease and 6.5% with cancer) of the study population [Chang et al., 2016].

Sepsis was found in 11.6% of patients [Chou et al., 2014], with only 1 case of septic shock [Huang et al., 2017]. Multiple organ failure was encountered in 48.8% [Chou et al., 2014] and 39.1% [Guenther et al., 2014] of the patients. Data related to complications associated with the use of ECMO were not reported in 4 studies [Negi et al., 2015; Sandoval et al., 2015; Jeon et al., 2018; Fu et al., 2017].

Opportunity to Switch to Ventricular Assist Devices: *Subgroup Analysis Transplantation and Assistive Devices*

(1) Heart Transplantation. A total of 2 out of 1,998 patients included in this review were eligible to receive a heart transplant, after weaning from ECMO [Wu et al., 2013; Guenther et al., 2014].

(2) Assistive Devices. The usage rate of assistive devices was low, being reported by 2 studies. In the study of Guenther et al. [Guenther et al., 2014], 2 patients underwent biventricular assist device implantation (Berlin Heart EXCOR®) and 2 left ventricular assist device implantations (HeartWare®); 4 out of 24 patients (16.6%) enrolled in the study conducted by Sandoval et al. [Sandoval et al., 2015] were further placed on left ventricular assist devices.

(3) Study Quality. Quality score of the included studies ranged from 5 to 9, with a mean quality score of 7. This corresponds to a medium-to-high quality of the included studies. The detailed scores are provided in Table V.

1.4.5. Discussion

Our review reveals a great variability in survival rates for patients treated with ECMO. The 9 analyzed studies with 1,998 patients showed that ECMO might be a useful instrument for increasing the survival rate in patients with cardiogenic shock due to myocardial infarction with rates varying from 30.0% to 76.2% [Asleh, Resar, 2019].

The heterogeneity of the data could be partially explained by the diverse populations of observational studies. The results are similar to the ones reported by the Extracorporeal Life Support Organization in 2017 with a survival-to-discharge rate of 41%, using V-A ECMO devices [ECLS, 2017].

Table V. Newcastle-Ottawa scale for assessment of quality of included studies (each asterisk represents if individual criterion within the subsection was fulfilled).

Quality assessment Criteria	Acceptable (*)	Wu et al.	Chang et al.	Guenther et al.	Fu et al.	Huang et al.	Chou et al.	Sandoval et al.	Jeon et al.	Negi et al.
(1) Representativeness of the exposed cohort	Representative of average adult in community (age/sex/being at risk of disease)	*	*	*	*	*	*	*	*	*
(2) Selection of the nonexposed cohort	Drawn from the same community as the exposed cohort	*	*	—	—	—	*	—	—	—
(3) Ascertainment of exposure	Secure record, structured interview	*	*	*	*	*	*	*	*	*
(4) Demonstration that outcome of interest was not present at the start of the study		*	*	*	*	*	*	*	*	*
(5) Adequate control for the most important confounder?		*	*	*	—	*	—	*	—	*
(6) Adequate control for any additional factor?		*	*	*	—	*	*	—	—	—
(7) Assessment of outcome	Independent or blind assessment	*	*	*	*	*	*	*	*	*
(8) Was follow-up long enough for outcomes to occur?		*	*	*	*	—	*	*	*	*
(9) Adequacy of follow-up of cohorts	Complete follow-up, or subjects lost to follow-up unlikely to introduce bias	*	*	*	—	—	*	*	*	*
Overall quality score (maximum = 9)		9	9	8	5	6	8	7	6	7

The 2017 European Society of Cardiology Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation supports short-term mechanical circulatory support (ECMO) in patients with refractory shock (class IIb, level C). [7]. The use of ECMO in critical cases increased from 1.06 to 1.77 cases per 100,000 patients by 2014 in the USA and from 1.1 cases in 2007 to 6.2 cases in 2014 in Germany [Stentz et al., 2019].

In order to assure a future success, ECMO should be initiated by multidisciplinary teams, facilitating the safest transportation to PCI/CABG centers. The SAVE score created by Schmidt et al. [Schmidt et al.], included in the 2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure should be considered a prognostic tool for predicting survival in these cases [Ponikowski et al., 2016].

Moreover, durable solutions such as ventricular assist devices that ensure a bridge-to-survival or transplantation could become the foundation of modern cardiology.

The chance of receiving a heart transplant could be increased through the aid of extracorporeal life support followed by ventricular assist devices, as it saves time to find the right donor [Guha et al., 2019].

It seems that the usage of V-A ECMO among patients with AMI-induced cardiogenic shock may provide benefits in terms of survival. Yet, treatment effects of V-A ECMO are questionable due to limitations in cohort methods and reporting [Ibanez et al., 2017].

From our point of view, complications such as multiple organ failure, cerebral complications, and kidney failure may be linked to cardiogenic shock, rather than to the use of ECMO.

ECMO was mostly associated with acute kidney failure, which is a common complication, as shown in a systematic review that included studies performed in patients treated with ECMO, where the occurrence rate was 52% [Burrell et al., 2019]. In our research, rates varied between 24% and 47%, a complication that may be prevented by reducing the time to insertion of V-A ECMO.

Furthermore, ECMO infection prevention may be realized by performing an accurate procedure. However, vascular complications such as hemorrhage and limb ischemia, seen in 8.5% of the included patients in our study, had similar rates, as reported in the literature.

Our review has its limitations and strengths. We performed a systematic literature search and a detailed survival analysis. Nonetheless, our study could only identify observational studies. Moreover, sample size was relatively small, and data were not fully reported.

We could not exclude publication bias of original studies, as authors who did not register positive results on ECMO, or did not find any effect at all, were less likely to publish their results.

1.4.6. Conclusions

We have analyzed the impact on survival, potential benefits, and side effects of V-A ECMO in patients with cardiogenic shock due acute myocardial infarction (ST-segment elevation myocardial infarction and non-ST segment elevation myocardial infarction).

V-A ECMO for patients with acute myocardial infarction-induced cardiogenic shock represents a temporary support that provides benefits compared to standards of care, being an upgradable device for advanced life support that could assure a higher survival rate.

We consider that complications such as multiple organ failure, cerebral complications, and kidney failure are linked to cardiogenic shock, rather than to the use of ECMO and that ECMO infection prevention may be attained via the performance of an accurate procedure.

Chapter 2. Valvular heart disease, atrial fibrillation, and heart failure

2.1. Scientific context

Congestive heart failure (CHF) stands as a severe complication of valvular heart disease. Nevertheless, the onset of CHF is commonly linked to a significant deterioration in the succeeding clinical course. For this reason, in clinical practice the prevention, rapid recognition, and appropriate treatment of CHF in patients with valvular disease are of extreme importance [Greenberg, 1994; Knuuti et al., 2020]. Individuals with heart failure and valvular heart disease are at increased risk of events including sudden cardiac death [Collet et al., 2020].

The underlying mechanisms of CHF development in valvular heart disease are the direct effect of excessive loading conditions that overcome the reserve capacity of the myocardium, and secondly, myocardial dysfunction that emerges as a long-term consequence of these overloading circumstances [Gunther et al., 1979; Greenberg, 1994].

In acutely developing valve lesions, the damaging effects of an abrupt increase in volume or pressure faced by the left ventricle or left atrium contribute to the onset of CHF. Nevertheless, in chronic conditions, it is challenging to make the difference between the effects of abnormal loading conditions and the onset of myocardial dysfunction as the source of CHF [Greenberg, 1994; Collet et al., 2020].

During an acute valvular insufficiency of either mitral or aortic valve, the left ventricle (LV) suffers from an unexpected increase in blood volume. Under normal circumstances, the LV is relatively non-compliant because of the structure of the myocardium and the influence of the surrounding pericardium. Consequently, in the early stages of mitral or aortic insufficiency, the LV has a limited ability to accommodate an augmented diastolic volume without an increase in the filling pressures.

Moreover, in mitral regurgitation, an additional problem is the fact that during systole, the LV can eject blood into either the aorta or the left atrium (LA), where the impedance to flow is significantly lower than in the systemic circulation. Consequently, if the valve is seriously damaged, direct regurgitation of blood from the LV to the LA during systole produces severe increases in pressure in the upstream cavity [Greenberg, 1994; Collet et al., 2020].

Atrial fibrillation (AF) and heart failure (HF) share common risk factors (e.g., hypertension, diabetes, obesity, ischemic heart disease, arteriosclerosis, age) and mutual pathophysiologic mechanisms. It is known that atrial contraction significantly contributes to ventricular filling; thus, atrial fibrillation promotes the clinical deterioration of patients with preexisting heart failure.

Also, atrial fibrillation can even supplementary compromise ventricular function by inducing tachycardiomyopathy. So far, it was demonstrated that patients with heart failure benefit from a rhythm control concept regarding symptom management and hospitalization. Currently, different heart failure-specific therapies are offered with a mixed impact on new onset or persistence of atrial fibrillation [Hohendanner et al., 2018].

Regarding risk assessment in cardiac arrhythmias, a detailed literature review using PubMed and EMBASE database was performed in 2020 by European Heart Rhythm Association (EHRA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS)[Lip et al., 2017].

By analyzing the relationship between HF and the type of underlying heart disease, it was concluded that the prevalence of AF increases significantly with the severity of HF. Structural valvular heart disease may determine heart failure or may worsen the clinical evolution of patients with heart failure.

Epidemiological studies proved that among all valvular diseases, left-sided valve stenosis has the highest prevalence rates of AF. Moreover, the coexistence of coronary artery disease (CAD) or hypertrophic cardiomyopathy promote the emergence and progression of AF [Robinson et al., 1990; Nielsen et al., 2020].

There is a noticeable heterogeneity in the definition of valvular and non-valvular AF. The management of AF in association with valvular heart disease has been less evaluated by randomized trials when compared to 'non-valvular AF' patients. It was concluded that thrombo-embolic risk also differs according to valve lesion and may also be related to CHA_2DS_2VASc score risk factor components [Lip et al., 2017].

In order to assess the risk of AF in patients with heart failure, a careful evaluation of the clinical characteristics generally associated with increased risk for AF should be performed. Imaging techniques such as echocardiography and cardiac MRI are useful in identifying cardiac features linked with a higher risk for AF.

Moreover, the usefulness of biomarkers in identifying individuals with high degree of atrial fibrosis and increased risk of developing AF should be considered. With regard to common genetic modifications associated with AF risk, genetic molecular analysis seems not to be useful in routine clinical practice.

This research direction is reflected in the following published article and projects:

Ardeleanu I, Floria M, Badulescu OV, Bararu Bojan I, Vladeanu M, Anghel L, Tanase A, Macovei L, **Stătescu C**, Ciocoiu M, Sîrbu PD, Arsenescu Georgescu C. Clinical and Biological Profile of Patients with Non-Valvular Atrial Fibrillation and Hemodynamic Significant Valvular Heart Disease. *Rev Chim* 2019; 70(9) : 3412-3415. **IF: 1.755**
https://revistadechimie.ro/pdf/68%20ARDELEANU%209%2019.pdf

Research projects

„EMANATE" – Phase IV trial to assess the effectiveness of apixaban compared with usual care anticoagulation in subjects with non-valvular atrial fibrillation undergoing cardioversion - international contract, multicentric, randomized, double-blind; 2014-2016; subinvestigator
„COMPASS" – Cardiovascular OutcoMes for People using Anticoagulation StrategieS - international contract, multicentric, randomized, double-blind; ongoig from 2014; study coordinator.

2.2. Profile of Patients with Non-Valvular Atrial Fibrillation and Valvular Heart Disease

2.2.1. Introduction

Atrial fibrillation is a common cardiac arrhythmia, with an incidence of 1–2% in the general population. Epidemiological studies proved an increasing prevalence, which is expected to double in the next 50 years as the population ages [Qian et al., 2010; Camm et al., 2012; Widgren et al., 2012]. The most common valvulopathies are aortic stenosis (AS) and mitral regurgitation (MR), while aortic regurgitation (AR) and mitral stenosis (MS) are less frequent [Widgren et al., 2012; Scarsoglio et al., 2016]. The valvulopathies involving the mitral valve apparatus causes significantly changes in the left atrial structure, promoting the onset of AF which further predisposes to thrombogenesis [Luo et al., 2014; Zoni-Berisso et al., 2014; Dahl et al., 2015; Breithardt and Baumgartner, 2015]. The meaning of valvular or non-valvular AF is still unclear to cardiologists and internists who deal with AF [Molteni et al., 2014]. Regarding the patients with non-valvular AF, the risk of thromboembolic event can be estimated using CHA2DS2-VASc score [Hirsh et al., 2015; Guichard et al., 2017].

2.2.2. Aim

The study aimed to assess the clinical and biological profile of patients with non-valvular AF and hemodynamic major valvular heart disease beyond the guidelines definition of valvular AF [Fuster et al., 2006; January et al., 2014].

2.2.3. Material and methods

The study group consisted of patients with non-valvular AF admitted in our hospital within 6 months. Valvular AF was defined as AF related to rheumatic mitral stenosis and mechanical or biological valvular prostheses or mitral valve repair (annuloplasty, commissurotomy and/or valvuloplasty) [Fuster et al., 2006; Qian et al., 2010; January et al., 2014].

We established as *inclusion criteria* patients older than 18 years, with documented non-valvular AF [Fuster et al., 2006; Qian et al., 2010; January et al., 2014], admitted to our hospital, regardless of arrhythmia type: paroxysmal, persistent or permanent.

The *exclusion criteria* included patients with valvular AF; patients with major contraindications to oral anticoagulation; patients with chronic kidney disease with creatinine clearance <30 ml/min, pacemaker or automatic implantable cardioverter-defibrillator, hyperthiroidia, neoplasia.

The study population was divided into two groups according to the presence of significant hemodynamic valvular heart disease: the control group - patients without significant hemodynamic valvular heart disease and the study group - patients with significant hemodynamic valvular heart disease. We performed standard 12 lead ECG and/or 24-hour ECG Holter monitoring in order to diagnose the non-valvular AF.

At the beginning of the study the following clinical parameters were recorded: age, sex, smoker status, obesity (defined as a body mass index - BMI - higher than 30 kg/m^2), comorbidities (dyslipidemia, hypertension, aortic atheroma plaques, diabetes mellitus, heart failure, ischemic heart disease and peripheral arterial disease).

We also performed laboratory measurements on fasting blood samples: total cholesterol, high density lipoprotein cholesterol (HDL-col), low density lipoprotein cholesterol (LDL-col), triglyceride, alanine aminotransferase (ALT), aspartate amino transaminase (AST), blood glucose, creatinine, C reactive protein (CRP), thyroid stimulating hormone (TSH). Echocardiographic measurements using standardized transthoracic two-dimensional echocardiography evaluation were focused on valves morphology and function.

Therefore, in all eligible patients valvular regurgitation was scored from 0 through 5: 0 = no regurgitation, 1 = mild, 2 = mild-moderate, 3 = moderate, 4 = severe. Grades 2–4 were considered significant. Also, stenosis severity was assessed as: 0 = no stenosis, 1 = mild stenosis, 2 = moderate stenosis, 3 = severe stenosis. All degrees of severity were considered hemodynamically significant for aortic valve, but according with the inclusion criteria, only patients with mitral stenosis were included in the study.

Within the study, the ethical principles of the hospital and University Ethics Committee were respected. Each patient signed an informed consent before the inclusion in the study.

Statistical analysis

All statistical tests were two-tailed and performed with SPSS 18.0 (SPSS Inc., Chicago, IL, USA). A *P*-value <0.05 was set as statistical significance. The tests used for the statistical evaluation included: ANOVA test consisting in analyzing the dispersion of the dependent variable: intro and intergroup, the coefficient of variation (CV%), the t-Student test, the Kruskal-Wallis correlation and the "Pearson" (r) coefficient.

2.2.4. Results

The study population included 513 patients with mean age of 69.33 ± 10.23 years: 48.9% with permanent AF, 16% with persistent AF, and 35.1% with paroxysmal AF. Almost two third of patients (333 patients; 64.9%) were included in the study group and one third (180 patients; 35.1%) in the control group. Data regarding demographic and valve disease distribution in the study population are shown in table VI. Mitral regurgitation was the most frequent valvular heart disease (75%), the moderate degree being most frequently described (32.2%). Tricuspid regurgitation was noted in 67.6% of patients, particularly with moderate degree (35.9%).

Twenty-eight patients (5.5%) associated all valve disease (mitral, aortic, tricuspid and pulmonary), 137 patients (26.7%) associated MR, AR and TR and 369 patients (71.9%) associated two valve regurgitation.

In the study group, the patients were statistically significant older than 70 years, less often smokers and obese (Table VII). Analysis by age group distribution revealed that the majority of patients from the study group (42%) was in decade 70-79 years, while the majority of patients from the control group (40%) was in decade 60-69 years (P=0.001). We noticed that the percentage

of patients with valvular heart disease was significantly higher in older age (Chi-square=30,54; df=5; P=0.001).

Table VI. Demographic parameters and valvular heart disease distribution in the study population

PARAMETER	N (%)
Mean age (mean ± SD), years	**69.3 ± 10.2**
Men, n (%)	**290 (56.5)**
Smokers, n (%)	**111 (21.6)**
Alcohol consumers, n (%)	**64 (12.5)**
Mitral regurgitation	
II degree, n (%)	**165 (32.2)**
III degree, n (%)	**62 (12.1)**
IV degree, n (%)	**9 (1.8)**
Aortic regurgitation	
II degree, n (%)	**76 (14.8)**
III degree, n (%)	**13 (2.5)**
Tricuspid regurgitation	
II degree, n (%)	**184 (35.9)**
III degree, n (%)	**56 (10.9)**
IV degree, n (%)	**5 (1.0)**
Pulmonary regurgitation	
I degree, n (%)	**45 (8.7)**
II degree, n (%)	**12 (2.3)**

Distribution by gender was relatively homogeneous; male patients were more frequent in the both groups. As shown in table VIII, the evaluation of cardiovascular risk factors revealed that arterial hypertension was present in 61.5% of patients, without significant differences in the study group (59.8% vs 56.7%, P = 0.498). Diabetes mellitus was present in 21.3% of the patients, being significantly more common in patients form the control group (31.1% vs 17.4%, P = 0.011).

14.5% of patients had dyslipidemia, more frequently in patients from the control group (11.4% vs 18.3%, P= 0.033). Diabetes mellitus (RR = 1.36; IC95%: 1.12-1.64), dyslipidemia (RR=1.25; IC95%: 0.99-1.56) and coronary heart disease (RR = 3.70; IC95%: 1.83-7.46) showed a significantly higher estimated risk for AF (as shown in Table VIII).

Table VII. Demographic parameters of the study subgroups

	TOTAL		**PARAMETERS**									
	N	%	Men	%	≥70 years	%	Smoker	%	Alcohol	%	Obesity	**%**
Study group	333	64.9	178	53.5	203	61.0	63	18.9	36	10.8	71	**21.3**
Control group	180	35.1	112	62.2	68	37.8	48	26.7	28	15.6	57	**31.7**
Chi2 test (p value)			**0.069**		0.001		0.044		**0.126**		0.050	

Table VIII. Clinical parameters of the study groups and relative risk for atrial fibrillation

COMORBIDITY	**Study group N=333**	**Control group N=180**			**Relative risk for AF**		
	n	n	CHI^2	P	OR	RR	**IC95%**
Hypertension, n (%)	199 (59.8)	102(56.7)	0.46	0.498	1.05	0.96	**0.84-1.27**
DM, n (%)	58 (17.4)	56 (31.1)	12.3	**0.001**	0.56	**1.36**	**1.12-1.64**
Dyslipidemia, n (%)	38 (11.4)	33 (18.3)	4.55	**0.033**	0.62	**1.25**	**0.99-1.56**
CHD, n (%)	11 (3.3)	22 (12.2)	14,0	**0.001**	0,25	**3,70**	**1,83-7,46**
Apnea/COPD, n (%)	27 (8.1)	17 (9.4)	0.26	0.608	0.86	1.06	**0.83-1.36**
Anemia, n (%)	6 (1.8)	1 (0.6)	1.56	0.212	3.00	0.75	**0.55-1.03**
VA, n (%)	9 (2.7)	2 (1.1)	1.55	0.214	0.56	0.79	**0.59-1.05**
Stroke/TIA, n (%)	7 (2.1)	5 (2.8)	0.23	0.633	0.70	1.12	**0.69-1.81**
Hyperthyroidism, n (%)	12 (3.6)	6 (3.3)	0.03	0.873	0.98	0.97	**0.70-1.36**
Hypothyroidism, n (%)	17 (5.1)	16 (8.9)	2.67	0.102	0.57	1.28	**0.91-1.79**

Laboratory measurements (shown Table IX) indicated elevated cholesterol and triglyceride levels in patients from control group, while for LDL-cholesterol, HDL-cholesterol, thyroid stimulating hormone, C reactive protein and creatinine values did not.

Table IX. Biological parameters of the study subgroups: I = study group, II = control group

PARAMETER	Group	N	Average	Standard deviation	Confidence Interval 95%	Test F (ANOVA) p
Cholesterol (mg/dL)	I	323	172.61	42.42	167.97	**0.008**
	II	168	183.93	49.06	176.46	
LDL-Cholesterol (mg/dL)	I	316	104.62	33.04	100.96	0.098
	II	165	110.43	42.27	103.93	
HDL-Cholesterol (mg/dL)	I	321	47.52	14.42	45.94	0.075
	II	167	50.22	18.31	47.42	
Trygliceride (mg/dL)	I	322	104.80	58.16	98.42	**0.032**
	II	168	116.68	58.15	107.83	
Thyroid Stimulating Hormon (UI/mL)	I	23	2.44	2.81	1.22	0.692
	II	12	3.02	5.84	-0.69	
C Reactive Protein (mg/dL)	I	158	29.30	45.71	22.11	0.503
	II	76	25.08	43.60	15.12	
Serum creatinine (mg/dL)	I	329	1.19	0.53	1.13	0.499
	II	178	1.15	0.58	1.07	

HDL: high density lipoprotein; LDL: low density lipoprotein.

Within the study, mean values of CHA_2DS_2-VASc and HAS-BLED were 3,05 ± 1,54 and 2.38 ± 0.97, respectively. Mean CHA_2DS_2-VASc and HAS-BLED score values were significantly higher in the study group: 3.19 vs. 2.79; P= 0.006, and 2.44 vs 2.27; P= 0.05, respectively. In this study, 82% of patients had a CHA_2DS_2VASc score ≥ 2; only 52% of these patients received appropriate anticoagulation treatment. In patients who associated hypercholesterolaemia (RR = 1.25, IC95%: 0.99-1.56), hypertriglyceridaemia (RR = 1.30, IC95%: 0, 45-3, 47), and right bundle branch block (RR = 1.21; IC95%: 0.42-1.37) we observed a slightly higher estimated risk of valve disease.

2.2.5 Discussion

It is known that patients with non-valvular AF, left-sided valve disease (excluding mitral stenosis and prostheses) have a higher CHA_2DS_2VASc score [Philippart et al., 2015].

Consequently, patients with non-valvular AF seems to be a heterogeneous group of patients substantially different from those without hemodynamic significant valvular heart disease. Table X reveals the profile of these patients which are older, with less comorbidity like obesity and chronic coronary disease, higher thromboembolic and hemorrhagic risk.

Table X. Clinical profile of patients with non-valvular atrial fibrillation and hemodynamic significant valvular heart disease

PARAMETER	**Study group (N=333)**	**Control group (N=180)**	**P**
Age≥70 years (%)	61.0	37.8	**0.001**
Smoker (%)	18.9	26.7	**0.044**
Diabetes Mellitus (%)	17.4	31.1	**0.001**
Dyslipidemia (%)	11.4	18.3	**0.033**
Chronic Coronary Disease (%)	3.3	12.2	**0.001**
Mean CHA2DS2-VASc	3.19±1,53	2.79±1.52	**0.006**
Mean HAS-BLED	2.44±0.95	2.27±0.99	**0.05**

SD: standard deviation

Diabetes mellitus and dyslipidemia were statistically significant more frequent in the control group. In these patients we found a significantly higher estimated risk for AF. Generally, in the clinical practice is mandatory to assess the thromboembolic risk via the CHA_2DS_2VASc score in patients with non-valvular AF.Subjects with a CHA_2DS_2VASc score of 0 have a 0 annual risk of thromboembolic events, which might be due to the heterogeneity of non-valvular AF patients and hemodynamic significant valvular heart disease (other than valvular prosthesis or rheumatic mitral valve disease)(Di Biase, 2016; Potpara et al., 2016).

Limitations of the study: This analysis has the limitations of an observational retrospective study with many variables which were analyzed.

2.2.4. Conclusions

In the study group, more precisely in subjects with non-valvular AF and hemodynamic significant valvular heart disease, dyslipidemia showed a significantly higher estimated risk for AF, as well as diabetes mellitus and coronary heart disease. Consequently, these patients, beyond the current guidelines, could have a completely different profile and prognosis.

Chapter 3. Obstructive sleep apnea and heart failure

3.1.Scientific context

Sleep-disordered breathing (SDB) affects more than one-third of patients with HF [McKelvie et al., 2011], with the most common types being central sleep apnea (CSA), obstructive sleep apnea (OSA), and a mixed pattern of the two. These patients are more prevalent in patients with AHF [Khayat et al., 2015]. However, sleep disturbance may be linked to depression and anxiety as well.

Thus, the management of HF patient must include an assessment of sleep history. Epidemiological studies proved that CSA and OSA are associated with a worse prognosis in HF [Khayat et al., 2015; Nakamura et al., 2015]. Also, OSA is linked with an increased risk of incident HF in men [Gottlieb et al., 2010].

The main features of OSA are repetitive nocturnal upper airway collapses, along with hypoxic episodes and microawakenings [Spicuzza et al. 2015]. It is known that chronic sleep fragmentation leads to daytime somnolence and cognitive impairment [Gagnon et al., 2014]. Previous studies showed that hypoxia is related to autonomic and hormonal imbalance, endothelial dysfunction and oxidative stress [Drager et al., 2017], clarifying the increased cardiovascular morbidity and mortality in OSA [Spicuzza et al. 2015; Drager et al., 2017].

To objectify OSA, the standard methods are in-hospital polysomnography, with cardiorespiratory polygraphy seen as an acceptable alternative [Sateia et al, 2014; Lévy et al., 2015; La Rovere et al., 2015].

OSA is classified as mild, moderate or severe based on the apnea-hypopnea index (AHI). AHI is defined as the number of apneic or hypopneic episodes per hour of sleep [Berry et al., 2012]. Epworth questionnaire may be used in order to objectively assess daytime sleepiness, which represents the dominant symptom in OSA.

All cases of moderate-severe OSA (AHI $\geq$ 15 events/h), as well as patients with mild OSA having symptoms or cerebrovascular comorbidities require an appropriate management [Veasey and Rosen, 2019]. The treatment alternatives include continuous positive airway pressure (CPAP), which is limited by reduced treatment adherence, especially among children, mandibular advancement devices, maxillo-facial surgery and nocturnal hypoglossal nerve stimulation [Lin et al., 2006; Woodson et al., 2018].

Several studies have been focused on the relationship between obstructive sleep apnea and HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF). It was proved that OSA prevalence is higher in these patients than in the general population [Khattak et al., 2018].

Obstructive sleep apnea affects the cardiovascular system through mechanical, neurohumoral, chemical, and inflammatory mechanisms [Mann et al., 2011]. The main events in OSA are overstated drop in the intrathoracic pressure, hypoxia, and arousal. These causes decreased LV filling, marked and repeated elevations in systemic blood pressure (BP), and increased sympathetic nervous system activity.

The consequences are myocardial oxygen supply/demand discrepancy, acutely predisposition to cardiac ischemia and arrhythmias, and chronically LV hypertrophy, LV enlargement, and finally HF [Khattak et al., 2018].

Previous studies have shown a prevalence of OSA varying between 12%–53% in HFrEF patients [Kasai and Bradley, 2011], with older age, male sex, higher BMI, and habitual snoring as major risk factors for OSA [Javaheri, 2006; Yumino et al., 2009; Khattak et al., 2018]. Patients with HFrEF and OSA describe less subjective daytime sleepiness regardless of shorter sleep duration. Epworth Sleepiness Scale (ESS) does not bring satisfactory results in identifying OSA in these patients.

In the last decades, several echocardiographic studies were performed in order to assess the prevalence of diastolic dysfunction in OSA patients without clinical evidence of HF, but information are sparse.

There are no studies focused on the effects of CPAP on mortality rates in patients with OSA and HFpEF, previous data being focused only in OSA patients with HFrEF. Additionally, minimal advancement has been made in managing OSA in HFpEF, in spite of considerable developments in the treatment of OSA in HFrEF. Consequently, further research is needed to evaluate the effects of CPAP on HF progression and survival in HFpEF patients with OSA.

With regard to the relationship between OSA and HF, there are few issues that need to be investigated. Firstly, which HF patients need a screening sleep study when the ESS is unpredictable for screening.

Some authors suggested sleep studies in all HFrEF patients with a LVEF < 40% [Schulz et al., 2007], but this was not being generally accepted because of the uncertainty about whether and how to treat OSA in this population [Franklin, 2007]. The lack of guidelines does that indications for sleep studies to evaluate OSA in patients without HF to apply similarly to patients with HF [Khattak et al., 2018].

Secondly, it should be clarified whether in patients with OSA and HF without subjective excessive daytime sleepiness, CPAP treatment is required. This question applies even to patients with OSA and no evidence of HF. Several reports support CPAP in patients with HF, despite of daytime symptoms, but large-scale clinical trials are needed [Wang et al., 2007; Kasai et al., 2008].

Thirdly, there is a need for an innovative sleepiness scale that can better predict the risk of OSA in patients with HF. This scale should take quality of life into consideration as the poor quality of life in HF might cover sleepiness as a predominant symptom [Khattak et al., 2018].

This direction of research is reflected in the following published articles:

Sascău R, Zota IM, Stătescu C, Boișteanu D, Roca M, Maștaleru A, Leon Constantin MM, Vasilcu TF, Gavril RS, Mitu F. Review of Echocardiographic Findings in Patients with Obstructive Sleep Apnea. *Can Respir J* 2018; 2018:1206217. **IF:1.803**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6276396/pdf/CRJ2018-1206217.pdf

Zota IM, Leon Constantin MM, Statescu C, Sascau RA, Roca M, Gavril RS, Vasilcu TF, Boisteanu D, Cojocaru E, Mastaleru A, Mitu O, Mitu F. Clinical and biological impact of CPAP therapy in patients

with obstructive sleep apnea and cardio-metabolic comorbidities. *Acta Medica Mediterranea* 2020; 36:1975. **IF: 1.249**
https://www.actamedicamediterranea.com/archive/2020/medica-3/clinical-and-biological-impact-of-cpap-therapy-in-patients-with-obstructive-sleep-apnea-and-cardio-metabolic-comorbidities

Zota IM, **Stătescu C**, Sascău RA, Roca M, Gavril RS, Vasilcu TF, Boișteanu D, Maștaleru A, Jitaru A, Leon Constantin MM, Mitu F. CPAP Effect on Cardiopulmonary Exercise Testing Performance in Patients with Moderate-Severe OSA and Cardiometabolic Comorbidities. *Medicina (Kaunas)* 2020;56(2):80. **IF: 1.205**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7074283/pdf/medicina-56-00080.pdf

Zota IM, Sascău RA, **Stătescu C**, Boișteanu D, Roca M, Leon Constantin MM, Vasilcu TF, Gavril RS, Anghel L, Mitu O, Costan V, Cumpat CM, Mitu F. Quality of life in moderate-severe OSA patients from north-eastern Romania. *Rev Cercet Interv So* 2020; 68: 250-260. **IF: 0.736**
https://www.rcis.ro/images/documente/rcis68_17.pdf

3.2. Review of Echocardiographic Findings in Patients with OSA

3.2.1. Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive collapse of the upper respiratory airways, causing persistent apneas or hypopneas, intermittent oxygen desaturations and nocturnal microawakenings. Current pandemic obesity seems to be responsible for the partial increase in OSA prevalence in the general population. Epidemiological data showed that 4% of middle-aged males and 2% of females suffer from OSA [Young et al., 1993], a disorder that leads to increased cardiovascular risk by inducing refractory hypertension, oxidative stress, endothelial dysfunction and increased sympathetic tone [Korcarz et al., 2016]. Moreover, obesity, diabetes and metabolic syndrome are commonly connected with OSA [Korcarz et al., 2016a; Korcarz et al., 2016]. The standard diagnostic investigation in OSA is an overnight sleep study or polysomnography which counts the number of apneic and hypopneic episodes. It also allows the evaluation of the apnea-hypopnea index (AHI), classifying OSA severity into mild, moderate and severe forms (AHI 5-14, 15-30 and >30 events/hour, respectively) [Lee et al., 2017]. Previous studies reported a higher incidence of cardiac structural or functional alterations in patients with OSA.

Continuous positive airway therapy (CPAP) is considered the gold standard treatment for moderate-severe OSA. The limitations of the method are the inadequate patient adherence to and acceptance of device therapy. Lee et al. showed that only 57% of patients diagnosed with moderate-severe OSA started the recommended CPAP therapy, and that only half of them continued to use the device after 1 year [Lee et al., 2017].

Optimal CPAP therapy requires a minimum of 4 hours of nightly use. Additionally, up to 83% of patients following CPAP therapy do not reach the recommended threshold of 4 hours of nightly use [Weaver and Grunstein, 2008].

3.2.2. Aim

The aim of this review is to highlight the utility of standard and advanced echocardiographic parameters in the identification of OSA patients, which are at risk of developing heart failure and future adverse events.

3.2.3. Material and methods

We revised the existing literature concerning the contribution of echocardiography in OSA subjects evaluation. Echocardiographic screening might raise awareness with regard to the cardiovascular implication of OSA. This could complete the current educational, technological and psychosocial techniques aimed to improve patient adherence to both device therapy and lifestyle changes [Sawyer et al., 2011].

3.2.4. Results

By conducting a literature search on several databases, as Medline, PubMed, Embase, CINAHL, PsycInfo, and Ageline and reviewing Clinical Evidence, UpToDate, and the websites of major guideline development organisations an updated information on the implications of echocardiography in OSA diagnostic and therapeutic management was obtained.

3.3.5. Discussion

Left chamber dimensions

Within our revision, left atrial enlargement is more common among subjects with moderate-severe OSA (52,1%) than in patients with an apnea-hypopnea index (AHI) <15 (31%, $p < 0.001$) [Holtstrand et al., 2018] and is reported in 18% of newly diagnosed OSA patients [Baguet et al., 2010]. Left atrial diameter is higher in patients with severe OSA than in subjects with mild sleep apnea (36.1±5.7 mm versus 32.8±2.3 mm, $p<0.01$) [Dursunoglu et al., 2005]. Previous studies revealed that both indexed left atrial volume (LAVI) [Romero-Corral et al., 2007; Altekin et al., 2012; Imai et al., 2015; Varghese et al., 2017] and left atrial area (LAA) [Holtstrand et al., 2018] increase with OSA severity (table XI). Moreover, OSA is associated with left ventricular hypertrophy, even in the absence of hypertension, obesity and diabetes [Dursunoglu et al., 2005; Altekin et al., 2012] (table XII). Left ventricular posterior wall (LVPW) thickness, interventricular septum (IVS) thickness and left ventricular mass (LVM) are higher in patients with severe OSA than in patients with moderate and mild OSA [Dursunoglu et al., 2005; Wachter et al., 2013]. A study conducted in 2016 also found a significant difference regarding IVS thickness in subjects with severe and moderate OSA versus controls ($p=0.001$, $p=0.002$ respectively) [Zhou et al., 2016]. Regarding LVM index, it was significantly increased in subjects with severe OSA than in controls [Dursunoglu et al., 2005; Baguet et al., 2015], but no statistically important variations in LV end-systolic and end-diastolic diameters were reported [Dursunoglu et al., 2005; Holtstrand et al., 2018]. LVH seems to be correlated to mean nocturnal oxygen saturation, which is an

independent predictor of left ventricular mass and wall thickness (for every 1% decrease in saturation the authors reported a mass gain of 4.38 g and an increase in wall thickness of 0.14 cm) [Akyol et al., 2016].

Table XI. Left atrial volume and area in relationship with OSA severity

Echocardiographic variables		AHI <5 events·h^{-1}	Mild OSA	Moderate OSA	Severe OSA	p
LAVI (ml/m^2)	Altekin et al., 2012	21.6±4.7	22.2±4.8	27.44±6.9†	32.3±5.1 †,‡	<0.03
	Varghese et al., 2017	28.3±4.1	NA	NA	30.6±3.5	0.02
	Romero-Corral et al., 2007	26.8±11	32.5±15 †	30.4±11 †		<0.05
	Imai et al., 2015	NA	20.3±4.9		23.3±5.2	<0.0001
LAA (cm^2)	Holtstrand et al., 2018	21.6±4.5		23.7±5.5		<0.001

Abbreviations: LAVI – left atrial volume index. LAA – left atrial area. AHI – apnea hypopnea index. OSA – obstructive sleep apnea. AHI – apnea hypopnea index. OSA – obstructive sleep apnea; † - significantly different from AHI < 5 events·h−1; ‡ - significantly different from mild OSA; NA – not applicable

Table XII. Left ventricular bidimensional parameters in relationship with OSA severity

Echocardiographic variables		AHI <5 events·h^{-1}	Mild OSA	Moderate OSA	Severe OSA	P
IVSD (cm)	Altekin et al., 2012	0.89±0.09	1.03±0.1	1.03±0.13 †	1.13±0.13 †	<0.05
	Zhou et al., 2016	0.92±0.11	0.97±0.17	1.12±0.16 †	1.14±0.19 †	<0.005
	Dursunoglu et al., 2005	NA	0.99±0.09	1.09±0.13 ‡	1.12±0.11 ‡	≤0.01
	Wachter et al., 2013	1.17±0.16	1.22±0.19 †	1.24±0.18 †		<0.05
	Holtstrand et al., 2018	1.04±0.14		1.07±0.14		0.028
	Varghese et al., 2017	1.12±0.12	NA	NA	1.18±0.13	0.05
	Vural et al., 2017	0.95±0.11	0.95±0.11	1.00±0.12	1.01±0.11 †	<0.05
PWD (cm)	Altekin et al., 2012	0.88±0.07	1.03±0.09 †	1.04±0.12 †	1.11±0.13 †	<0.05
	Dursunoglu et al., 2005	NA	0.98±0.08	1.08±0.09 ‡	1.14±0.09 ‡	≤0.01

	Wachter et al., 2013	1.08±0.14	1.12±0.14 †	1.13±0.14 †		<0.05
	Varghese et al., 2017	1.07±0.11	NA	NA	1.14±0.13	0.05
LVMI (g/m^2)	Altekin et al., 2012	86.5±18.7	93.2±16.6	94.5±22.9	103.5±22.9 †	<0.05
	Varghese et al., 2017	92.4±9.8	NA	NA	98.5±13.5	0.04
	Dursunoglu et al., 2005	NA	100.5±42.3	126.5±41.2 ‡	144.7±39.8 ‡	≤0.002
	Wachter et al., 2013	113±26	119±26	125±29		<0.001
	Imai et al., 2015	NA	107.2±18.5	117.4±19.9		<0.0001
RWT (cm)	Imai et al., 2015	NA	0.4±0.05	0.4±0.04		<0.0001

IVSD – interventricular septum thickness. PWD – posterior wall thickness. LVMI – left ventricular mass index. RWT – relative wall thickness. AHI – apnea hypopnea index; † - significantly different from AHI < 5 events·h−1; ‡ - significantly different from mild OSA; NA – not applicable

Left ventricular systolic function

Published data regarding LV ejection fraction (EF) and LV fractional shortening in OSA patients are debatable. There are publications showing a normal LVEF (59±10%) among patients with OSA [Dursunoglu et al., 2005; Wachter et al., 2013] and other studies that reported no significant differences between OSA severity and left ventricular EF or fractional shortening [Dursunoglu et al., 2005; Altekin et al., 2012; Varghese et al., 2017]. Nevertheless, a study of 411 men, average age 71-years-old showed that LVEF is slightly lower in patients with moderate-severe OSA (61.0±8.9%) than in subjects with AHI <15 (62.7±6.3%, p=0.028) [Holtstrand et al., 2018] and another recent report found that OSA severity is significantly correlated with a reduction in LVEF (p=0.005) [Hammerstingl et al., 2013] (table XIII). The data were confirmed by another study of 119 OSA patients monitored over 18 years, presenting that for every tenfold increase in AHI, the left ventricular ejection fraction showed a 1.3% independent decrease [Akyol et al., 2016].

Table XIII. Left ventricular ejection fraction and OSA severity

Echocardiographic variables		**AHI <5 events**	**Mild OSA**	**Moderate OSA**	**Severe OSA**	**p**
LV-EF (%)	Hammerstingl et al., 2013	NA	65.0±6.9	59.5±6.9	57.5±5.6	<0.0001
	Holstrand et al., 2018	62.7±6.3	61.0±8.9	NA	NA	0.028

NA – not applicable

Left ventricular diastolic dysfunction

Experimental studies concerning artificially induced OSA in a canine model [Brooks et al., 1997] have revealed that each hypoxic episode affects LV diastolic function by increasing left ventricular afterload, and that LV systolic dysfunction develops after only 3 months.

OSA-induced systolic and diastolic dysfunction seems to follow a similar pattern in humans, although it characteristically progresses in a much longer period of time, as it begins by impacting diastolic function, leading to systolic dysfunction only after extended exposure (>10 years) [Parker et al., 1999; Yang et al., 2012]. Studies of Yang et al. revealed that a nocturnal minimum oxygen saturation <70% was an independent predictor of diastolic dysfunction (OR=4,34, p=0.02) [Yang et al., 2012].

A study from 2016 reported that 44% of OSA patients with normal biventricular systolic function presented varied degrees of diastolic dysfunction [Korcarz et al., 2016]. Wachter et al. in 2013 showed that diastolic dysfunction prevalence was 56.8% among patients with mild OSA and it reached 69.7% in the moderate- to-severe OSA group (p=0.002) [Wachter et al., 2013]. Baguet et al. found that 22.7% of subjects with newly diagnosed OSA had a mitral inflow pattern suggesting impaired LV relaxation [Baguet et al., 2010].

It seems that an increased AHI was associated with decreased mitral E wave [Dursunoglu et al., 2005] and increased mitral A wave velocity [Dursunoglu et al., 2005; Holtstrand et al., 2018] (table XIV).

Even though Varghese et al. did not find a significant difference regarding mitral E/A ratio in patients with severe OSA (1.1±0.2) versus controls (1.2±0.2, p=0.09) [Varghese et al., 2017], several other studies reported that mitral E/A ratio decreases with OSA severity [Dursunoglu et al., 2005; Imai et al., 2015; Vural et al., 2017]. Unexpectedly, other authors found significantly lower E/A ratio only in patients with mild OSA (p=0.0009), but not in subjects with moderate or severe OSA [Altekin et al., 2012].

According to Altekin et al., E wave deceleration time (E-DecT) is higher in patients with OSA than in control subjects but no significant differences regarding E-DecT were found among patients with different degrees of OSA severity [Altekin et al., 2012].

A similar tendency was described for LV isovolumic relaxation time (IVRT) [Altekin et al., 2012] and it seems that both E-DecT and IVRT have a positive correlation with AHI [Dursunoglu et al., 2005]. Moreover, other studies reported significant differences regarding E-Dec and IVRT among OSA subjects (table XIV).

Left ventricular Tei-index (LV-MPI), illustrating both systolic and diastolic function, is higher in subjects with severe sleep apnea (0.64±0.14) compared to those with mild OSA (0.50±0.09; p<0.01) [Dursunoglu et al., 2005] or to controls [Altekin et al., 2012], being a valuable parameter in the early diagnosis of LV dysfunction [Fung et al., 2002; Dursunoglu et al., 2005]. Only two studies reported a positive correlation between LV-MPI and AHI (p<0.001, r = 0.825) [Dursunoglu et al., 2005] and (p=0.02, r=0.27) [Romero-Corral et al., 2007], while other authors found no significant difference regarding LV-MPI between patients with severe OSA and controls (p=0.12) [Varghese et al., 2017] (table XV).

Consequently, conventional Doppler echocardiography yields conflicting results regarding OSA impact on left ventricular diastolic function. Several Doppler parameters are not applicable in patients with atrial fibrillation, while others are influenced by patients' heart rate and blood pressure values, or exhibit age-dependency. The necessity of a more comprehensive echocardiographic analysis has been accepted by current international echocardiography guidelines, which have included tissue doppler imaging (TDI) in the diagnostic algorithms of LV diastolic dysfunction [Nagueh et al., 2016].

Table XIV. Left ventricular diastolic function in relationship with OSA severity

Echocardiographic variables		AHI <5 events	Mild OSA	Moderate OSA	Severe OSA	p
E velocity (cm/s)	Dursunoglu et al., 2005	NA	92±12	77±24	61±13	0.01
A velocity (cm/s)	Dursunoglu et al., 2005	NA	67±25	105±90	87±14	0.01
	Vural et al., 2017	75.1±20.9	78.3±21.5	76.9±13.8	86.2±17.8 †	<0.05
E/A ratio	Dursunoglu et al., 2005	NA	1.37±0.02†	0.73±0.01 ‡	0.70±0.01 ‡	0.01
	Imai et al., 2015	NA	1.38±0.45		1.03±0.39	<0.0001
	Vural et al., 2017	1.0±0.3	1.0±0.3	1.0±0.3	0.8±0.2 †	<0.05
	Altekin et al., 2012	1.19±0.24	0.96±0.16†	1.01±0.3	1.11±0.28	0.009
DecT (ms)	Altekin et al., 2012	163±26.2	227.4±31.1 †	216.4±60.4†	199.4±39.5 †	<0.001
	Dursunoglu et al., 2005	NA	170.1±20.9	210.0±47.7	240.1±57.7	0.01
	Imai et al., 2015	NA	187.1±33.7		198.4±36.6	0.003
	Vitarelli et al., 2013	143±14	175±17	NA	229±15 †	0.004
	Oliveira et al., 2009	NA	189.2±34.5	231.8±45.2	247.6±48.2 ‡	<0.05
IVRT (ms)	Altekin et al., 2012	88.3±12.5	106.3±12.8†	108.8±12.9	113.2±10.4 †	<0.001
	Vitarelli et al., 2013	74±11	103±9	NA	125±10 †	0.004
	Fung et al., 2002	92.7±16.6			106.4±19.1	0.005
	Dursunoglu et al., 2005	NA	72.0±12.6	100.2±13.7 ‡	125.5±13.1 ‡	0.01

Abbreviations: DecT – deceleration time. IVRT – isovolumic relaxation time. AHI – apnea hypopnea index. OSA – obstructive sleep apnea; † - significantly different from AHI < 5 events·h−1; ‡ - significantly different from mild OSA; NA -not applicable

Table XV. Left ventricular myocardial performance index in relationship with OSA severity

Echocardiographic variables		AHI <5 events·h−1	Mild OSA	Moderate OSA	Severe OSA	p
LV MPI	Dursunoglu et al., 2005	NA	0.50±0.09	0.60±0.10 ‡	0.64±0.14 ‡	0.01
	Altekin et al., 2012	0.46±0.08	0.48±0.08	0.55±0.06†	0.6±0.13†‡	<0.05
	Vitarelli et al., 2013	0.39±0.08	0.43±0.07	NA	0.58±0.09 †	0.039

Abbreviations: LV-MPI – left ventricular myocardial performance index. AHI – apnea hypopnea index. OSA – obstructive sleep apnea; † - significantly different from AHI < 5 events·h−1; ‡ - significantly different from mild OSA; NA – not applicable

TDI seems to detect subtle changes in systolo-diastolic ventricular function, even in patients with normal EF, but it is limited by its angle-dependence, by the need to acquire high frame rate imaging and by the influence of myocardial translation and tethering forces. LV-S' wave velocity is an indirect marker of ventricular systolic function. Previous studies found no significant difference regarding LV-S' wave velocity among patients with OSA and controls [Altekin et al., 2012; Zhou et al., 2016], consistent with the controversial reports regarding LV-EF in OSA.

A study conducted in 2013 by Wachter et al., found that only tissue Doppler-derived parameters (and not mitral flow pattern) are significantly different in the presence of sleep apnea, reporting that lateral e` was significantly lower in subjects with AHI ≥ 15 (7.4±2.1) than in controls (8.3±2.6) [Watcher et al., 2013]. Varghese et al. revealed that subjects with very severe obstructive sleep apnea (AHI > 40) present lower e` velocities than controls [Varghese et al., 2010], similar results being reported by several other authors (table XVI).

Several studies proved that E/e` mean ratio, an estimate of LV end-diastolic pressures, is higher in subjects with moderate-severe OSA than in controls [Oliveira et al., 2009; Varghese et al., 2010; Oliveira et al., 2012; Altekin et al., 2012; Wachter et al., 2013;] and positively correlated to AHI (r=0.202, p=0.014) [Vural et al., 2017].

As E/E` is recognized to be connected to myocardial fibrosis, Altekin et al. suggest that fibrosis, along with increased LV filling pressures promote subclinical LV systolic dysfunction in OSA subjects [Altekin et al., 2012]. Average A' wave velocity and also LA volumes (precontraction, maximum and minimum volumes measured in 3D echocardiography) are higher in patients with severe OSA, as opposed to E'/A' ratio, which decreases with OSA severity [Oliveira et al., 2009].

Table XVI. Left ventricular tissue Doppler parameters in patients with OSA

Echocardiographic variables		AHI <5 events·h−1	Mild OSA	Moderate OSA	Severe OSA	p
E' (cm/s)	Imai et al., 2015	NA	10.7±3.0		8.7±1.9	<0.0001
	Varghese et al., 2017	10.6±1.1	NA	NA	9.2±2.1	0.01
	Vural et al., 2017	11.6±1.5	9.6±1.7	6.3±1.1 †,‡	6.1±1.4 †,‡	<0.05
	Oliveira et al., 2009	NA	7.7±1.5	7.3±2.0	6.2±1.8 ‡,*	<0.05
	Vitarelli et al., 2013	12.1±2.2	11.4±2.1	NA	7.7±2.8 †	0.016
E/E`	Altekin et al., 2012	6.88±1.7	6.91±1.9	8.56±2.37	10.29±1.48†,‡,*	<0.001
	Wachter et al., 2013	11.0±3.6	11.7±3.5	12.7±5.3 †		<0.05
	Imai et al., 2015	NA	7.6±2.2		7.8±2.3	0.04
	Varghese et al., 2017	8.44±1.6	NA	NA	9.69±2.6	0.03
	Altekin et al., 2012	8.13±2.22	8.62±2.68	11.31±2.87 †,‡	13.89±2.32 †,‡,*	<0.05
	Vural et al., 2017	6.5±1.2	8.4±2.4 †	11.9±2.2 †,‡	12.0±2.8 †,‡	<0.05
	Vitarelli et al., 2013	5.6±1.6	5.5±1.8	NA	8.8±2.5 †	0.025
	Oliveira et al., 2009	NA	9.7±1.9	10.4±3.1	11.6±3.6 ‡,*	<0.05
	Oliveira et al., 2012	9.4±2.9	10.6±3.0			0.02
A' (cm/s)	Oliveira et al., 2009	NA	6.1±1.4	6.8±1.7	8.2±1.9 ‡,*	<0.05
E'/A'	Oliveira et al., 2009	NA	1.3±0.4	1.1±0.3	0.8±0.3 ‡,*	<0.05

Abbreviations: AHI – apnea hypopnea index. OSA – obstructive sleep apnea; † - significantly different from AHI < 5 events·h−1; ‡ - significantly different from mild OSA; * - significantly different from moderate OSA; NA – not applicable

OSA impact on right chambers

Sanner et al. showed that right ventricular failure is more frequent in patients with OSA even in the absence of any other respiratory conditions [Sanner et al., 1997]. Previous reports revealed that right atrial volume index (RAVI) is increased in patients with severe OSA than in those with mild OSA or controls [Altekin et al., 2012].

The results of Framingham study did not find any difference regarding right ventricular (RV) volumes, end-diastolic dimensions and systolic function between subjects with sleep disordered breathing and controls [Guidry et al., 2001]. The systolic and diastolic volumes of RV cannot be appropriately calculated using 2D echocardiography due to its complex anatomical

shape. RV fractional area change and MPI are surrogate markers that estimate RV global function, while other parameters such as TAPSE and S' have the main disadvantage of offering only a partial representation of RV systolic function [Venkatachalam et al., 2017].

It was concluded that acceptable RV volume estimations are not possible without the 3D technique and such studies showed that patients with moderate-severe OSA have higher indexed RV end-diastolic and end-systolic volumes compared to controls ($p<0.05$) [Oliveira et al., 2012; Güvenç et al., 2016]. While some data found that RV-EF is comparable in patients with and without OSA [Buonauro et al., 2017], others have reported a minor, but statistically significant difference in RV-EF (table XVII) [Oliveira et al., 2012].

Table XVII. Right atrial and ventricular parameters in relationship with OSA

Echocardiographic variables		AHI <5 events·h^{-1}	Mild OSA	Moderate OSA	Severe OSA	p
AVI (ml/m^2)	Altekin et al., 2012	15.56±4.94	17.31±6.24	21.89±7.91	28.85±7.97 †,‡	<0.05
RVESV index (ml/m^2)	Güvenç et al., 2016	22.15±3.85	NA	26.50±8.11		0.01
	Oliveira et al., 2012	15.4±3.6	18.7±4.3			<0.05
RVEDV index (ml/m^2)	Güvenç et al., 2016	41.48±6.45	NA	48.15±11.48		0.009
	Oliveira et al., 2012	49.9±6.0	52.2±7.3			0.02
RV-EF (%)	Oliveira et al., 2012	68.4±5.9	64.3±6.8			<0.01
TAPSE (mm)	Altekin et al., 2012	24.76±1.55	22.30±2.39	21.11±1.56 †	19.42±1.64 †,‡,*	<0.05
	Zakhama et al., 2016	NA	NA	26.1±3	22.7±4	0.012
RV MPI	Romero-Corral et al., 2007	0.23±0.10	0.26±0.16 †	0.37±0.11 †		<0.05
	Altekin et al., 2012	0.43±0.09	0.46±0.09	0.53±0.08 †	0.56±0.11 †,‡	<0.05
	Shivalkar et al., 2006	0.25 ± 0.03	0.29 ± 0.05			0.008
	Zakhama et al., 2016	0.46±0.14	0.55±0.12			0.024
S`RV (cm/s)	Shivalkar et al., 2006	13.5±1.8	11.4±2.3			<0.001
	Zakhama et al., 2016	14.5±3	12.2±2			<0.001
RV E/E`	Güvenç et al., 2016	3.83±1.16	NA	5.23±2.58		**0.008**
	Altekin et al., 2012	4.19±1.22	4.37±1.22	5.77±1.27 †,‡	7.12±2.29 †,‡	<0.05

Abbreviations: RAVI – right atrial volume index. RVESV – right ventricular end systolic volume. RVEDV – right ventricular end diastolic volume. RV-EF – right ventricular ejection fraction. TAPSE – tricuspid annular plane excursion. RV-MPI – right ventricular myocardial performance index. AHI – apnea hypopnea index. OSA – obstructive sleep apnea: † - significantly different from AHI < 5 events·h−1; ‡ - significantly different from mild OSA; * - significantly different from moderate OSA; # - significantly different in OSA compared to controls; NA – not applicable

A strong relationship between AHI, RV diameter (r=0.482, p=0.0009) [Shivalkar et al., 2006] and RV-EF (r=−0.362, p=0.02) [Güvenç et al., 2016] was also described. RV wall thickness is higher in subjects with more severe forms of OSA (0.78±0.02 versus 0.68±0.02, p=0.005) [Guidry et al., 2001] and is apparently correlated with AHI (r=0.356, p=0.026) [Güvenç et al., 2016].

While Wachter et al. did not find a significant decrease in the right ventricular Tei index (RV-MPI) in patients with severe sleep apnea [Wachter et al., 2013], a previous report proved a significant difference in RV-MPI between controls and patients with moderate and severe OSA [Romero-Corral et al., 2007] and also found a positive correlation between RV-MPI and AHI (r=0.40, p=0.002) [Romero-Corral et al., 2007]. These data are sustained by other reports showing that RV-MPI is significantly higher in OSA patients than in controls (but not between patients with mild-moderate versus severe OSA) [Altekin et al., 2012; Zakhama et al., 2016]. It seems that an increase in AHI has a superior effect on RV global function than on the LV one [Altekin et al., 2012]. The authors speculate that OSA induced RV dysfunction may contribute to the development of subsequent LV dysfunction due to ventricular interdependence [Altekin et al., 2012].

It is known that 2D echocardiographic parameters that assess global RV function include tricuspid annular plane systolic excursion (TAPSE), myocardial performance index and RV fractional area change (RV-FAC) [Altekin et al., 2012]. Still, tissue Doppler is more sensitive than 2D echocardiography in detecting subclinical RV dysfunction [Altekin et al., 2012]. While RV E/A ratio did not significantly differ in subjects with moderate-severe OSA living at high altitudes compared to healthy controls, RV E/E` ratio was significantly higher in the OSA group [Güvenç et al., 2016]. A study conducted in 2012 by Altekin et al., did not find significant differences regarding RV A wave velocity or PAP, but he found that E wave deceleration time, A' velocity, and E/E' ratio were higher in subjects with severe OSA compared to controls and subjects with mild OSA [Altekin et al., 2012]. TAPSE, E' wave velocity and RV E/A ratio were lower in patients with moderate-severe OSA than in the control and mild OSA groups [Altekin et al., 2012].

Data regarding the impact of OSA on RV S' are controversial, with some authors affirming that it does not significantly differ between patients with and without OSA [Dobrowolski et al., 2016]. Other authors detected different results [Zakhama et al., 2016], reporting a significant correlation between AHI and RV S` [Shivalkar et al., 2006]. While two recent articles did not find any significant differences regarding TAPSE between patients with and without OSA [Dobrowolski et al., 2016; Ozkececi et al., 2016], another paper reported a correlation between TAPSE and AHI (r=−0.285, p=0.079) [Güvenç et al., 2016].

Pulmonary hypertension

Epidemiological reports show that the prevalence of pulmonary hypertension (PH) among patients with OSA ranges between 12% and 70%. PH prevalence depends on OSA severity, pulmonary artery pressure (PAP) assessment method, time of measurement and other possible confounding factors and is usually evaluated via the modified Bernoulli equation to estimate pulmonary artery systolic pressure (PASP) [Ozkececi et al., 2016]. Still, other formulas have been proposed for calculating mean PAP in patients without tricuspid insufficiency [Dabestani et al., 1987].

While Altekin et al. [Altekin et al., 2012] found no significant differences between PASP or mean PAP among patients with different degrees of OSA severity and controls, other reports showed that patients with moderate and severe OSA present higher PASP than healthy controls [Shivalkar et al., 2006; Zhou et al., 2016] (table XVIII); also, PASP was significantly higher in patients with moderate-severe OSA living at high altitudes than in controls (p=0.002) [Güvenç et al., 2016].

In a study conducted in 2016, pulmonary acceleration time was significantly lower in subjects with moderate-severe OSA living at high altitudes versus controls (p=0.001) and was directly correlated to AHI (r=−0.282, p=0.077) [Güvenç et al., 2016].

Table XVIII. Pulmonary hypertension parameters in relationship with OSA severity

Echocardiographic variables		AHI <5 events·h^{-1}	Mild OSA	Moderate OSA	Severe OSA	p
PAPS (mmHg)	Güvenç et al., 2016	30.94±6.47	NA	38.35±8.6		0.002
	Zhou et al., 2016	16.7±6.2	18.2±6.6	31.2±5.6 †	32.8±6.7 †	<0.05
	Shivalkar et al., 2006	22±8	32±10			0.004
PAT (ms)	Güvenç et al., 2016	118.36±16.36	NA	103.13±18.42		0.001

Abbreviations: PAPS – pulmonary artery systolic pressure. PAT – pulmonary artery acceleration time. AHI – apnea hypopnea index. OSA – obstructive sleep apnea.; † - significantly different from AHI < 5 events·h−1; NA – not applicable

Pulmonary artery (PA) stiffness seems to be correlated both with AHI and mean oxygen saturation and represents the ratio between pulmonary artery maximal frequency shift and pulmonary acceleration time [Ozkececi et al., 2016]. A previous report showed that subjects with OSA present increased PA stiffness even in the lack of pulmonary hypertension. Moreover, the authors recommend PA stiffness as a more reliable parameter than PAP in patients with OSA [Ozkececi et al., 2016].

Other parameters

Epicardial fat thickness, as an indirect marker of visceral adiposity, is significantly higher in patients with moderate or severe OSA (AHI>15). Previous research showed that 24 weeks of CPAP treatment induces a significant regression of epicardial fat thickness, even in the absence of any significant changes in BMI or waist circumference [Dabestani et al., 1987]. A more recent study conducted in 2018 that included patients with heart failure (LVEF <45%) revealed that epicardial adipose thickness was significantly higher in subjects with sleep disordered breathing than in patients without sleep apnea (10.7±2.8 vs. 8.13±1.8; p = 0.001) [Parisi et al., 2018].

Another report showed that OSA is more frequent among patients with Marfan syndrome and that the aortic root diameter is 0.8 cm higher in OSA patients (p<0.0001), suggesting therefore that OSA might contribute to aortic root enlargement in such patients [Kohler et al., 2009].

Speckle tracking echocardiography

In contrast to tissue Doppler imaging, two-dimensional speckle tracking echocardiography is not angle dependent. Also, global and segmental systolic function are more accurately characterized. Subjects with severe OSA present significantly reduced global longitudinal strain values compared to the other groups [Altekin et al., 2012] and significant difference regarding basal, mid and apical strain values between subjects with severe OSA and all other groups [Altekin et al., 2012]. Other authors showed that global left ventricular longitudinal strain is decreased in patients with very severe OSA [Varghese et al., 2017].

In 2017, Varghese et al. revealed that apical and middle LV segments showed more pronounced longitudinal strain anomalies (table XIX), but circumferential strain did not significantly differ between subjects with very severe OSA and controls [Varghese et al., 2017]. A different report found an epicardial-to-endocardial strain gradient at each myocardial level [Zhou et al., 2015].

Only longitudinal (and not circumferential) strain was directly correlated with AHI. Also, subjects with severe OSA presented decreased three-layer longitudinal LV strain, despite having a normal ejection fraction [Zhou et al., 2015].

Diastolic dysfunction is often associated to abnormal GLS even in the presence of normal LVEF and LV volumes [Park et al., 2008]. Longitudinal myocardial fibers, mainly located in the subendocardium, are very vulnerable to fibrosis in such cases, resulting in decreased longitudinal shortening and a compensatory elevation of circumferential shortening and torsion [Wang et al., 2008]. LV torsion is the twist of the ventricle around its long axis, given by the antagonistic rotation of the basal and apical segments [Vural et al., 2017] and increased LV torsion is an early indicator of left ventricular dysfunction in patients with normal LVEF.

The published data showed contradictory results regarding LV torsion in OSA patients: whereas Vural et al. found that LV torsion is decreased in subjects with AHI>30 and in controls compared to patients with mild or moderate sleep apnea [Vural et al., 2017], Vitarelli et al. reported a significant increase in LV torsion in severe sleep apnea versus controls [Vitarelli et al., 2013].

Table XIX. Left and right ventricular strain parameters in subjects with OSA

Echocardiographic variables		AHI <5 events·h^{-1}	Mild OSA	Moderate OSA	Severe OSA	p
LV GLS (%)	Varghese et al. 2017	-19±1.6	NA	NA	-15±1.8	<0.01
	Vural et al., 2017	-22.3±4.0	- 20.0±2.3	-17.2±2.0 †	- 15.6±5.6 †,‡	<0.05
	Vitarelli et al. 2013	−21.9±2.8	−21.2±2.5	NA	−18.4±2.7 †	0.011
	Altekin et al. 2012	-25.6±2.2	-23.9±-3.9	-21.3±2.6 †,‡	-16.9±-2.7 †,‡,*	<0.03
LS basal strain (%)	Varghese et al. 2017	-17±1.7	NA	NA	-15±1.9	0.02
	Altekin et al. 2012	-21.4±-1.9	-19.9±-2.4	-18.4±2.6 †	-15.3±-2.9 †,‡,*	<0.03
LS mid strain (%)	Varghese et al. 2017	-18±1.8	NA	NA	-15±2.3	<0.01
	Altekin et al. 2012	-23.3±-2.1	-21.5±-2.4	-19.7±2.6 †	-16.9±-2.9†,‡,*	<0.03
LS apical strain (%)	Varghese et al. 2017	-20±1.7	NA	NA	-16±2.5	<0.01
	Altekin et al. 2012	-27.4±-3.7	-24.6±-2.9	-23.5±3.9†	-19.2±-3.9†,‡,*	<0.03
LV radial strain (%)	Vural et al., 2017	45.7±6.1	44.4±7.7	39.8±7.8 †	39.8±8.9 †	<0.05
LV circumferential strain (%)	Vural et al. 2017	-21.6±3.5	-21.2±1.8	-19.3±2.8 †	-18.8±2.7 †	<0.05
LV apical rotation °	Vural et al. 2017	8.6±1.0	8.7±1.7	9.1±1.1	7.4±1.3 †,‡,*	<0.05
LV torsion °	Vural et al. 2017	15.6±1.5	16.1±1.9	16.5±1.6	14.8±1.6 ‡,*	<0.05
2D global RV SI	Hammerstingl et al., 2013	NA	-21.5±6.3	-14.3±5.3	-14.5±8.2	<0.0001
	Buonauro et al. 2017	22.8±3.3	20.9±4.9			<0.05
2D apical RV SI	Hammerstingl et al., 2013	NA	-17.3±8.7	-9.8±6.0	-6.3±5.7	<0.0001

2D basal RV SI	Hammerstingl et al., 2013	NA	-27.4±13.6	-18.2±8.7	-21.6±14.9	0.03
RV strain (%)	Altekin et al. 2012	-34.05±-4.29	–31.4±–5.37	–22.75±–4.89 †,‡	–20.89±–5.59 †,‡	<0.05
RV systolic strain rate	Altekin et al. 2012	–2.93±–0.64	–2.85±–0.73	–2.06±–0.43 †,‡	–1.43±–0.33 †,‡,*	<0.05
RV early diastolic strain rate	Altekin et al. 2012	2.38±0.63	2.32±0.84	1.66±0.55 †	1±0.54 †,‡	<0.05
RV late diastolic strain rate	Altekin et al. 2012	2.25±0.33	2.32±0.54	2.79±0.66 †	3.29±0.54 †,‡	<0.05

Abbreviations: LV GLS – left ventricular global longitudinal strain. LS basal – left ventricular basal longitudinal strain. LS mid - left ventricular longitudinal strain in medium segments. LS apical - left ventricular apical longitudinal strain. LV – left ventricular. 2D global RV SI – bidimensional global right ventricular strain index. 2D apical RV SI - bidimensional apical right ventricular strain index. 2D basal RV SI - bidimensional basal right ventricular strain index. RV – right ventricular. AHI – apnea hypopnea index. OSA – obstructive sleep apnea; † - significantly different from AHI < 5 events·h−1; ‡ - significantly different from mild OSA; * - significantly different from moderate OSA; NA – not applicable

Vural et al. showed that left atrial strain rate values are significantly higher in subjects with severe OSA and found a positive correlation between AHI and LA contractile strain, which can be partially improved after 12 weeks of CPAP therapy [Vural et al., 2017]. Although standard tissue Doppler techniques are limited by tethering forces and myocardial translational motion, 2D speckle tracking imaging (2D-STE) is not influenced by Doppler beam angling or load dependency and can provide a more accurate assessment of RV function. RV radial function study is exposed to major errors due to the anterior position of the RV in parasternal views and frequent artifacts, making the RV longitudinal strain and strain rate values to be preferred [Altekin et al., 2012]. Additionally, strain and strain rate assessment of the RV should only include the RV free wall as seen in the apical view as the interventricular septum motion is under the greater influence of the left ventricle, [Jurcut et al., 2010; Leung, 2010].

To conclude, the effect of OSA on RV function is controversial. Hammerstingl et al. showed that RV global, apical and basal longitudinal strains are correlated to the severity of OSA [Hammerstingl et al., 2013] but after multivariate regression analysis, only apical RV longitudinal strain parameters were independently associated with severe sleep apnea [Hammerstingl et al., 2013]. The results of the study suggest that apical RV longitudinal strain is a sensitive parameter for the diagnosis of subclinical RV dysfunction [Wachter et al., 2013]. Still, additional reports did not show any significant difference regarding segmental RV strain and strain rate between subjects with moderate-severe OSA and controls [Güvenç et al., 2016]. Subjects with moderate-severe OSA have lower RV strain and RV systolic strain values than controls or subjects with AHI<15 [Altekin et al., 2012]. RV early diastolic strain rate decreases with disease severity, but RV late diastolic strain rate increases with AHI [Altekin et al., 2012]. Moreover, 2D speckle tracking

parameters correlate better with AHI than any other echocardiographic parameters and should be used in detecting early, subclinical RV dysfunction [Altekin et al., 2012]. The same result is supported by Buonauro et al. who have shown that subclinical RV dysfunction can be evaluated via speckle tracking echocardiography [Buonauro et al., 2017].

3.2.5. Conclusions

Moderate and severe forms of OSA are associated with decreased ventricular function and increased atrial volume, explaining the high incidence of chronic heart failure and also atrial fibrillation in these patients. 2D-STE is not influenced by Doppler beam angling or load dependency. Abnormal strain values, a marker of subclinical systolo-diastolic dysfunction, can be detected even in patients with normal EF and chamber volumes. Still, the role of 2D-STE in OSA patients should be addressed by further studies, as current information yields contradictory results.

Zota IM, Leon Constantin MM, Statescu C, Sascau RA, Roca M, Gavril RS, Vasilcu TF, Boisteanu D, Cojocaru E, Mastaleru A, Mitu O, Mitu F. Clinical and biological impact of CPAP therapy in patients with obstructive sleep apnea and cardio-metabolic comorbidities. *Acta Medica Mediterranea* 2020; 36:1975. **IF: 1.249**
https://www.actamedicamediterranea.com/archive/2020/medica-3/clinical-and-biological-impact-of-cpap-therapy-in-patients-with-obstructive-sleep-apnea-and-cardio-metabolic-comorbidities

3.3. CPAP therapy in patients with OSA and cardio-metabolic comorbidities

3.3.1. Introduction

Obstructive sleep apnea (OSA) has a potential impact on cardiovascular morbidity and mortality. The succeeding activation of the sympathetic nervous system and the renin-angiotensin-aldosterone axis, along with smoldering systemic inflammation, elucidate the high incidence of cardiovascular complications associated with OSA [Turnbull, 2018]. Sleep apnea is strongly linked with insulin resistance, systemic inflammation, hypertension and obesity, clarifying the emerging relationship between OSA and metabolic syndrome [Castaneda et al., 2018]. While polysomnography remains the gold standard diagnostic test for sleep disordered breathing, cardiorespiratory polygraphy remains an accepted alternative for OSA diagnosis [Corlateanu et al., 2017]. It is known that CPAP is the standard therapy for moderate up to severe OSA and it seems to partially reverse the increased cardiovascular risk associated with OSA [Campos-Rodriguez et al., 2012; Fava et al., 2014], as well as to improve blood pressure level [Fava et al., 2014], arterial stiffness [Korcarz et al., 2016], lipid and glucose metabolism [Castaneda et al., 2018]. Still, CPAP effectiveness is limited in patients with low daytime sleepiness [Wons et al., 2015], which can be assessed via the Epworth, Berlin or STOP questionnaires [Amra et al., 2018]. The usefulness of other OSA treatment options, such as mandibular devices or oropharyngeal exercises, is inferior to that of CPAP [Lorenzi-Filho et al., 2017].

3.3.2. Aim

Our study aims to highlight the benefit of CPAP therapy in patients with cardio-metabolic comorbidities (hypertension, diabetes, obesity) assessed in a cardiovascular rehabilitation clinic.

3.3.3. Material and Methods

Our prospective study included 33 patients newly-diagnosed with moderate to severe OSA, who were evaluated before and after 2 months of CPAP therapy. OSA diagnosis was made by ambulatory or in-hospital six-channel cardio-respiratory polygraphy. The recordings were manually scored by a trained physician, according to the American Academy of Sleep Medicine (AASM) standards. Patients with an apnea-hypopnea index (AHI) of 15 – 30 and > 30 were considered to have moderate and severe OSA, respectively. The study protocol was approved by the Ethics Committee and all individuals signed a written informed consent prior to their inclusion in the study. We performed clinical examination (weight, body mass index (BMI), abdominal circumference (AC), blood pressure (BP), heart rate (HR)), routine blood tests and completed the Epworth [Amra et al., 2018] and Euro Quality of Life (EQ-5D-5L)[Schmidlin et al., 2010] questionnaires, before and after 2 months of CPAP therapy.

Hypertension was defined as office blood pressure ≥ 140/90 mmHg or hypertensive patients currently on blood pressure lowering treatment. Diabetes and impaired fasting glucose diagnosis were established according to the American Diabetes Association criteria. Dyslipidemia was defined as total cholesterol ≥ 200 mg/dl, serum triglycerides ≥ 150 mg/dl or patients currently on lipid lowering treatment.

Statistical analysis was performed in SPSS v 20.0, using chi-square and student's t test for comparisons between groups. A potential relationship between variables was evaluated using Pearson correlation coefficient. Descriptive data was expressed as means ± SD (standard deviation) or percentages, as appropriate. A p value < 0.05 was considered statistically significant.

3.3.4. Results

Our study cohort comprised 24 males and 9 females, with a medium apnea-hypopnea-index of 41 events/h (table XX, table XXI). From the total number 63,63% patients were diagnosed with diabetes or impaired fasting glucose. When analysing hypertension and dyslipidemia, the results showed that these two conditions were present in 96,96% and 87,87% of cases, respectively. While average nocturnal oxygen saturation (O_2Sa) was similar in the 2 subgroups, patients with severe OSA presented a significantly lower minimum nocturnal O_2Sa, a higher CPAP pressure regimen being necessary.

Within the research, abdominal obesity was highly prevalent in the study group, but we found no significant differences regarding BMI and AC between the two subgroups (table XXII).

Though, patients with severe OSA presented a poorer lipid profile and higher erythrocyte sedimentation rate (ESR).

Our results showed no statistically significant correlations between apnea severity and BMI (p=0,53), age (p=0,07), AC (p=0,65) or blood pressure values. Still, AHI was correlated to resting heart rate (R=0,41; p=0,01), inflammation markers (ESR: R=0,43, p=0,01; CRP: R=0,40, p=0,02) and total cholesterol (R=0,37, p=0,03). 12,12% of the patients did not tolerate CPAP or APAP therapy and returned the device in less than 14 days. 2 patients (6,06) were not present for the second clinical evaluation. Average CPAP use in our study group was 4,1 h/night. Resting HR, ESR and CRP were not significantly different after 2 months of CPAP therapy (p=0,14, 0,47 and 0,96, respectively). Average SBP and DBP values were lower after treatment, with borderline statistical significance (Δ=-7,04 mmHg, p=0,07 and Δ=-4,55 mmHg, p=0,07, respectively).

Table XX. Study group analysis – associated comorbidities

	Moderate-severe OSA	**Moderate OSA**	**Severe OSA**
N	33	13	20
Age	57,57 ± 8,93	57,38 ± 8,46	57,7 ± 9,43
M	24 (72,72%)	9 (69,23%)	15 (75%)
F	9 (27,27%)	4 (30,76%)	5 (25%)
Type 2 diabetes	14 (42,42%)	7 (53,84%)	7 (35%)
Impaired fasting glucose	7 (21,21%)	2 (15,38%)	5 (25%)
HT	32 (96,96%)	12 (92,3%)	20 (100%)
Hypercholesterolemia	24 (72,72%)	9 (69,2%)	15 (75%)
Hypertrygliceridemia	5 (15,15%)	2 (15,38%)	3 (15%)

OSA – obstructive sleep apnea; N – number; M – males; F – females; HT – hypertension.

Table XXI. Study group analysis – associated comorbidities

	Moderate-severe OSA	**Moderate OSA**	**Severe OSA**	**P value**
AHI (events/h)	41,16 ± 18,47	23,55 ± 2,81	52,59 ± 14,22	0,00
Average nocturnal O2Sa (%)	91,4 ± 3,59	92 ± 3,18	91,05 ± 3,78	0,45
Minimum nocturnal O2Sa (%)	73,15 ± 11,55	79,54 ± 7,32	68,45 ± 11,8	0,02
Recommended CPAP pressure (cmH20)	11,39 ± 2,64	9,8 ± 2,34	12,28 ± 2,41	0,014
Epworth score	7,12 ± 5,68	7,69 ± 5,57	6,74 ± 5,88	0,64

OSA – obstructive sleep apnea; AHI – apnea hypopnea index; DI – desaturation index; O2Sa – oxygen saturation; CPAP – continuous positive airway therapy.

Table XXII. Anthropometric and biological parameters

	Moderate-severe OSA	**Moderate OSA**	**Severe OSA**	**P value**
Weight (kg)	104,68 ± 18,02	104,19 ± 20,7	105 ± 16,61	0,90
BMI (kg/m^2)	35,33 ± 5,26	35,15 ± 6,4	35,44 ± 4,54	0,88
AC (cm)	116,2 ± 11,32	117,04 ± 12,69	115,68 ± 10,7	0,75
SBP (mmHg)	141,3 ± 19,67	141,69 ± 21,79	141,05 ± 18,74	0,92
DBP (mmHg)	86,18 ± 12,12	85,46 ± 13,92	86,65 ± 11,15	0,78
HR (bpm)	71,78 ± 10,29	66,69 ± 7,36	75,1 ± 10,72	0,01
Glycemia (mg%)	116,8 ± 24,55	115,23 ± 32,16	117,83 ± 18,96	0,77
ESR (mm/h)	17,57 ± 18,44	9 ± 4,43	23,15 ± 21,85	0,01
CRP (mg%)	0,93 ± 1,24	0,56 ± 0,39	1,19 ± 1,54	0,15
Uric acid (mg%)	5,08 ± 1,36	4,86 ± 1,29	5,23 ± 1,41	0,44
Total cholesterol (mg%)	177,51 ± 40,66	159,08 ± 45,4	189,49 ± 33,16	0,03
LDL (mg%)	94,22 ± 33,36	79,72 ± 32,85	103,65 ± 30,9	0,04
TG (mg%)	165,87 ± 94,24	156,63 ± 76,67	171,87 ± 105,59	0,65
HbA1c (%)	6,74 ± 1,28	7,05 ± 1,67	6,53 ± 0,96	0,33
Perceived health status (%)	64,43 ± 19,81	60,15 ± 19,89	67,36 ± 19,74	0,32

OSA – obstructive sleep apnea; BMI – body mass index; AC – abdominal circumference; SBP – systolic blood pressure. DBP – diastolic blood pressure. HR – heart rate ESR - Erythrocyte sedimentation rate; CRP – C reactive protein; TC – total cholesterol; TG – triglycerides; HbA1c – glycated hemoglobin.

CPAP therapy was associated with a significant improvement in weight status, total cholesterol, glycated hemoglobin, daytime sleepiness and perceived health status (according to the EQ-5D-5L visual analog scale).

Figure 3 and Figure 4 emphasize the above mentioned improvements.

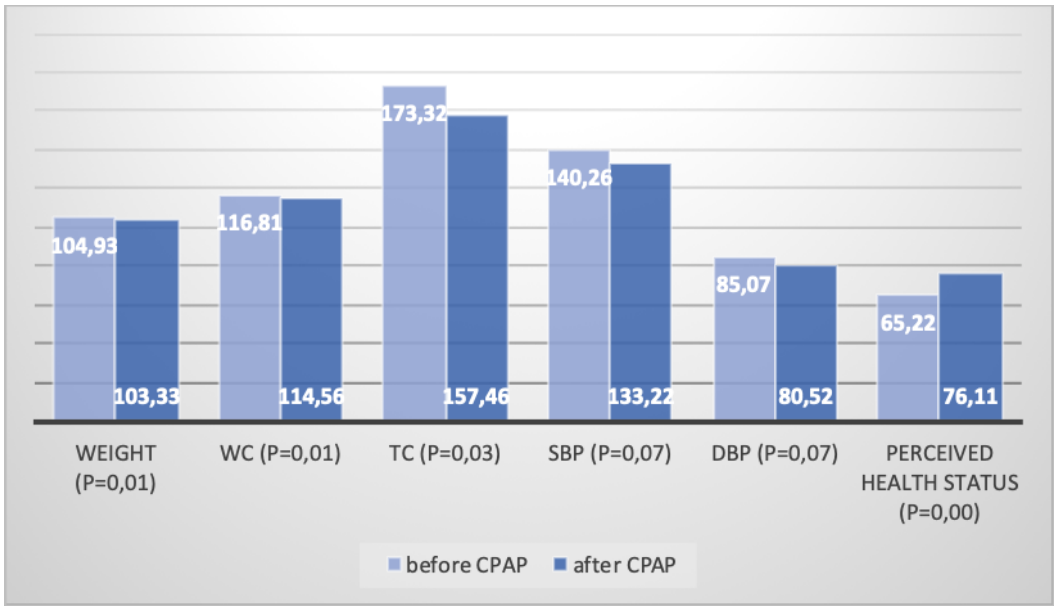

Figure 3. Changes in weight, waist circumference, total cholesterol, systolic and diastolic blood pressure and perceived health status after 2 months of CPAP

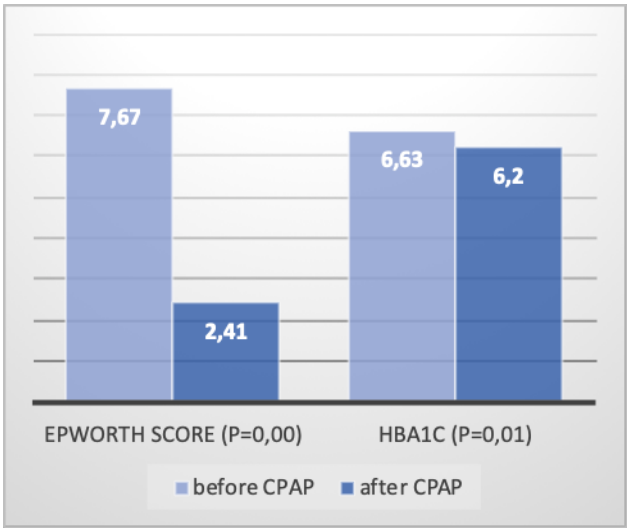

Figure 4. Changes in Epworth score results and HbA1c after 2 months of CPAP

3.3.5. Discussion

OSA is twice more common in males than in females according to previous reports [Heinzer et al., 2015], similar to our data (male: female ratio 2,53). Although obesity was highly prevalent in our group, severe and moderate OSA patients had a similar average BMI and AC, proving that abdominal obesity is not the only trigger for OSA [Castaneda et al., 2018]. In 2015, a meta-analysis of Lin et al. revealed that CPAP is effective in reducing TC (-6,23 mg/dl, $p<0,001$) and TG (-12,6 mg/dl, $p<0,001$), but not LDL cholesterol (-1,01 mg/dl, $p=0,62$)[Lin et al., 2015].

The high prevalence of abdominal obesity which aggravates the systemic proinflammatory status seems to explain the strong link between OSA and an atherogenic lipid profile. While the general lipid profile was poorer in subjects with severe OSA, we only set up a statistically significant correlation between AHI and total cholesterol levels, which also demonstrated a significant decrease after 8 weeks of CPAP therapy (-16 mg/dl, p=0,03). The link between AHI and LDL had borderline statistical significance (R=0,336 and p=0,06) and should be further analyzed in larger study groups. It is known that metabolic syndrome (MS) and obstructive sleep apnea coexist in up to 60% of cases [Castaneda et al., 2018]. The results of our study revealed an extremely high prevalence of hypertension, impaired glucose and lipid metabolism, highlighting the importance of OSA screening in patients with MS.

Currently, CPAP use is consistently associated with effective weight loss. Our analysis also illustrated a significant weight loss and abdominal circumference reduction. But, a recent meta-analysis showed that noninvasive ventilation induces only a mild weight loss [Drager et al., 2007] and other authors reported even a reduced basal metabolic rate by 75 kilocalories after CPAP therapy [Tachikawa et al., 2016].

Previous data sustained the role of systemic inflammation in OSA pathogenesis [Bouloukaki et al., 2017]. The results of our research confirmed the presence of a significant correlation between AHI, ESR and CRP, but failed to show a significant impact of CPAP in reversing systemic inflammation. Some reports underlined the association of obstructive sleep apnea with an impaired glucose metabolism and of a high BMI with a greater risk of insulin resistance in OSA patients [Archontogeorgis et al., 2019].

As far as we know, this was the first report showing higher HbA1c values in the moderate OSA subgroup. Even though not statistically significant (p=0,33), this surprising result was probably due to the small population included in the research, and also to a higher prevalence of diabetes in our moderate versus severe OSA subgroups (53,84% versus 35%, respectively). Other studies reported divergent results concerning the effect of CPAP on HbA1c in diabetics [Gallegos et al., 2014; Feng et al., 2015; Morariu et al., 2017]; still, we found that HbA1c levels improve after 8 weeks of CPAP (-0,43% p=0,01).

The link between CPAP and hypertension was previously studied. It was shown that CPAP is associated with a reduction in systolic and diastolic BP values by 2,6 and 2 mmHg, respectively [Fava et al., 2014]. Our results did not reach statistical significance (p=0,07) even though we obtained a higher reduction of resting BP. Additional studies on larger number of patients are needed in order to support our data.

Within our study, Epworth score did not correlate with AHI and did not reflect OSA severity. Although our patients did not present significant daytime sleepiness, CPAP therapy improved Epworth score results (p=0,000), similar to other literature reports [Antic et al., 2011].
As documented by the use of several questionnaires such as Short Form 36, Functional Limitations Profile and EQ-5D-5L, OSA is associated with impaired quality of life. In our study, we did find a significant improvement in perceived health status according to the EQ-5D-5L visual analogue

scale after 8 weeks of CPAP therapy, the results being consistent with those reported by Schmidlin et al [Schmidlin et al., 2010].

Important limitation of our study consisted of the suboptimal average use of CPAP along with the small number of patients, the presence of cardiovascular and metabolic comorbidities and also the different treatment regimens applied in each case. Additionally, the low Epworth score in our study group reflects a less symptomatic form of apnea, which is known to have a poor response to CPAP therapy. Moreover, during the first clinical evaluation, all patients received medical advice concerning the importance of lifestyle changes which could explain the marked improvements in weight status, lipid and glucose metabolism. However, we were not able to objectively evaluate individual patient adherence to lifestyle changes.

3.3.6. Conclusion

Our study showed that abdominal obesity and male sex are strong predictors of OSA. As well, impaired glucose metabolism, dyslipidemia and hypertension are common comorbidities in patients with obstructive sleep apnea. Noninvasive ventilation is associated with improved weight status, total cholesterol, HbA1c levels and quality of life, but OSA therapy is limited by poor device tolerance and suboptimal CPAP use.

Zota IM, **Stătescu C**, Sascău RA, Roca M, Gavril RS, Vasilcu TF, Boișteanu D, Maștaleru A, Jitaru A, Leon Constantin MM, Mitu F. CPAP Effect on Cardiopulmonary Exercise Testing Performance in Patients with Moderate-Severe OSA and Cardiometabolic Comorbidities. *Medicina (Kaunas)* 2020;56(2):80. **IF: 1.205**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7074283/pdf/medicina-56-00080.pdf

3.4. CPAP Effect on Exercise Testing Performance in Patients with OSA and Cardiometabolic Comorbidities

3.4.1. Introduction

Abnormalities of lung function related to obesity and weight have an increased prevalence among OSA patients [Lin et al., 2006]. Hypertension, heart failure, pulmonary hypertension, hypoxia-induced erythropoiesis [Khan et al., 2011] with consequent hematological alterations and muscular mitochondrial dysfunctions are factors contributing to a decreased exercise tolerance [Lin et al., 2006; Stavrou et al., 2018].

The cardiopulmonary exercise testing (CPET) is a useful tool for risk stratification and prognosis assessment in patients with OSA, offering an integrative assessment of the cardiopulmonary, muscular, neuropsychological and hematopoietic systems [Albouaini et al., 2007]. CPET helps to create a personalized exercise training program for OSA patients.

However, current reports [Berger et al., 2019] offer contradictory results regarding CPET usefulness in OSA patients and the role of CPAP in improving exercise performance.

3.4.2. Aim

We aimed to evaluate the impact of short-term (8 weeks) CPAP therapy on exercise capacity of patients with moderate-severe OSA and cardiometabolic comorbidities.

3.4.3. Material and methods

Our prospective study included 64 patients with moderate-severe OSA, admitted in a local cardiovascular rehabilitation clinic during one year. OSA diagnosis was made through the help of cardio-respiratory polygraphy. The recordings were manually scored, according to the American Academy of Sleep Medicine (AASM) standards. Patients with an apnea-hypopnea index (AHI) of 15 – 30 and > 30 were considered to have moderate and severe OSA, respectively.

The study protocol was approved by the Ethics Committee of "Grigore T. Popa" University of Medicine and Pharmacy in Iasi and all patients signed a written informed consent before enrollment. Patients underwent physical examination, lipid profile assessment, and cardiopulmonary exercise testing. Also, they were asked to complete the Epworth questionnaire, before and after 2 months of CPAP therapy. Obesity was defined as a body mass index (BMI) ≥ 30 kg/m2. High blood pressure (HBP) was defined as current BP lowering treatment, prior diagnosis of HBP or resting BP values greater than 140 and 90 mmHg for systolic and diastolic BP, respectively. Dyslipidemia was defined as total cholesterol ≥ 200 mg/dl and/or triglycerides ≥ 150 mg/dl. Ischemic heart disease was defined as history of myocardial infarction or prior angiographically documented significant coronary artery stenosis. According to the results of the Epworth questionnaire, daytime sleepiness was categorized as normal, mild, moderate and severe (0-10 points, 11-12 points, 13-15 points and 16-24 points, respectively). Functional capacity was assessed according to peak VO2, using the Weber classification.

CPET was performed by a certified pulmonologist. The CPET was performed under continuous HR, ECG and pulse oximetry monitoring. BP was recorded every 2 minutes. Extreme fatigue, myocardial ischemia, complex ventricular premature beats, grade 2 or grade 3 atrio-ventricular block, a sudden drop in BP levels by more than 20 mmHg, increased BP (SBP > 220 mmHg, DBP > 120 mmHg), SpO_2<80%, confusion, dizziness and sudden pallor were indications for stopping exercises.

We used SPSS v 20.0 program for statistical analysis. Chi-square, student's t test, Pearson correlation coefficient, ANCOVA test were performed. Descriptive data were expressed as means ± SD (standard deviation) or percentages, as appropriate and p value < 0.05 was considered statistically significant.

3.4.4. Results

The patients recruited in the analysis were aged between 36-79 years old (57,53 ± 8,74 years old), mean BMI 34,04 ± 5,30 kg/m^2, with newly diagnosed OSA (AHI 39,96 ± 19,04 events/h, desaturation index 38,67 ±19,67 events/h, average nocturnal O2Sa 91,63 ±3,64%, CPAP pressure 11,27 ± 2,43 cmH20). Within the study, approximately two thirds of subjects had severe OSA (59,37%). Male sex was predominant in our study group, with a M:F ratio of 2,55 (Figure 5).

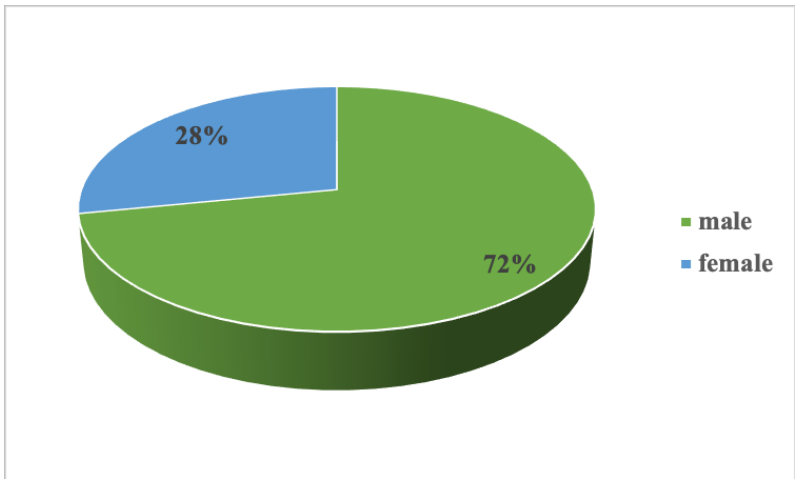

Figure 5. Gender distribution in our study group

Cardiometabolic comorbidities (particularly hypertension) were highly prevalent among our patients (Figure 6).

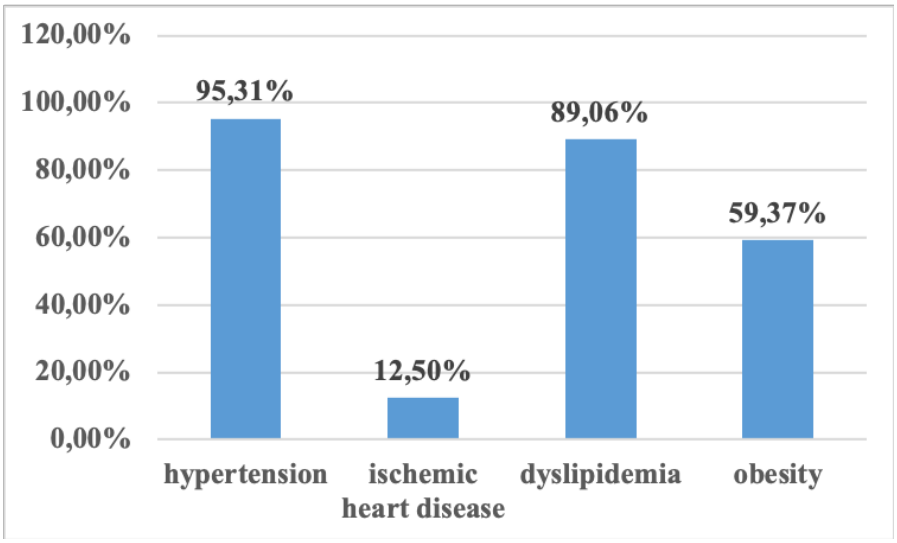

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Figure 6. Prevalence of cardio-metabolic comorbidities in our study group

49,21% of our patients exhibited a moderate or severe decrease in functional capacity, according to the Weber classification (Weber C or D) (figure 7). Only 1 in 5 patients with moderate-severe OSA had a normal functional capacity (Weber A). We found no significant differences regarding average AHI values between the 4 functional capacity subgroups (Weber A-D) ($p>0,05$). Maximal instantaneous forced expiratory flor (MEF) 25% was higher in the severe OSA subgroup, but we did not find any statistically significant differences regarding spirometry results between patients with moderate and severe OSA (table XXIII).

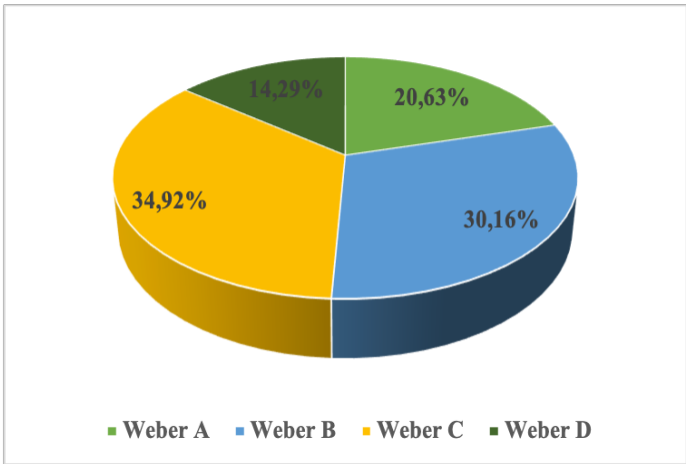


Figure 7. Functional capacity in our study group according to the Weber classification

Basal metabolic rate (BMR) and minute ventilation (VE) max were significantly higher among males (Δ = 366 kCal/24 h and Δ = 8,35 l/min, respectively). Even though males achieved a higher average peak workload (Δ = 34,07 W), % predicted workload and % predicted VO2 max were significantly higher in the female subgroup (Δ=13,33% and Δ= 20,24%, respectively).

Table XXIII. Spirometry results in patients with moderate-severe OSA

	Moderate-severe OSA		**Moderate OSA**		**Severe OSA**		**p**
	Average	**SD**	**Average**	**SD**	**Average**	**SD**	
FVC (l)	3,76	0,92	3,84	0,85	3,71	0,97	0,46
FVC% (%)	94,89	19,03	94,00	18,47	95,45	19,67	0,79
FEV 1,0 (l)	3,05	0,68	3,12	0,66	3,00	0,69	0,54
FEV 1,0% (%)	91,61	19,96	88,00	19,39	93,90	20,30	0,31
FEV1,0/FVC	77,24	2,12	77,54	1,86	77,06	2,28	0,44
FEV1,0/FVC%	101,20	10,82	97,67	11,79	103,32	9,80	0,07
PEF (l/sec)	7,64	1,37	7,73	1,31	7,59	1,42	0,72
PEF% (%)	77,00	19,63	75,22	18,92	78,07	20,28	0,63
MEF 25 (l/sec)	1,59	0,39	1,65	0,37	1,55	0,41	0,43
MEF 25% (%)	69,90	23,39	61,17	24,04	75,33	21,64	0,04
MEF 50 (l/sec)	4,22	0,61	4,28	0,58	4,17	0,63	0,56
MEF 50% (%)	75,93	25,80	68,11	27,96	80,78	23,56	0,10
MEF 75 (l/sec)	6,74	1,16	6,80	1,12	6,69	1,20	0,75
MEF 75% (%)	76,44	20,75	72,89	21,67	78,65	20,22	0,36

FVC – forced vital capacity; FVC% – percent predicted forced vital capacity; FEV1 – forced expiratory volume in one second; FEV1% – percent predicted forced expiratory volume in one second; PEF – peak expiratory flow; PEF% – percent predicted peak expiratory flow; MEF – maximal instantaneous forced expiratory flow; MEF% – percent predicted maximal instantaneous forced expiratory flow.

CPET was influenced by gender, but not by apnea severity (tables XXIV, table XXV). CPET parameters did not significantly differ between the two apnea severity subgroups, excepting for baseline SBP (table XXIV).

Table XXIV. Gender influence on CPET parameters among patients with moderate-severe OSA

	Male		**Female**		**p**
	Average	**SD**	**Average**	**SD**	
BMR (kCal/24 h)	1860,18	264,14	1494,06	187,26	<0,0000001
Maximal load (W)	114,85	33,54	80,78	23,41	0,0001
% predicted maximal load	56,74	16,04	70,07	15,49	0,004
VO2 max	1553,20	504,55	1301,67	352,11	0,07
% predicted VO2 max	61,59	21,73	81,83	15,56	0,0005
AT	1202,82	397,46	1083,07	288,10	0,33
Weight-indexed AT	11,82	3,79	11,83	3,15	0,99
VCO2 max	1434,52	460,30	1392,83	330,89	0,75
VE max (l/min)	48,64	12,88	40,29	8,79	0,02
Resting HR	79,20	12,27	83,80	15,85	0,21
Peak HR	117,02	19,34	123,73	18,52	0,25
% predicted peak HR	71,48	11,62	77,80	11,29	0,07
Peak O2 pulse	14,46	5,46	12,37	5,40	0,20
Weight-indexed O2 pulse	0,14	0,06	0,14	0,07	0,97
Baseline SBP	124,72	16,05	127,87	16,12	0,51
Baseline DBP	78,46	9,83	79,27	13,29	0,78
Peak SBP	183,16	28,01	185,33	18,85	0,80
Peak DBP	98,64	17,61	102,53	9,52	0,46

CPET – cardiopulmonary stress test; OSA – obstructive sleep apnea; BMR – basal metabolic rate; VO2 – peak oxygen uptake; AT – anaerobic threshold; VCO2 – peak CO2 output; VE – minute ventilation; HR – heart rate;
SBP – systolic blood pressure; DBP – diastolic blood pressure.

Table XXV. Differences regarding CPET parameters between moderate and severe OSA subgroups

	Moderate-severe OSA		**Moderate OSA**		**Severe OSA**		
	Average	**SD**	**Average**	**SD**	**Average**	**SD**	**p**
BMR (kCal/24 h)	1755,57	264,14	1726,27	276,57	1776,16	256,87	0,46
Maximal load (W)	105,27	33,54	111,08	34,20	101,29	32,94	0,25
%predicted maximal load	60,02	16,04	61,84	13,81	58,75	17,50	0,46
VO2 max	1482,45	504,55	1464,31	473,61	1494,87	530,57	0,81
% predicted VO2 max	67,28	21,73	67,27	21,98	67,29	21,86	0,99
AT	1168,92	397,46	1109,32	367,95	1211,23	417,85	0,36
Weight-indexed AT	11,83	3,79	11,59	4,24	12,00	3,49	0,70
VCO2 max	1422,80	460,30	1421,54	476,78	1423,66	455,16	0,98
VE max (l/min)	46,58	12,88	47,12	9,21	46,21	15,03	0,78
%VE	43,05	12,51	41,89	15,86	44,05	10,40	0,57
Resting HR	80,33	12,27	77,88	11,59	82,03	12,59	0,19
Peak HR	118,67	19,34	121,84	18,81	116,47	19,66	0,29
% predicted maximum HR	73,03	11,62	74,68	11,70	71,89	11,59	0,36
Peak O2 pulse	13,95	5,46	14,00	5,34	13,91	5,62	0,95
Weight-indexed O2 pulse	0,14	0,06	0,15	0,06	0,14	0,06	0,42
Baseline SBP	125,49	16,05	120,04	11,64	129,28	17,69	0,02
Baseline DBP	78,66	9,83	76,88	7,32	79,89	11,18	0,24
Peak SBP	183,70	28,01	175,50	26,32	189,17	28,12	0,06
Peak DBP	99,62	17,61	97,79	13,01	100,83	20,20	0,51

CPET – cardiopulmonary stress test; OSA – obstructive sleep apnea; BMR – basal metabolic rate; VO2 – peak oxygen uptake; AT – anaerobic threshold; VCO2– peak CO2 output; VE – minute ventilation; HR – heart rate;
SBP – systolic blood pressure; DBP – diastolic blood pressure.

Within the study, apnea severity was significantly correlated with resting HR (r= -0,30, p=0,01) (figure 8), % predicted workload (r=-0,30, p=0,01) (figure 9) and BMR (r=0,33, p=0,008) (figure 10) (table XXVI).

No statistically significant correlations was found between AHI and the analyzed spirometry parameters (p>0,05).

Table XXVI. Correlations between AHI and CPET among patients with moderate-severe OSA.

	r	p		r	p
BMR (kCal/24 h)	0.33	0.008	VCO2 max	0.10	0.42
Maximal load (W)	-0.07	0.55	VE max (l/min)	0,05	0.72
% predicted maximal load	-0.30	0.01	Resting HR	0.25	0.04
VO2 max	0.02	0.88	Peak HR	-0.12	0.33
% predicted VO2 max	-0.20	0.10	% predicted peak HR	-0.21	0.09
AT	0.15	0.28	Peak O2 pulse	-0.05	0.67
Weight-indexed AT	-0.02	0.85	Weight-indexed O2 pulse	-0.19	0.13

AHI – apnea hypopnea index; CPET – cardiopulmonary stress test; OSA – obstructive sleep apnea; BMR – basal metabolic rate; VO2 – peak oxygen uptake; AT – anaerobic threshold; VCO2– peak CO2 output; VE – minute ventilation; HR – heart rate.

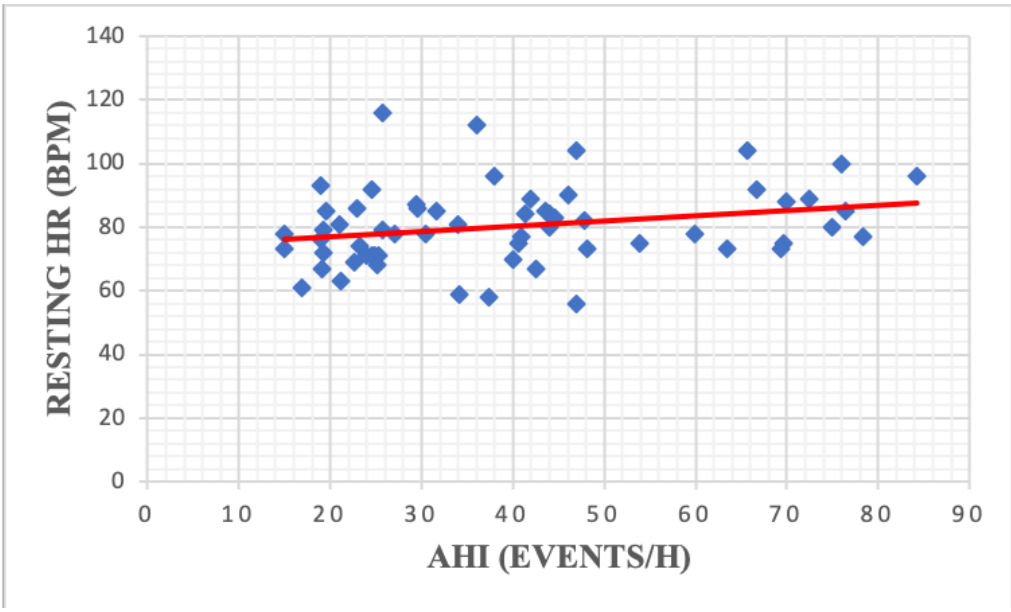


Figure 8. Correlation between apnea severity and resting heart rate among patients with moderate-severe OSA (r=0,25, p=0,04). HR - heart rate; AHI – apnea hypopnea index; OSA – obstructive sleep apnea.

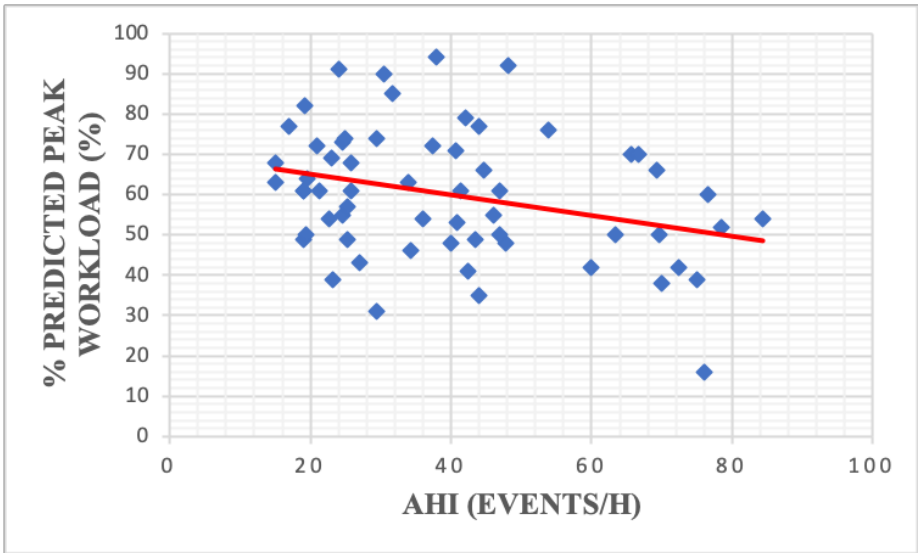


Figure 9. Correlation between apnea severity and % predicted peak workload among patients with moderate-severe OSA (r=-0,30, p=0,01). AHI – apnea hypopnea index; OSA – obstructive sleep apnea.

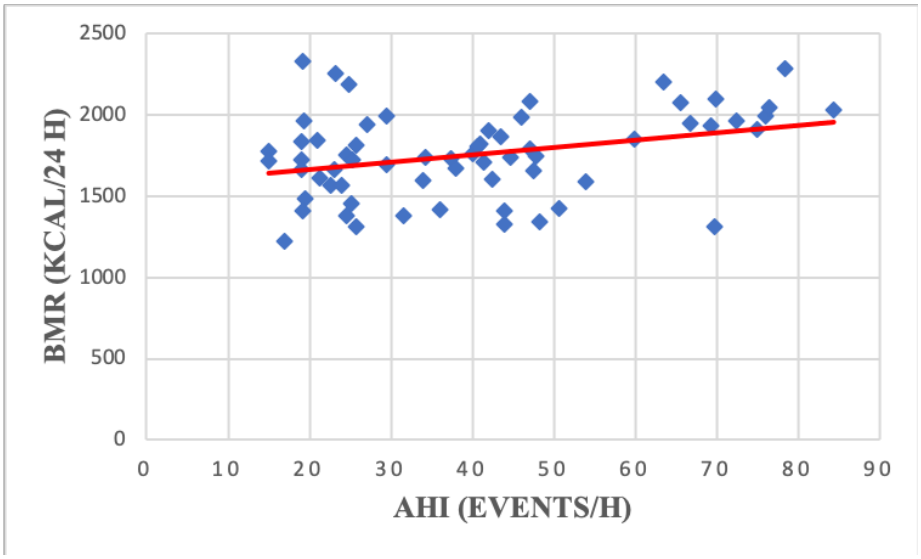


Figure 10. Correlation between apnea severity and BMR among patients with moderate-severe OSA (r=0,33, p=0,008). BMR – basal metabolic rate; AHI – apnea hypopnea index; OSA – obstructive sleep apnea.

Although all subjects started CPAP therapy, 13 patients were unable to tolerate it or were lost during follow-up. 51 patients successfully completed the CPET and the Epworth questionnaires before and after 2 months CPAP. In the study group, average Epworth score was 8,11 ± 5,23 points, and average CPAP use was 241,67 (±128,38) minutes/night. Only 51,16% of our patients used the device as recommended - at least 4 h/night. CPAP use did not significantly impact basal

blood pressure values (SBP Δ = -4,58 mmHg p=0,13; DBP Δ = -1,52 mmHg p=0,35) and was not associated with statistically significant weight loss (Δ = -1,01 kg, p=0,57).

We analyzed the maximal exercise load after 2 months of CPAP, with the results showing significant improvements in maximal exercise load (Δ = 14,23 W, p= 0,0004), VO2 max (Δ = 203,87 ml/min, p= 0,004), anaerobic threshold (AT) (Δ=316,4 ml/min, p=0,001) and VE max (Δ = 5,1 l/min, p=0,01) (table XXVII, figure 11-12). Maximal exercise load and VO2 max improvement remained significant after adjustment for BMI (table XXVIII, p=0,04 and p=0,02, respectively). We also observed an increase in peak oxygen pulse (Δ = 2,46, p=0,007) and VCO2 max (Δ = 232,14 ml/min, p=0,0006), which remained significant after adjusting for BMI (table XXVII, figure 11-12 p= 0,02 and p=0,01, respectively). Epworth score in our study group decreased by 4.58 points (p<0,000001).

Table XXVII. CPAP impact on CPET parameters in moderate-severe OSA patients

	Baseline		**After CPAP**		**p***	**p****
	Average	**SD**	**Average**	**SD**		
BMR (kCal/24 h)	1771,50	281,49	1763,12	273,79	0,04	0,78
Maximal load (W)	103,16	34,21	117,39	36,17	0,0004	0,04
% predicted maximal load	59,83	16,48	68,69	14,35	0,0001	0,01
VO2 max	1458,27	435,29	1662,14	454,50	0,004	0,02
% predicted VO2 max	64,54	17,49	76,82	18,47	0,000005	0,001
AT	1134,30	419,42	1450,70	450,54	0,001	0,08
Weight-indexed AT	11,41	4,07	14,62	4,66	0,001	0,07
VCO2 max	1464,34	383,13	1696,48	465,62	0,0006	0,01
VE max (l/min)	46,46	13,57	51,56	14,23	0,016	0,09
%VE	43,07	12,69	47,52	11,48	0,04	0,04
Resting HR	80,37	13,15	76,19	14,46	0,05	-
Peak HR	118,22	20,06	121,67	23,94	0,28	-
% predicted maximum HR	72,59	11,84	73,84	11,96	0,42	-
Peak O2 pulse	13,59	4,14	16,05	5,83	0,007	0,02
Weight-indexed O2 pulse	0,14	0,05	0,16	0,06	0,01	0,26
Baseline SBP	126,77	17,63	122,19	15,93	0,13	-
Baseline DBP	78,94	10,29	77,42	8,77	0,35	-
Peak SBP	184,62	29,35	185,35	23,27	0,85	-
Peak DBP	101,52	13,74	98,33	10,40	0,11	-

CPAP – continuous positive airway pressure; CPET – cardiopulmonary stress test; OSA – obstructive sleep apnea; BMR – basal metabolic rate; VO2 – peak oxygen uptake; AT – anaerobic threshold; VCO2– peak CO2 output; VE – minute ventilation; HR – heart rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; **p*** - statistical significance for non-adjusted student's t test; p** - statistical significance for BMI-adjusted results of ANCOVA test.

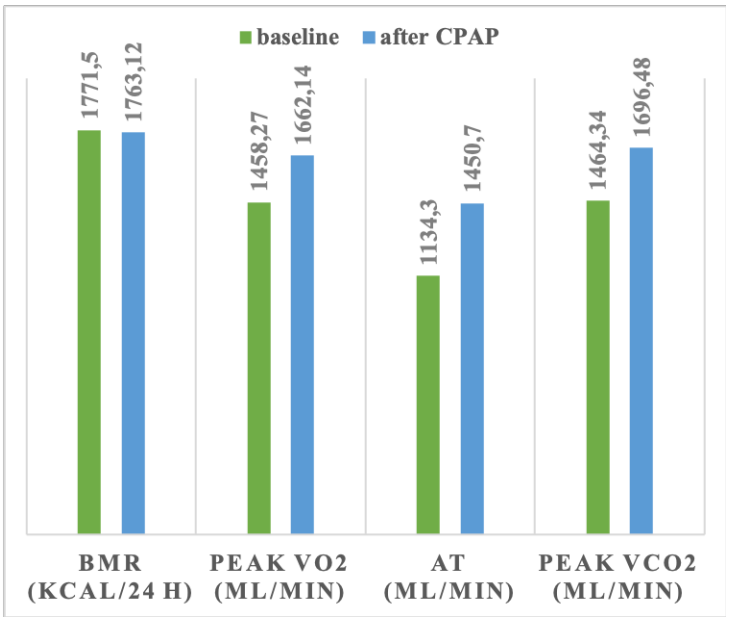


Figure 11. CPAP induced changes in BMR (Δ=-8,38 kCal/24 h, p=0,04), peak VO2 (Δ = 203,87 ml/min, p= 0,004), AT (Δ=316,4 ml/min, p=0,001) and peak VCO2 max (Δ=232,14 ml/min, p=0,0006). BMR – basal metabolic rate; peak VO2 – peak oxygen uptake; AT – anaerobic threshold; peak VCO2– peak CO2 output.

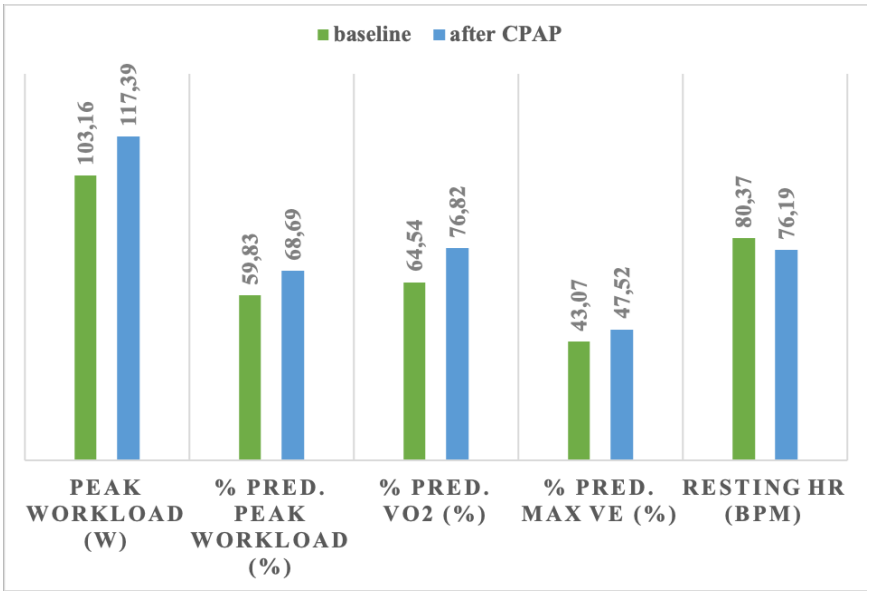


Figure 12. CPAP induced changes in peak workload (Δ = 14,23 W, p= 0,0004), % predicted peak workload (Δ = 8,86 %, p= 0,0001), % predicted peak VO2 (Δ = 12,28 %, p=0,000005), % predicted VE max (Δ = 4,45 %, p= 0,01), and resting HR (Δ = -4,18 bpm, p= 0,05), in moderate-severe OSA patients. CPAP – continuous positive airway pressure; OSA – obstructive sleep apnea; VO2 – peak oxygen uptake; VE – minute ventilation; HR – heart rate.

3.4.5. Discussion

Our patients were 57,53±8,74 years old with newly diagnosed moderate-severe OSA, slightly higher than other reports on average OSA age at diagnosis (40-50 years old) [Young et al., 1993]. The prevalence in women is more reduced as female sex hormones increase genioglossus contractility and avoid upper airway collapse during sleep [Popovic et al., 1998; Hou et al., 2010]. Additionally, the distinctive distribution of adipose tissue among the two genders (with central obesity being more strongly associated with OSA) [Soriano-Co et al., 2011], as well as the higher pharyngeal resistance in men [Trinder et al., 1997], elucidate why OSA is more prevalent among male patients. Within our study, male-female ratio was slightly lower than in previous studies (2,55:1 versus 3:1-5:1) regardless of the evident predominance of the males in our study group [Lin et al., 2008].

Severe fatigue in OSA patients can be explained by the presence of energetic mitochondrial dysfunctions especially in muscle cells [Stavrou et al., 2018]. The major cause for early test end in our group was dyspnea accompanied by muscular exhaustion, comparable to other literature reports [Tapan et al., 2016]. This was followed by an exaggerated SBP response (SBP > 250 mmHg). We registered no arrhythmic events, confusion or a decrease in BP values during exercise.

Patients with moderate-severe OSA presented baseline middling CPET performance. 20,63% of our subjects had a baseline normal functional capacity according to the Weber classification and most cases (34,92%) were classified as moderately decreased. Przybyłowski et al. [Przybyłowski et al., 2007] reported an overall better CPET performance in 111 obese OSAS patients (% predicted peak VO2 85,3±17,8, peak VCO2 2800±900 ml/min, VE max 91,2±24,7, % predicted maximum HR 92,5±10,3), regardless of a minimal difference in OSA severity between the two groups (average AHI 47,2±23,1 versus 39,96 ± 19,04 events/h). Nevertheless, Przybyłowski's study group included an unusually low percentage of hypertensives (29% versus 95,31% in our study group), indicating that HBP could be an important confounding factor when analyzing CPET performance [Przybyłowski et al., 2007]

The impact of OSAS on cardiopulmonary exercise testing performance was analyzed in several studies, but the results were contradictory and included a limited number of patients [Lin et al., 2006; Kaleth et al., 2007; Vanhecke et al., 2008; Cintra et al., 2011; Stavrou et al., 2018]. Reports associating OSAS with an impaired exercise capacity (decreased exercise duration, workload, VO2, oxygen pulse, AT and/or VE max) were conducted generally on obese or overweight subjects [Lin et al., 2006; Vanhecke et al., 2008; Stavrou et al., 2018]. Consequently, these data could be influenced by the known negative impact of obesity on exercise capacity, as shown by Rizzi et al. [Rizzi et al., 2013]. Rizzi et al. found that CPET performance is comparable among normoponderal OSAS subjects and controls, although it is worth mentioning that the analyzed group had a relatively low average AHI (15.4±9.2) and included a large number of women (63%) [Rizzi et al., 2010]. A report conducted in 2019 [Powell et al., 2019] studied exercise performance among military personnel with and without moderate-severe OSAS. The lack of significant differences among the two subgroups could be explained by the low average age in the OSAS and control groups (40,7 and 39,4, respectively) but also by the higher grade of habitual

physical activity (characteristic for this population subset) [Mendelson et al., 2018]. Though, a previous meta-analysis has revealed that VO2 max is considerably lower in OSA subjects compared to controls (Δ 2.7 mL/kg/min), the difference being of greater clinical impact among non-obese patients (Δ 4,1 ml/kg/min) [Mendelson et al., 2018].

Other reports showed that male sex associated with diabetes negatively impacts VO2 max. Consistent with their results, our female subgroup obtained significantly higher percent predicted workload and percent-predicted maximum HR, suggesting a higher effort capacity [Rizzi et al., 2013].

Studies regarding apnea severity found correlation with several CPET parameters including VO2 max [Vanhecke et al., 2008], percent predicted peak VO2 [Beitle et al., 2014] and BP rise during exercise [Przybyłowski et al., 2007]. Yet, our results only found a significant association between AHI resting HR, BMR and percent predicted workload. The high prevalence of cardio-metabolic comorbidities in the study group could explain the lack of statistically significant correlations between AHI and other CPET variables.

Several reports [Kaleth et al., 2007; Vanhecke et al., 2008; Mendelson et al., 2018] revealed that OSAS patients have higher DBP values and decreased HR recovery compared to controls. After analyzing the two apnea severity subgroups, we observed significantly higher baseline and AT - SBP values (but no significant differences regarding HR response during exercise) in the severe OSA subgroup.

The impact of CPAP on VO2 max in OSAS patients have yielded inconsistent results. CPAP therapy with variable lengths (1 week-8 months) were associated with significant VO2 max enhancements [Lin et al., 2004; Maeder et al., 2009; Quadri et al., 2017; Mendelson et al., 2018]. Still, in a different study, VO2 max presented a mild negative trend (22.52±6.62 mL/min/kg to 21.32±5.26 mL/min/kg; p=0.111) in CPAP compliant patients, and a borderline statistically significant decline in patients with suboptimal CPAP use (21.31±5.66 mL/min/kg to 19.92±5.40 mL/min/kg, p=0.05) [Ozsarac et al., 2014].

Our patients displayed an important improvement in percent predicted maximum workload, percent predicted VO2 max, AT and oxygen pulse, even with a middling CPAP adherence (241,67 minutes/night). Even after adjusting for BMI, improvements regarding maximal load, VO2 max, VCO2 max, %VE and peak O2 pulse remained significant. No statistically significant gender-related differences regarding these changes were noticed. Quadri et al. also studied the effect of 2 months CPAP in a smaller group of moderate-severe OSAS patients and reported similar improvements in percent predicted maximum workload (9 vs 8,86 W%), percent predicted VO2 peak (9,7% vs 12,28%), but a less marked increase regarding AT (99 vs 316,4 ml/min) [Quadri et al., 2017]. In contrast, Tapan et al. analysed the benefit of 8 weeks of CPAP therapy in patients with severe OSA and observed a greater improvement in maximum workload and VE (16,9 W and 10,3 l/min respectively), but a less significant increase in percentage-predicted peak VO2 (7,6% vs 12,28%)[Tapan et al., 2016].

Some authors described diurnal variations in spirometric indices in OSA patients. Significant associations between AHI, evening FEV1 and FVC have also been noticed, proving

important influences of BMI, hypertension, dyslipidemia and several cardiovascular drugs on the relationship between lung function and apnea severity [Kunos et al., 2017]. Most of our patients presented cardiometabolic comorbidities, and were under treatment with a statin, beta blocker or a renin-angiotensin-aldosterone axis inhibitor [Kunos et al., 2017]; this fact could explain the lack of association between AHI and the analyzed spirometry parameters (p>0,05).

Limitations of our study are the lack of a control group and the high prevalence of cardio-metabolic comorbidities among our patients.

3.4.6. Conclusions

Moderate-severe OSA patients have a mediocre baseline CPET performance. AHI was correlated with some CPET parameters (BMR, % predicted effort, resting HR), but not with VO2 or AT. CPAP performed during 2 months improved most CPET parameters suggesting that OSAS *per se* negatively impacts effort capacity.

Zota IM, Sascău RA, **Stătescu C**, Boișteanu D, Roca M, Leon Constantin MM, Vasilcu TF, Gavril RS, Anghel L, Mitu O, Costan V, Cumpat CM, Mitu F. Quality of life in moderate-severe OSA patients from north-eastern Romania. *Rev Cercet Interv So* 2020; 68: 250-260. **IF: 0.736**
https://www.rcis.ro/images/documente/rcis68_17.pdf

3.5. Quality of life in moderate-severe OSA patients from north-eastern Romania

3.5.1. Introduction

Even though OSA prevalence was previously thought to be up to 4% [Young et al., 1993; Hoyos et al., 20], in line with the contemporary rise in obesity and recent changes regarding OSA diagnosis criteria, it is estimated that 10-49,7% of adults suffer from various degrees of sleep apnea [Lorenzi-Filho, Almeida and Strollo, 2017]. As stated before, OSA is a recognized risk factor for cardio-metabolic and cerebro-vascular disease [Hoyos et al., 2012] and is also associated with a significant reduction in general quality of life [D'Ambrosio, Bowman and Mohsenin, 1999; Chakravorty, Cayton and Szczepura, 2002; Kuhn et al., 2017].

The world health organization (WHO) generally defines quality of life (QoL) as "the individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations and concerns" ("WHO | WHOQOL," n.d.). The concept of health-related QoL (HR-QoL) was developed in order to minimize the effect of social status, environment and other confounding factors on medical analysis.

The most common tools that evaluate HR-QoL, both generally and within certain domains are The European Quality of Life Questionnaire (EuroQoL), Short Form 36 (SF-36), Patient generated index (PGI) and Nottingham Health Profile (NHF) [Dutt and Chaudhry, 2016]. Generic questionnaires are less sensitive compared to disease specific instruments such as Functional Outcomes of Sleep Questionnaire, Obstructive Sleep Apnea Patient-Oriented Severity Index and

Sleep Apnea Quality Of Life Index [Dutt and Chaudhry, 2016]. Yet, generic questionnaires allow a comparison between different populations and medical conditions, being considered more suitable for research. The European Quality of Life 5 Domain questionnaire (EQ-5D-5L) was developed in 1990 and has become one of the most widely used tools for the assessment of health-related QoL. EQ-5D questionnaire evaluates firstly 5 health-related domains (mobility, self-care, usual activities, pain/discomfort and symptoms of anxiety/depression) on a scale of 1 to 5 (no problems, slight, moderate, severe or extreme problems, respectively). In the second part of the questionnaire, the patient chooses a self-assessed level of health, using a visual analogue scale labeled from 0 to 100 (the worst and the best health status that one can imagine, respectively). Utility indices facilitate the analysis of HR-QoL by providing a general summary score of the analysed dimensions, but they are influenced by several factors, including age, sex and, to some degree, socioeconomic status [Schmidlin et al., 2010].

CPAP used as therapy for moderate-severe OSA [Kuhn et al., 2017], has proved metabolic and cardiovascular benefits [Montesi et al, 2012], and also improves overall cognitive performance [Wang et al., 2019]. It is known that chronic sleep interruption is also linked with neuropsychiatric consequences affecting patients both professionally and personally [Jing, Huang, Cui and Shen, 2008; Wang et al., 2019]; thus, an in-depth analysis of CPAP usefulness requires subjective outcomes such as health-related quality of life. While a recent report established that CPAP use rises QoL in moderate-severe OSA [Dutt and Chaudhry, 2016], previous meta-analyses have generated contradictory data [Jing et al., 2008; Okuno et al., 2014].

3.5.2. Aim

The objective of this study was to investigate HR-QoL using the EQ-5D-5L among Romanian patients with moderate-severe OSA, at baseline and after 2 months of CPAP.

3.5.3. Material and methods

The study group included 75 CPAP naïve patients with moderate-severe OSA (apnea-hypopnea index ≥ 15), diagnosed by using ambulatory or in-hospital 6-channel cardio-respiratory polygraphy. All results were manually interpreted, according to the 3rd International Classification of Sleep Disorders [Sateia, 2014]. In order to evaluate CPAP effective pressure, an automatically determination was made in the sleep laboratory. From the total number of subjects, 16 patients were intolerant to CPAP or did not return for re-evaluation. Before and after 2 months of CPAP, the EQ-5D-5L and Epworth Sleepiness Scale (ESS) questionnaires were completed. In the absence of a Romanian value set [Olariu et al., 2019], we decide to compute the Index Value using the UK crosswalk value sets, similar to other analysis of Romanian patients [Rencz et al., 2016], using the calculator provided by the EQ-5D official website (available at https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/). The 59 patients who were present for reassessment were telephonically contacted after 1 month to question whether they decided to continue CPAP therapy.

All variables were reported by means and SD or percentages. Student's t test was used to compare moderate and severe OSA subgroups. Z test helped in analysing the decision to continue CPAP in relation with returns level. Spearman 's correlations were computed between apnea severity (AHI), Epworth score results, EQ-5D-5L utility index, age and income. A p value <0.05 was considered statistically significant.

3.5.4. Results

We included 30 and 45 patients with moderate and severe OSA, respectively, aged 36-79 years old (58,40±8,89) in the final analysis (Table XXVIII). No significant differences regarding age, income, the EQ-5D-5L index and VAS between moderate and severe OSA were noticed. Even though the overall Epworth score was comparable in the two apnea severity subgroups, patients with severe apnea were more likely to doze or fall asleep while ”sitting inactive in a public place” and while ”sitting quietly after lunch without alcohol” (Table XXVIII).

Table XXVIII. Descriptive statistics of our study group (N=75 patients)

	Moderate-severe OSA	**Moderate OSA**	**Severe OSA**	**P**
Age	58,40±8,89	58,27±8,71	58,49±9,09	0,91
Income	1899,17±1438,20	1836,8±1490,29	1939,41±1427,06	0,80
AHI	39,94±19,87	21,82±4,16	52,01±16,73	< 0.00001
EQ-5D-5L Index	0,70±0,27	0,72±0,28	0,70±0,27	0,75
EQ-5D-5L VAS	63,71±17,74	62,57±18,50	64,52±17,35	0,64
Epworth Score	8,14±5,45	6,97±4,54	8,98±5,92	0,12
Sitting and reading	1,49±1,21	1,37±1,22	1,57±1,21	0,48
Watching TV	1,83±1,06	1,73±1,17	1,90±0,98	0,50
Sitting inactive in a public place (theatre or a meeting)	0,65±1,06	0,30±0,65	0,90±1,23	0,016
As a passenger in a car for an hour without a break	0,75±1,08	0,67±0,88	0,81±1,21	0,58
Lying down to rest in the afternoon when circumstances permit	2,06±1,09	1,97±1,10	2,12±1,09	0,56
Sitting and talking to someone	0,19±0,55	0,13±0,43	0,24±0,62	0,42
Sitting quietly after lunch without alcohol	1,06±1,14	0,73±1,08	1,29±1,13	0,04
In a car, while stopped for a few minutes in traffic	0,08±0,33	0,10±0,40	0,07±0,26	0,71

The most common cardio-metabolic comorbidities in our study group were hypertension, obesity and type 2 diabetes, respectively.

Our results showed no significantly correlation between health index value and apnea severity (r=-0,08, p=0,49) or income (r=0,12, p=0,40). Moreover, self-assessed health status according to the VAS was not significantly correlated with income (r=0,26; p=0,06) or apnea severity (r=0,16; p=0,16). No statistically significant correlations between AHI and overall ESS score (r=0,19; p=0,11) were registered.

In our group, average CPAP use was 240,9±133,38 minutes/night. EQ-5D-5L index and VAS significantly improved after 2 months CPAP (p=0,0008 and p=0,00002, respectively) (Table XXIX). Global Epworth score decreased after CPAP, with statistically significant improvements in all domains except for ”sitting and talking to someone” and ”in a car, while stopped for a few minutes in traffic” (Table XXIX).

Table XXIX. EQ-5D-5L and Epworth Sleepiness Scale results, before and after 2 months CPAP (N=59 patients)

	Before CPAP	**After CPAP**	**P**
EQ-5D-5L Index	0,72±0,26	0,82±0,21	0,0008
EQ-5D-5L VAS	66,83±17,77	76,21±15,34	0,00002
Epworth Score	8,41±5,58	3,97±3,70	<0,0000001
Sitting and reading	1,64±01,22	0,86±1,02	0,00005
Watching TV	1,86±1,08	0,98±0,96	0,000003
Sitting inactive in a public place (theatre or a meeting)	0,66±1,04	0,26±0,55	0,002
As a passenger in a car for an hour without a break	0,79±1,14	0,29±0,68	0,002
Lying down to rest in the afternoon when circumstances permit	2,05±1,13	1,03±1,06	<0,0000001
Sitting and talking to someone	0,21±0,59	0,07±0,26	0,11
Sitting quietly after lunch without alcohol	1,10±1,13	0,41±0,70	0,00005
In a car, while stopped for a few minutes in traffic	0,09±0,24	0,05±0,29	0,57

By analyzing our data, we concluded that the decision not to continue CPAP was more common among subjects with a low income (< 1000 lei: 52,63% versus 21,21%, p=0,01) (Table XXX).

Table XXX. Income level in relation with the decision to continue CPAP use or not

Income level	**Continues CPAP treatment**			
	YES	NO		
	%	%	Z test	p
< 1000	*21,21*	52,63	2,33	0,01
1000-1499	12,12	10,53	0,17	0,43
1500-1999	24,24	15,79	0,72	0,24
2000-2499	6,06	10,53	0,58	0,28
2500-2999	9,09	5,26	0,50	0,31
3000-3499	6,06	5,26	0,12	0,45
3500-3999	0	0	/	/
4000-4499	3,03	0	0,77	0,22
4500-4999	3,03	0	0,77	0,22
5000-5499	6,06	0	1,09	0,14
5500-5999	0	0	0	0
6000-6499	6,06	0	1,09	0,14
6500-6999	3,03	0	0,77	0,22

All patients with an income > 4000 lei decided to continue CPAP (21,21% versus 0%, p=0,015). There was no significant difference regarding the decision to continue the treatment among patients with an income between 1000 and 3500 lei.

3.5.5. Discussion

Over time researchers have tried to convert QoL into a quantifiable, research-appropriate parameter by developing different questionnaires. Even though common tools are less sensitive than disease-specific questionnaires, the previous are preferred if the patient is suffering from

multiple medical conditions as in our study [Dutt and Chaudhry, 2016]. The HR-QoL reveals the individual's discernment regarding the impact of disease on every-day life.

The mean age in our study group was 58,40±8,89 years old, with a marked prevalence of OSA among male subjects (M:F ratio – 57:18), comparable to other reports [D'Ambrosio et al., 1999]. Within our study, OSA had an important impact on HR-QoL in the Romanian population, with an average EQ-5D-5L index similar to that of Romanian patients with stable coronary artery disease (0,72 versus 0,75)[De Smedt et al., 2016]. Several studies analyzed HR-QoL among CPAP naïve OSA patients, and described only a slightly higher EQ-5D utility index than ours (0,73 - 0,79) [Chakravorty et al., 2002; Jenkinson, Stradling and Petersen, 1997; Mar et al, 2003; Jenkinson, Stradling and Petersen, 1998]. Yet, Schmidlin et al. reported a considerably higher EQ-5D-3L utility index (0,92) among 66 OSA patients with a more severe form of OSA (average AHI 57 events/h, average ESS 12). The high prevalence of cardio-metabolic conditions in our study group could explain such differences, and probable a 3 level EQ-5D form was used in the other report [Schmidlin et al., 2010].

Comparable to the CPAP treated subgroup of d'Ambrosio et al. (59±19.8%), our baseline VAS was 63,71±17,74% [D'Ambrosio et al., 1999], though significantly lower than other reports (80%) [Schmidlin et al., 2010]. We did not find a significant correlation between AHI and the two analyzed HR-QoL parameters, similar to other reported data [Dutt and Chaudhry, 2016].

Still, the impact of CPAP on quality of life remains debatable [Dutt and Chaudhry, 2016; Jing et al., 2008; Schmidlin et al., 2010]: despite the fact that some reports have shown that CPAP use is able to "pseudonormalize" QoL up to the level of healthy controls, other studies failed to show a significant QoL improvement after CPAP. These differences are related to different grades of CPAP compliance among the studied subjects explained not only by the mask-associated discomfort, but also by a chronic privation of energy and motivation, which characterize most OSA patients [Chakravorty et al., 2002]. Within our study group, we noticed a borderline CPAP adherence, with an average CPAP use of 4 hours/night.

EQ-5D utility index detected in our study group was higher than in other reports [Chakravorty et al., 2002; Jenkinson et al., 1998]. Jenkinson et al. found a significant improvement after 3 months of CPAP in both patient generated index (PGI) and 36-item Short Form Health Survey (SF-36) scores, but a small variation regarding EQ-5D-3L index (0,78 to 0,83) and EQ VAS (66,57% to 71,72%) [Jenkinson et al., 1997]. Whereas PGI was closely correlated with ESS (r=-0,49), the only non-significant correlation between the analyzed forms (PGI, SF-36, EQ and ESS) was that between PGI and the EQ index [Jenkinson et al., 1997]. Yet, the previous study had important limitations, as it included only male patients and offered no data concerning apnea severity (average AHI) of their group [Jenkinson et al., 1997].

Even if the SF-36 is the most studied QoL instrument in OSA [Kuhn et al., 2017], the EQ-5D-5L VAS is also recommended for patients with sleep apnea [Schmidlin et al., 2010]. An improvement in the EQ-5D-5L VAS similar to ours (11% versus 9,37%) was reported by a previous randomized control trial ($p<0.001$) [D'Ambrosio et al., 1999]. As EQ-5D-5L does not consider stamina and social life (which are severely impaired by chronic fatigue), some authors

consider that the questionnaire may not be appropriate for OSA patients [Chakravorty et al., 2002; Jenkinson et al., 1997]. This could explain why our study, along with other studies [Chakravorty et al., 2002] did not find a link between AHI and the EuroQoL parameters; however, this does not account for the statistically significant improvement in both the EQ-5D-5L index and VAS after short term CPAP use.

As stated before, CPAP is more effective in decreasing cardiovascular risk and BP levels among symptomatic patients with higher ESS scores [Zhang et al., 2016]. Yet, our data show that the impact on quality of life remains significant even in a group with an average ESS of 8,41, corresponding to a higher normal level of daytime sleepiness.

We did not find a significant association between overall Epworth score, apnea severity and the analyzed EQ-5D-5L parameters, even though previous studies have shown an association between ESS and HR-QoL [Kuhn et al., 2017]. CPAP use was associated with a 4,44 point decrease in ESS score, similar to that reported by Patel et al. [Patel et al., 2003](4,75 points), but significantly lower than the one observed by a more recent study [Goel, Talwar and Jain, 2015] (8,5 points). The differences regarding OSA severity and CPAP adherence between groups could explain these variations, but also the impact of age, body mass index, smoking status and neuropsychiatric comorbidities [Antic et al., 2011].

It should be mentioned that governmental policies regarding CPAP use significantly impact treatment compliance [Shapiro and Shapiro, 2010]. It is known that OSA screening has recently become part of the compulsory medical examination to obtain or renew a driver's license in Romania, but only for group 2 license holders. The cost of CPAP is not covered by the public health care system and is relatively high, compared to the average income in Romania. The data of our study showe that financial difficulties seem to play an important part in the decision to use CPAP in Romanian patients. Still, our study group exhibited only borderline treatment adherence (4 hours/night) even while offered a free 2 months CPAP trial, indicating that other factors (stigma, mask-related discomfort, pressure intolerance) also significantly influence CPAP compliance. Consequently, we would like to underline the need for medical education programs and OSA support groups, as well as the essential role of family encouragement in supporting CPAP adherence [Shapiro and Shapiro, 2010]. As far as we know, this was the first analysis of quality of life among Romanian OSA patients and also one of the first reports regarding EQ-5D-5L in the Romanian population. The main limitations of our study are the absence of a control group and the presence of multiple cardio-vascular and metabolic comorbidities in our subjects. Yet, the every-day OSA patient generally exhibits a pattern of multiple associated pathologies, thus emphasizing the clinical applicability of our data.

3.5.6. Conclusions

According to EQ-5D-5L questionnaire, OSA has a significant impact on quality of life. Short-term CPAP use improves ESS and EQ-5D-5L results among OSA patients. Lack of CPAP adherence remains a major concern among Romanian patients with OSA. Income level impacts the decision to continue CPAP therapy.

Chapter 4. Predictors of cardiovascular outcome in patients with heart failure

4.1. Scientific context

Heart failure management is hampered by ageing, comorbidities, frailty, cognitive impairment, and inadequate social care. In HF there is an unpredictable exacerbating-remitting course associated with disease progression. Therefore, data regarding the prognosis are difficult to be given. Limited data concerning the significance of precise lifestyle guidance in improving quality of life or prognosis are available; yet, this data are an essential part of education as they help patients to make choices on lifestyle changes and self-care. All lifestyle recommendations should be done before discharge and more important, these should be customed to every patient, considering individual comorbidities [Lainscak et al., 2011; Ponikowski et al, 2016].

Systematic reviews and meta-analyses performed in patients with HF underlined the significance of exercise training in refining exercise tolerance, health-related quality of life and HF hospitalization rates. Only one single clinical trial revealed an uncertain and non-significant decrease in the primary outcome of all-cause mortality or all-cause hospitalization [O'Connor et al., 2009]. A Cochrane review of exercise training performed in 2014 [Taylor et al., 2014], comprising 33 trials and 4740 patients with HF (predominantly HFrEF), showed a reduction in mortality with exercise in those trials with 1 year follow-up. The results showed that exercise training decreased the rate of overall and HF-specific hospitalization and enhanced quality of life. With this regard, there are published applied recommendations on exercise training [Piepoli et al., 2011]. By analyzing patients with HFpEF, it has been proved that exercise training has numerous benefits, as improvements in exercise capacity, quality of life and diastolic function, as assessed by echocardiography [Edelmann et al., 2011; Ponikowski et al, 2016]. In heart failure, properly planned exercise training should be performed, irrespective of LVEF.

More and more data suggest that significant cost saving may be accomplished by using cardiac rehabilitation and secondary prevention programs as they reduce subsequent hospital admissions and total expense of medical care. Although studies of cost benefit and effectiveness are not widely reported, it seems that cardiac rehabilitation programs have benefits and effectiveness similar to other successful interventions in the treatment of cardiac and vascular diseases.

Generally, patients with HF are monitored in order to identify the development of complications and disease progression as well as to properly manage changes. Of note, more frequent visits will be required in older adults or in clinically unstable patients, until optimization of treatment.

Data regarding the prognosis and clinical course of HF are useful for patients, their families and physicians as to choose the right type and timing of therapies. Several prognostic markers of death and/or HF hospitalization have been identified and analyzed in patients with HF, but their clinical utility is only partial understood. For instance, it was proved that high circulating NPs is

to with unfavorable outcomes in patients with HF. On the opposite, a decrease in NP levels during the recovery phase is related to a better prognosis [Santaguida et al., 2014; Savarese et al., 2014; Volpe et al., 2014; Ponikowski et al., 2016]. Even though we could monitor clinical status and tailor treatment based on the changes of circulating NPs in patients with HF, published reports revealed contradictory results. Therefore, a broad application of such an approach it is not recommended [Ponikowski et al., 2016].

An accurate risk stratification in HF is still into the attention of researchers. In the last years, multivariable prognostic risk scores have been imagined for patients with HF [Pocock et al., 2013; Rahimi et al., 2014; Ouwerkerk et al., 2014; Ponikowski et al., 2016] as they may help predict death in patients. However, these scores remain less valuable for the estimation of HF hospitalizations [Rahimi et al., 2014; Ouwerkerk et al., 2014; Ponikowski et al., 2016]. Risk scores based on clinical evaluation, comorbidities analysis, heart rate variability, sleep disorders, baroreflex sensitivity, laboratory tests, echocardiographic imaging, and cardiopulmonary exercise test parameters were considered, especially for chronic heart failure.

Advanced heart failure represents a challenging problem as more patients with this illness are living longer. HF has received much consideration with regard to prognostication, several prognostic scores being designed - the Heart Failure Survival Score, the Seattle Heart Failure Model, the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure predictive schemes, the Acute Decompensated Heart Failure National Registry regression tree discrimination, etc.

This direction of research is reflected in the following published articles:

Burlacu A, Siriopol D, Nistor I, Voroneanu L, Nedelciuc I, **Statescu C**, Covic A. Clinical SYNTAX Score - a good predictor for renal artery stenosis in acute myocardial infarction patients: analysis from the REN-ACS trial. *Arch Med Sci* 2017;13(4):837-844. **IF:2.344**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5510498/pdf/AMS-13-27700.pdf

Vasilcu TF, **Statescu C**, Sascau R, Roca M, Costea CF, Zota M, Bararu I, Constantin ML, Mitu F. Cardiopulmonary Testing and Biochemical Profile of Coronary Patients Subject to Cardiovascular Recovery Programs. *Rev Chim* 2018; 69(8):2283-2286. **IF: 1.605**
https://www.revistadechimie.ro/Articles.asp?ID=6516

Găitan A, Stătescu C, Sascau R, Balasanian M, Georgescu CA. Predictors of Positive Response to Resynchronization Therapy in Patients with Recurrent Episodes of Acutely Decompensated Advanced Heart Failure. *Journal of Cardiovascular Emergencies* 2018;4:24-31.
https://www.jce.ro/wp-content/uploads/2018/03/jce-2018-0003-1.pdf

Butcovan D, Mocanu V, Timofte DV, Costan VV, Danila R, Veselin AP, Ciuntu BM, Haliga RE, Sascau RA, Ghiga G, **Statescu C**. Macrophage Accumulation and Angiogenesis in Epicardial Adipose Tissue in Cardiac Patients with or without Chronic Heart Failure. *Appl Sci* 2020; 10: 5871. **IF: 2.474**
https://www.mdpi.com/2076-3417/10/17/5871/htm

Siriopol D, Popa R, Mihaila M, Rusu F, Sascau R, **Statescu C**, Cătălina Z, Vasiliu V, Bucur A, Neamtu A, Siriopol I, Cianga P, Kanbay M, Covic A. Application of survival classification and regression tree analysis for identification of subgroups of risk in patients with heart failure and reduced left ventricular ejection fraction. *Int J Cardiovasc Imaging* 2021 Jan 16. **IF: 1.969**
https://pubmed.ncbi.nlm.nih.gov/33454896/

4.2. SYNTAX Score as a predictor for renal artery stenosis in acute myocardial infarction patients

4.2.1. Introduction

Multifaceted atherosclerotic coronary artery disease (CAD) management generated overtime numerous debates and updates in risk stratification and treatment strategies. The SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score (SS) was introduced in 2005 and represent a valuable instrument in therapeutic decision algorithms for CAD affecting more vessels. This score helps in choosing between percutaneous coronary interventions (PCI) or coronary arterial bypass grafting (CABG) [Sianos et al., 2005] having a significant role in short- and long-term prognosis assessment (major adverse cardiac events – MACE, target vessel revascularization – TVR) in this particular patients [Capodanno et al., 2009; Valgimigli et al., 2007]. During the last years, other directions regarding the use of SS were developed, as follows:
- Development of derived Syntax scores (Clinical Syntax Score – CSS, Functional Syntax Score, Global Risk Classification, Residual Syntax, and CABG Syntax), by adding several clinical and biochemical variables to the coronary burden score computing system in order to improve its discriminatory power [Yadav et al., 2013].
- Testing SS (and derived score) on real-world patients (including 1- and 2-vessel disease) in order to demonstrate its utility in prognostic assessment and treatment [Capodanno et al., 2011].
- Addition of patients with acute coronary syndrome (ACS) and validation of SS in the acute setting, with SS becoming a good predictor for post-procedural outcomes [Palmerini et al., 2011]).
- Correlation of SS with "softer" end-points (estimated glomerular filtration rate (eGFR) in stable CAD [Ucar et al., 2014] and in ACS [Duran et al., 2014], high-sensitivity C-reactive protein (CRP) in ACS [Karadeniz et al., 2015], NT-proBNP in ACS [Kurtul et al., 2016], and myocardial injury post-PCI). An analysis performed on patients with an atherothrombotic event (myocardial infarction or ischemic stroke) proved that the rate of a first recurrent event at 1 year was almost double for patients with multisite atherosclerotic disease [Tendera et al., 2011] compared with those with a single affected vessel (5.6% vs. 2.9%) [Ferrieres et al., 2006]. Furthermore, a study performed in the acute setting revealed that including clinical and paraclinical variables into a single score increases the overall ability to predict a wide range of ischemic endpoints. Other two studies [Coskun et al., 2011; Yan et al., 2011] demonstrated an opposite correlation between SS and renal function both in the stable and acute setting of CAD. In previous analyses, we confirmed that atherosclerotic renal artery stenosis (RAS) prevalence in STEMI patients is

significant (16%) and also has a strong association with eGFR [Burlacu et al., 2015]. A study on STEMI patients prospectively examined per protocol for the presence and severity of RAS and renal function would provide a perspective on how to improve the prognostic capabilities of the SS and derived score.

4.2.2. Aim

The objectives of our research were: 1) to stratify the study population according to Myocardial Infarction SYNTAX Score (MI SS) and the Myocardial Infarction Clinical SYNTAX Score (MI CSS), and to detect those variables correlated with the higher score; 2) to assess for the first time the predictive power of MI SS/CSS for RAS presence.

4.2.3. Material and methods

We analyzed 181 patients enrolled between October 2014 and March 2015 in REN-ACS study (Cardiovascular, Renal and Metabolic Profile in Patients with Acute Myocardial Infarction Included in the Romanian National Program of Primary Percutaneous Revascularization – a Single Center Observational Study). Data regarding study protocol, coronary and renal angiographic assessment, body composition analysis and arterial stiffness measurements have been described in previous work [Burlacu et al., 2015]. Firstly, we aimed to assess RAS incidence in consecutive STEMI patients included in the Romanian National Program of Primary Percutaneous Revascularization.

The protocol was approved by the "Gr. T. Popa" Iasi University Ethics Committee. All patients signed a written informed consent. The secondary outcome was the investigation of the cardio-renal-metabolic profile in patients with renal atherosclerotic disease. We used as inclusion criteria age > 18, confirmed diagnosis of STEMI and enrollment in the Romanian National Program of Primary Percutaneous Revascularization. In addition, we monitored the European CARDS registration data standards to gather data on medical history, cardiovascular risk factors and Killip class [Flynn et al., 2005].

Medical history consisted of information related to CAD and RAS. Also, we performed laboratory measurements as serum glucose, hemoglobin, leucocyte, platelets, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) fractions, uric acid, CRP, TnI, CKMB fraction, serum urea, and creatinine (eGFR by CKD-Epi formula). These was performed on the same day as the primary PCI procedure. Coronary and renal angiography were done in order to assess and evaluate coronary/renal artery lesions and percent diameter stenosis. Bioimpedance spectroscopy assessed extracellular (ECW), intracellular (ICW), and total body water (TBW), lean body mass (LBM) and fat tissue mass (FTM). At 24 h after PCI we acquired carotid-femoral (cf-PWV) and carotid-radial (cr-PWV) pulse wave velocities and the aortic augmentation index. Additional data on the measured characteristics was reported previously [Burlacu et al., 2015].

The myocardial infarction SYNTAX Score (MI SS) is an algorithm which analyses coronary atherosclerotic burden and its effect on arterial hemodynamics. Therefore, a severity score is given to each segment of the coronary artery corresponding to the mass of myocardium at

risk. Initially validated for elective non ACS patients, SS proved to be useful in prognostic assessment after ACS [Palmerini et al., 2011]. Within the study, we computed MI SS from the initial angiography of STEMI.

Myocardial Infarction Clinical SYNTAX Score (MI CSS) is computed only from angiographic data and has a lower prognostic ability compared with clinical characteristic-based scores (e.g. Age, Creatinine, and left ventricular Ejection Fraction (ACEF) score [Ranucci et al., 2009]).

CSS combines both scores (SS multiplied by modified ACEF) and is a better predictor for mortality in patients with complex CAD [18]. Novel data revealed that in patients with ACS experiencing percutaneous intervention CSS had better predictive accuracy for MACE than SS [Palmerini et al., 2012]. Consequently, we calculated MI CSS values for each patient with STEMI from our study.

Statistical analysis: Continuous variables were expressed as mean ± standard deviation and categorical data as number with percent frequency. All data were stratified according to SS tertiles (Table I) and CSS tertiles (Table II). Statistical analyses were performed with SPSS 19.0 (SPSS Inc, Chicago, IL) and MedCalc (MedCalc Software bvba, Belgium). A two-tailed p-value < 0.05 was considered significant.

4.2.4. Results

The study population included 181 consecutive STEMI patients, of whom 30 (16.6%) had significant renal artery stenosis (> 50%, defined as RAS+), while 5 of these had bilateral RAS. No significant difference between left and right prevalence of the RA stenosis was recorded. The MI SS ranged from 1 to 46.5, with a mean ± SD of 16.95 ±8.45 and a median of 17.5. The MI CSS ranged from 1.22 to 255.15, with a mean ± SD of 39.3 ±41.3 and a median of 28.

The study group was divided according to MI SS into tertiles as follows: tertile 1 MI SS ≤ 11 (n = 59), tertile 2 MI SS 11.1– 19.9 (n = 61), tertile 3 MI SS ≥ 20 (n = 61). Subsequently, the study group was split according to MI CSS into tertiles as follows: tertile 1 MI CSS ≤ 19.2 (n = 60), tertile 2 MI CSS 19.3–38.8 (n = 61), tertile 3 MI CSS ≥ 38.9 (n = 60).

Stratification according to SYNTAX Score At this stage, baseline clinical and paraclinical features together with post-procedural PWV and body composition monitoring (BCM) measurements were divided according to MI SS tertiles and presented in Table XXXI.

As seen in the table XXXI, in the tertiles 2 and 3 subgroups there were significantly older patients with higher prevalence of previous CAD, previous PCI, CHF, and hypertension. As well, they had more RAS+ and bi/tri coronary lesions, higher fibrinogen and CRUSADE score, and lower left ventricular ejection fraction (LVEF) and eGFR ($p < 0.05$). No differences were noted for PWV and BCM variables between MI SS tertiles.

A stepwise multivariate linear regression including all the variables associated with MI SS was performed. Independent variables correlated with MI SS were LVEF < 40%, RAS+, history of CHF, and multivascular CAD (Table XXXII). We performed the same stratification in tertiles for the MI CSS (Table XXXIII).

Table XXXI. Patients' characteristics according to MI Syntax Score tertiles

Variable	Tertile 1 MI SS ≤ 11 (*n* = 59)	Tertile 2 MI SS 11.1–19.9 (*n* = 61)	Tertile 3 MI SS ≥ 20 (*n* = 61)	*p*1 (I–II)	*p*2 (II–III)	*p*3 (I–III)
RAS+, *n* (%)	5 (8.5)	8 (13.1)	17 (27.8)	0.41	**0.043**	**0.006**
Male, *n* (%)	44 (74.5)	50 (82)	41 (67.2)	0.32	0.06	0.37
Age [years]*	59.27 ±12.22	61.80 ±11.47	63.49 ±11.58	0.24	0.42	0.05
Weight [kg]*	84.83 ±13.23	85.93 ±17.85	80.64 ±14.92	0.70	0.07	0.10
BMI [kg/m^2]*	29.26 ±4.36	29.32 ±5.09	28.42 ±4.53	0.94	0.30	0.30
History of CAD, *n* (%)	12 (20.3)	15 (24.6)	28 (46)	0.57	**0.01**	**0.002**
History of CKD, *n* (%)	2 (3.4)	8 (13.11)	3 (5)	0.053	0.11	0.67
History of PCI, *n* (%)	0	0	5 (8.2)	0.98	**0.02**	**0.02**
History of CHF, *n* (%)	6 (10.15)	10 (16.4)	20 (32.8)	0.31	**0.035**	**0.002**
History of stroke, *n* (%)	6 (10.15)	2 (3.3)	3 (5)	0.13	0.67	0.27
History of PAD, *n* (%)	3 (5)	4 (6.5)	4 (6.5)	0.73	1	0.73
History of DM, *n* (%)	9 (15.25)	12 (19.67)	16 (26.2)	0.52	0.38	0.13
Smoking, *n* (%)	38 (64.4)	37 (60.65)	38 (62.3)	0.98	0.98	0.98
History of HT, *n* (%)	25 (42.3)	35 (57.4)	37 (60.65)	0.10	0.71	**0.045**
Bi&Tri coro, *n* (%)	15 (25.4)	40 (65.5)	47 (77)	**0.001**	0.16	**0.001**
Hb [g/l]*	14.25 ±1.79	14.91 ±4.13	13.82 ±1.77	0.26	0.06	0.19
White blood cells, $n \times 10^3$	12.007 ±4.12	11.899 ±4.35	12.170 ±3.60	0.89	0.71	0.81
PLT, $n \times 10^3$	240686 ±51141	237786 ±53449	239122 ±72112	0.76	0.90	0.89
Glu [mg/dl]*	119.66 ±40.73	131.00 ±52.71	133.61 ±75.24	0.19	0.82	0.20
Cholesterol total*	199.15 ±53.60	187.73 ±44.57	191.27 ±44.90	0.20	0.66	0.38
LDL*	115.09 ±46.79	107.91 ±30.37	114.13 ±41.76	0.31	0.34	0.90
HDL*	57.73 ±25.23	52.17 ±22.13	51.51 ±18.31	0.20	0.85	0.12
CK-MB peak*	218.37 ±201.42	221.46 ±183.82	264.12 ±273.33	0.93	0.31	0.30

CK-MB admission*	79.86 ±70.12	75.61 ±81.30	93.89 ±127.69	0.76	0.34	0.45
Fbg [mg]*	486.13 ±172.45	485.51 ±125.70	538.89 ±163.28	0.98	**0.045**	**0.05**
CRUSADE*	23.27 ±12.06	25.16 ±9.73	29.18 ±12.42	0.34	**0.049**	**0.009**
eGFR*	85.10 ±19.27	78.04 ±17.97	75.48 ±21.76	**0.04**	0.48	**0.012**
BUN : Crea*	20.66 ±9.73	18.04 ±5.49	18.84 ±6.47	0.07	0.45	0.22
AIx*	23.25 ±12.57	23.86 ±11.34	21.25 ±14.12	0.77	0.26	0.41
cf-PWV*	9.14 ±1.97	9.35 ±2.62	9.65 ±2.92	0.61	0.55	0.26
cr-PWV*	7.25 ±1.13	6.84 ±1.15	6.92 ±1.12	0.051	0.68	0.11
LVEF < 40%, *n* (%)	22 (37.3)	31 (50.8)	34 (55.7)	0.13	0.58	**0.042**
AFO [l]*	–1.87 ±1.94	–1.85 ±2.88	–1.37 ±2.62	0.97	0.34	0.24
RFO (%)*	–11.12 ±11.56	–10.96 ±16.86	–9.77 ±16.48	0.95	0.69	0.60
TBW [l]*	40.57 ±6.70	40.54 ±8.87	38.20 ±7.41	0.98	0.11	0.07
ECW [l]*	17.31 ±2.21	17.33 ±3.02	16.68 ±3.33	0.96	0.25	0.22
ICW [l]*	23.25 ±5.25	23.20 ±6.73	21.53 ±5.00	0.96	0.12	0.06
LTM [kg]*	47.51 ±14.54	47.48 ±17.63	43.55 ±13.01	0.99	0.16	0.19
FTM [kg]*	28.96 ±12.33	28.73 ±13.87	28.50 ±10.96	0.92	0.23	0.82

**Mean ± standard deviation. Bold values are statistically significant. RAS – renal artery stenosis, CAD – coronary artery disease, CKD – chronic kidney disease, PCI – percutaneous coronary intervention, CHF – congestive heart failure, PAD – peripheral artery disease, Hb – hemoglobin, LDL – low-density lipoprotein, HDL – high-density lipoprotein, Crea – creatinine, eGFR – estimated glomerular filtration rate, LVEF echo – left ventricle ejection fraction, Aix – augmentation index, cf- and cr-PWV – carotid-femoral and carotid-radial pulsed wave velocity, BCM – body composition monitoring, AFO – absolute fluid overload, RFO – relative fluid overload, TBW – total body water, ECW – extracellular water, ICW – intracellular water, LTM – lean tissue mass, FTM – fat tissue mass.*

Table XXXII. Multivariate associates of MI SS

Variable	***B* value**	**95% CI**	***P*-value**
Renal artery stenosis > 50%	3.31	0.40–6.23	0.026
Previous CHF	3.53	0.80–6.27	0.012
LVEF < 40%	3.33	1.2–5.46	0.002
Number of affected vessels	6.21	3.99–8.42	0.001

Table XXXIII. Patients' characteristics according to Clinical Syntax Score tertiles

Variable	Tertile 1 MI CSS ≤ 19.2 (*n* = 60)	Tertile 2 MI CSS 19.3–38.8 (*n* = 61)	Tertile 3 MI CSS ≥ 38.9 (*n* = 60)	*p*1 (I–II)	*p*2 (II–III)	*p*3 (I–III)
RAS+, *n* (%)	5 (8.33)	6 (9.8)	19 (31.66)	0.77	**0.003**	**0.001**
Male, *n* (%)	49 (81.6)	47 (77)	39 (65)	0.53	0.14	**0.038**
Age [years]*	54.33 ±11.35	62.93 ±10.52	67.35 ±9.78	**0.0001**	**0.018**	**0.0001**
Weight [kg]*	86.85 ±13.26	82.72 ±16.79	81.82 ±16.16	0.13	0.76	0.065
BMI [kg/m^2]*	29.49 ±4.2	28.24 ±4.6	29.27 ±5.05	0.12	0.24	0.80
History of CAD, *n* (%)	10 (16.66)	16 (26.2)	29 (48.33)	0.20	**0.011**	**0.011**
History of CKD, *n* (%)	3 (5)	2 (3.3)	8 (13.33)	0.63	0.054	0.11
History of PCI, *n* (%)	1 (1.66)	0	5 (8.33)	0.98	**0.021**	0.08
History of CHF, *n* (%)	5 (8.33)	11 (18)	20 (33.3)	0.11	0.053	0.053
History of stroke, *n* (%)	2 (3.33)	4 (6.5)	5 (8.33)	0.41	0.70	0.24
History of PAD, *n* (%)	3 (5)	3 (5)	5 (8.33)	0.98	0.44	0.44
History of DM, *n* (%)	11 (18.33)	9 (14.75)	17 (28.33)	0.52	0.06	0.19
Smoking, *n* (%)	40 (66.6)	37 (60.65)	36 (60)	0.42	0.89	0.41
History of HT, *n* (%)	24 (40)	37 (60.65)	36 (60)	**0.02**	0.97	**0.02**
Bi&Tri coro, *n* (%)	25 (41.6)	30 (49.2)	47 (78.33)	0.40	**0.001**	**0.001**
Hb [g/l]*	14.90 ±4.13	14.46 ±1.47	13.62 ±2.05	0.43	**0.011**	**0.033**
White blood cells [$n \times 10^3$]	11897 ±3703	11812 ±4256	12371 ±4118	0.91	0.46	0.50
PLT [$n \times 10^3$]	241108 ±48387	245852 ±55358	230475 ±72002	0.61	0.19	0.34
Glu [mg/dl]*	121.17 ±48.53	125.31 ±48.66	138.12 ±73.50	0.64	0.26	0.13
Cholesterol total*	206.34 ±51.25	192.19 ±41.20	179.41 ±47.34	0.09	0.11	**0.003**
LDL*	122.04 ±45.75	110.27 ±36.76	104.76 ±35.63	0.12	0.40	**0.023**
HDL*	55.05 ±20.94	55.79 ±27.57	50.40 ±16.11	0.86	0.19	0.17
CK-MB peak*	212.80 ±180.65	230.37 ±204.32	261.40 ±274.30	0.61	0.48	0.25
CK-MB admission*	72.65 ±75.13	83.84 ±82.31	92.96 ±124.82	0.43	0.63	0.28

Fbg [mg]*	441.65 ±126.65	490.10 ±127.19	579.60 ±178.58	**0.038**	**0.002**	**0.001**
CRUSADE*	19.93 ±9.55	24.39 ±9.82	33.40 ±11.39	**0.013**	**0.001**	**0.001**
eGFR*	91.80 ±12.82	81.08 ±14.45	65.53 ±22.21	**0.001**	**0.001**	**0.001**
BUN : Crea*	19.08 ±9.54	19.27 ±5.14	19.15 ±7.21	0.89	0.91	0.96
AIx*	23.09 ±12.14	20.43 ±13.81	24.87 ±11.88	0.26	0.06	0.41
cf-PWV*	8.64 ±1.66	9.31 ±2.39	10.20 ±3.12	0.075	0.08	**0.001**
cr-PWV*	7.02 ±1.11	6.94 ±1.29	7.05 ±1.03	0.69	0.61	0.94
LVEF < 40%, *n* (%)	9 (15)	31 (50.8)	46 (76.6)	**0.001**	**0.003**	**0.001**
AFO [l]*	1.76 ±1.55	–2.41 ±3.00	–0.90	0.13	**0.004**	**0.029**
RFO (%)*	–10.46 ±9.82	–14.70 ±18.44	–6.61 ±14.91	0.11	**0.009**	0.09
TBW [l]*	41.53 ±6.81	40.81 ±8.30	36.93 ±7.42	0.61	**0.008**	**0.001**
ECW [l]*	17.75 ±2.62	16.96 ±2.68	16.61 ±3.27	0.10	0.51	**0.038**
ICW [l]*	23.77 ±4.70	23.84 ±6.70	20.32 ±4.95	0.95	**0.001**	**0.001**
LTM [kg]*	48.40 ±12.50	49.65 ±17.95	40.39 ±13.08	0.65	**0.002**	**0.001**
FTM [kg]*	30.36 ±10.77	26.15 ±14.26	29.73 ±11.59	0.07	0.13	0.76

**Mean ± standard deviation. Bold values are statistically significant. RAS – renal artery stenosis, CAD – coronary artery disease, CKD – chronic kidney disease, PCI – percutaneous coronary intervention, CHF – heart failure, PAD – peripheral artery disease, Hb – hemoglobin, LDL – low density lipoprotein, HDL – high density lipoprotein, Crea – creatinine, eGFR – estimated glomerular filtration rate, LVEF echo – left ventricle ejection fraction, Aix – augmentation index, cf- and cr-PWV – carotid-femoral and carotid-radial pulsed wave velocity, BCM – body composition monitoring, AFO – absolute fluid overload, RFO – relative fluid overload, TBW – total body water, ECW – extracellular water, ICW – intracellular water, LTM – lean tissue mass, FTM – fat tissue mass.*

In tertiles 2 and 3 there were significantly more females and hypertensives, with higher prevalence of RAS+ and multivascular CAD.

Higher tertiles of MI CSS had lower Hgb and total cholesterol, and higher fibrinogen values. Also, in tertiles 2 and 3 we observed significantly higher cf-PWV, and lower absolute fluid overload (AFO), relative fluid overload (RFO), TBW, ICW, ECW, and lean tissue mass (LTM).

The independent variables correlated with MI CSS in multivariate linear stepwise regression were: RAS+, cf-PWV, history of CAD, multivascular coronary disease, total cholesterol, and TBW (through ICW, but not ECW).

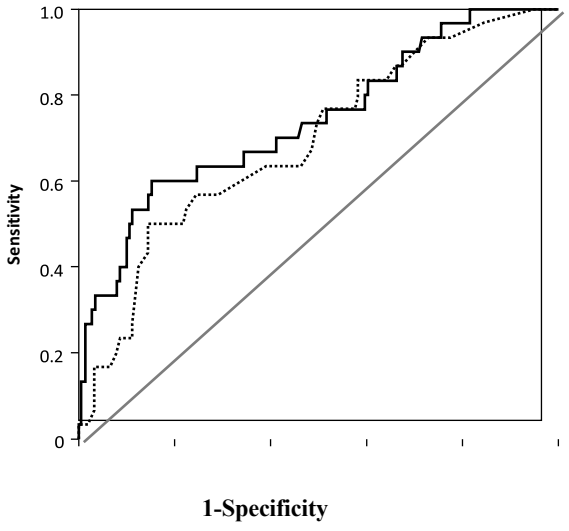
These findings were summarized in Table XXXIV.

Table XXXIV. Multivariate associates of MI CSS

Variable	*B* value	95% CI	*P*-value
Renal artery stenosis > 50%	26.46	12.43–40.48	0.001
Previous CAD	17.69	6.48–28.90	0.002
Number of affected vessels	16.75	6.45–27.04	0.002
Cf-PWV	3.18	1.14–5.21	0.002
TBW	–0.81	(–1.46)–(–0.153)	0.016
Total cholesterol	–0.12	(–0.22)–(–0.018)	0.022

MI Clinical SYNTAX Score versus MI SYNTAX Score as RAS+ predictor

As seen in figure 13, ROC curves and AUCs for MI SS and MI CSS were done in order to evaluate their performance and predictive accuracy for RAS+. The AUC for MI SS was 0.69 (95% CI: 0.58–0.79) and for MI CSS 0.74 (95% CI: 0.63–0.84) ($p < 0.05$ for both analyses, DeLong et al.). Comparison of both AUCs yielded no significant differences in predicting RAS+ between the two scores ($p = 0.12$). Youden's Index for MI CSS was 0.45 and for MI SS was 0.35 (Table XXXV) with the same specificity (85%) but a higher sensitivity (60% versus 50%) for MI CSS.



AUC – area under curve of ROC, ROC – receiver operating characteristics. Diaginal segments are produced by ties.

Figure 13. AUC ROC comparison between MI SS and MI CSS

Table XXXV. Youden index values

Variable	MI SS	MI CSS
Youden index J	0.3543	0.4477
Associated criterion	> 23	> 48.45
Sensitivity	50.00	60.00
Specificity	85.43	84.77

The results showed that the positive probability ratio for MI SS is 3.33 and for MI CSS 4. Negative probability ratios were 0.58 and 0.47, respectively. MI CSS has a strong negative predictive value (92%) but a fair positive predictive value (43%).

4.2.5. Discussion

This was the first study that used and compared directly SS and Clinical SS in consecutive STEMI primary PCI settings. Additionally, the two scores were analyzed and compared for the first time as predictors for RAS+ and arterial rigidity (PWV) and bioimpedance (BCM) parameters were investigated in relation to MI SS/MI CSS in this group. Multisite atherosclerotic disease represents a twofold challenge, in terms of the correct evaluation of prognosis and adequate and personalized management [Tendera et al., 2011].

The strong association between the extent of CAD and RAS presence in elective consecutive patients was noticed in previous studies; specifically, the number of coronary arteries involved raises RAS prevalence [Weber-Mzell et al., 2002]. Patients with previous history of an atherothrombotic event and multisite disease (vs. single disease location) proved a nearly double risk of recurrence at 1 year [Ferrieres et al., 2006]. Additionally, a previous study defined an important increase in RAS prevalence with the number of coronary arteries involved [de Mast and Beutler, 2009]. Moreover, we reported in 2015 that multivascular CAD is an independent predictor for RAS in STEMI patients [Burlacu et al., 2015]. Former data showed that the highest RAS prevalence (54%) was identified in a group of patients with CHF: 1 of 2 patients with LVEF < 40% and clinical symptoms and signs of CHF proved to have RAS+ [de Silva et al., 2007].

Our investigation showed a strong correlation between MI SS and various parameters that characterize extensive multisite atherosclerosis (bi/three vessel CAD, LVEF < 40%, clinical CHF, and RAS+). Therefore, it is safe to emphasize that patients with RAS+ have a high SS score, or, in other words, a high SS score is correlated with multisite atherosclerosis [Banach et al., 2015]. This data are useful for the risk prediction profile, being immediately available for the prevention of early deterioration of renal function.

A better description of resistant hypertension in the context of unstable CAD is very important. It was proved that performing renal angioplasty in the same procedure with primary

PCI might generate favorable outcomes [Su et al., 2013]. The results of our research revealed significant correlations between MI CSS and extensive atherosclerosis (RAS+, history of CAD and multivascular CAD), higher arterial rigidity (cf-PWV), and dehydration (lower TBW through ICW, but not ECW) and lower total cholesterol, suggesting for the first time that a higher MI CSS is associated with presence of RAS+, higher vascular rigidity and dehydration.

It seems that the strong correlation between dehydration and a higher MI CSS indicates either that the hydration status could be a novel risk factor in systemic atherosclerosis development, or that dehydration is a consequence of an extended atheromatous systemic syndrome.

With this regard, we assessed the ability of both MI scores to predict RAS+ and both ROC and AUCs showed a comparably good C-statistic (0.69 for MI SS, 0.74 for MI CSS, $p < 0.001$ for both). Still, adding 4 variables (age, LVEF, weight, and serum creatinine) to MI SS increased the prediction power of MI CSS for RAS+ (without statistical significance, $p = 0.12$).

As a screening test, the negative interpretation of the results (CSS < 44) is useful in supporting that a patient does not have RAS (negative predictive value (NPV) = 92.0%) and at this initial screen correctly identifies 85% of those who do not have RAS.

Thus, we intend to develop a better predictor incorporating into CSS a novel biomarker [Gluba-Brzozka et al., 2014; Gluba-Brzozka et al., 2016] in order to increase sensitivity from 60% to 80%, which would support the very good current specificity of 85%.

The limitations of our study are the low number of total patients and the low number of RAS+ patients, as well as the possible referral bias, given that the research was performed in a single center. Additionally, the reasonable sensitivity of the predictive scores may lead to a limited clinical value of the score valuation. Furthermore, we did not perform a trans-stenotic gradient in order to determine RAS hemodynamic relevance.

The estimation of MACE risk may be improved by identifying RAS through a simple formula [Franczyk-Skora et al., 2015]; this also enables the adjustment of antiplatelet, anticoagulant, and angiotensin-converting enzyme inhibitor treatment [Franczyk-Skora et al., 2013], and helps limit progression to end stage renal disease.

In addition, even if the clinical value of performing renal angioplasty is debatable and not widely accepted, performing this procedure in the same session with primary PCI could and should be tested in a formal prospective study. This could allow us to assess whether this procedure and its timing could effectively yield favorable outcomes in the setting of AMI patients.

4.2.6. Conclusions

We calculated the SYNTAX Score and the Clinical SYNTAX Score in consecutive STEMI patients referred for primary PCI. Both scores correlated with extensive atherosclerotic disease and presence of RAS+. Moreover, MI CSS was associated with higher vascular rigidity and dehydration. This extended score proved to be a good predictor tool for RAS+, with higher specificity and negative predictive value.

Vasilcu TF, **Statescu C**, Sascau R, Roca M, Costea CF, Zota M, Bararu I, Constantin ML, Mitu F. Cardiopulmonary Testing and Biochemical Profile of Coronary Patients Subject to Cardiovascular Recovery Programs. *Rev Chim* 2018; 69(8):2283-2286. **IF: 1.605**
https://www.revistadechimie.ro/Articles.asp?ID=6516

4.3. Coronary Patients Referred to Cardiovascular Recovery Programs

4.3.1. Introduction

The Cardio-Pulmonary Exercise Test (CPET) represents a valuable tool in the diagnosis and prognosis of patients, assessing effort capacity. The test evaluates all systems involved during effort: pulmonary, cardiovascular, hematopoietic, musculoskeletal and neuropsychic. CPET is the gold standard for the direct assessment of exercise intensity and exercise capacity as it provides the possibility of studying respiratory gases, with the measurement of VO_2 max and threshold determination [Mezzani et al., 2009; Gibelin et al., 2012; Guazzi et al., 2012].

A very important issue related to coronary heart disease is represented by cardiovascular rehabilitation (CR), which involves a set of activities that impacts disease progression. CR provides the best physical and mental condition, involving however a long-term effort from both physician and patient. Generally, the recovery program includes a multidisciplinary team consisting of a cardiologist, a physiotherapist, a nutritionist and a psychologist, who will determine the time, intensity and frequency of the effort according to the severity of the pathological process and the sequelae of the acute cardiovascular event [Billinger et al., 2014; Parviz et al., 2017; Safdar et al., 2018].

One of the major risk factors that require optimal control to reduce the risk of future cardiovascular ischemic events is dyslipidemia. Some authors have proved that patients with a history of CHD included into CR programs showed a significant decrease in the lipid fractions under medical treatment compared to those who are not integrated [Verges et al., 1998].

4.3.2. Aim

The objective of the study was to highlight the relationships between changes caused by CR on specific parameters of CPET and on the lipid profile. We included in our analysis patients from urban and rural areas, evaluated at admission and 6 months within the cardiac rehabilitation program.

4.3.3. Material and methods

Our study included 60 patients from urban and rural areas, investigated at the Cardiovascular Recovery Clinic from Recovery Hospital of Iasi, Romania. All subjects were evaluated at admission and 6 months later. Prior stable angina pectoris, chronic myocardial infarction or chronic ischemic cardiopathy no later than 3 months prior to admission constituted

the inclusion criteria. The study protocol was approved by the Ethics Commissions and all the patients signed the participation consent at the beginning of the study.

Within six months of cardiac rehabilitation, patients conducted endurance aerobic exercise at least five days a week, with training session varying from 30 to 60 minutes depending on physical condition and comorbidities, performed at medium intensity. Moreover, each patient underwent a CPET initial assessment, when the characteristics of the type of effort the patients needed to perform were established [Fletcher et al., 2001; Mezzani et al., 2013]. Frequency and exercise intensity were the main features of the physical effort [Thompson et al., 2003; Eagle et al., 2004].

During the study, we monitored VO_2, anaerobic threshold (AT), the cardiac frequency and the effort capacity using CPET. VO_2 represents the oxygen consumed by a patient during the test, which reaches a maximal value at one point (VO_2 max) even though the patient continues the physical effort [Johnson et al., 1992; van de Port et al., 2015].

AT estimates the occurrence of metabolic acidosis as a consequence of the inefficiency of the aerobic metabolism at muscle level. AT is an indicator of the patient's physical condition and it is used in the diagnosis of a limitation to effort [ERJ, 1997; Roca et al., 1997].

Maximum heart rate is important in monitoring the heart rate response to effort. The maximum value was calculated using the following accepted formula: 220 - patient age [Weisman et al., 1995].

Laboratory data as lipid profile, including total cholesterol levels, LDL-cholesterol, HDL-cholesterol and triglycerides (TG) were measured. Dyslipidemia was defined as total cholesterol values > 200 mg/dl and/or LDL-cholesterol > 100 mg/dl and/or HDL-cholesterol < 35 mg/dl and/or use of lipid-lowering drugs [Katsiki et al., 2016; Gavril et al., 2016; Salaru et al., 2018].

The statistical analysis was performed using SPSS software, version 7.0. A value of $p<0,05$ was considered statistically significant.

4.3.4. Results

The study population consisted of 60 subjects, predominantly males (86.67%), with an average age of 58±9.08 years, ranging from 36 to 77 years. From all patients, 33.33% undergone coronarography and coronary artery stenting, 13.33% aortocoronary bypass and 53.33% received conservative treatment. We assessed cardiovascular risk factors and these were present as follows: HTA in 66.7%, dyslipidemia in 76.7% and diabetes in 53.3% patients. Patients underwent a 6-month cardiovascular rehabilitation program and subsequent CPET were performed. The results showed a significant increase in VO_2 max values from 1078.77 ml/min to 1342.5 ml/min ($p <0.01$), as well as a significant improvement in the VO_2 max percentage from the theoretical value: 62.73% to 50.27% ($p<0.01$) (figure 14, table XXXVI).

AT values showed a statistically significant increase ($p <0.03$), pointing an improved physical condition after the cardiovascular recovery program (Figure 15).

Within the study, the maximum effort capacity of the patients obtained from the predicted value for each individual improved ($p <0.01$) from 49.77 W to 58.2 W.

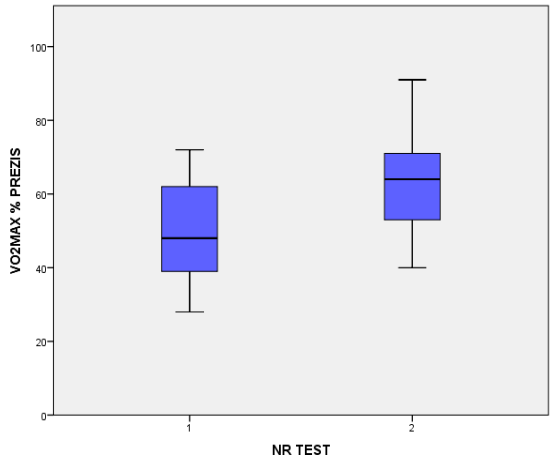


Figure 14. VO_2 max% at initial and second evaluation

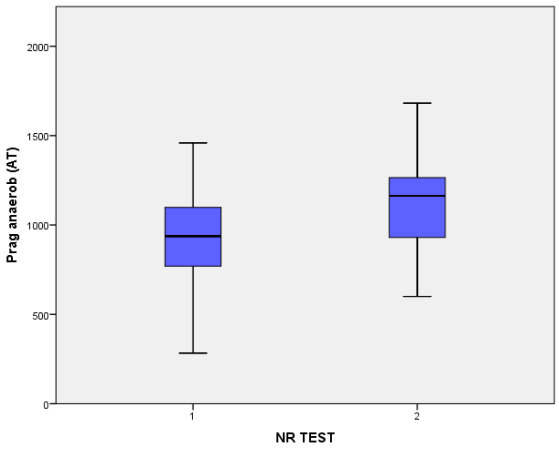


Figure 15. AT at initial and second evaluation

Table XXXVI. CPET parameters after 6 months of rehabilitation

Variables	Mean 1	Std. deviation 1	Mean 2	Std. deviation 2	Sig. (2-tailed)
VO_2 max	1078.77	261.58	1342.5	267.25	<0.001
VO_2 max% from theoretic	50.27	13.05	62.73	13.22	<0.01
Anaerobic threshold	911.47	265.34	1101.57	347.57	0.03
Maximum effort capacity	83.93	22.73	98.47	21.87	0.01
Maximum effort capacity % from theoretic	49.77	13.34	58.2	11.2	0.01
Maximum heart rate	103.57	16.39	115.7	17.75	0.04
Maximum heart rate % from theoretic	64.07	10.32	71.67	9.6	0.008

By analyzing the biochemical lipid profile we noticed a favorable evolution under exercises and statin treatment ($p<0.02$). However, no statistically significant change was detected for body mass index (BMI) ($p<0.22$).

Figure 16-19 emphasize the variations in lipid profile following exercise and statin treatment, at the completion of our study.

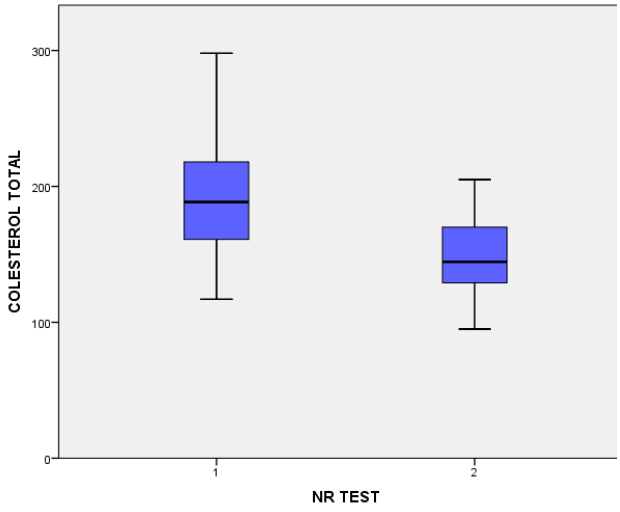


Figure 16. Total cholesterol at initial and second evaluation

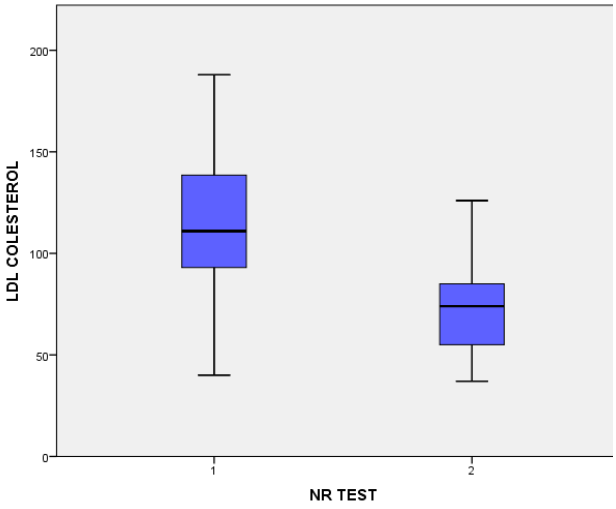


Figure 17. LDL-cholesterol at initial and second evaluation

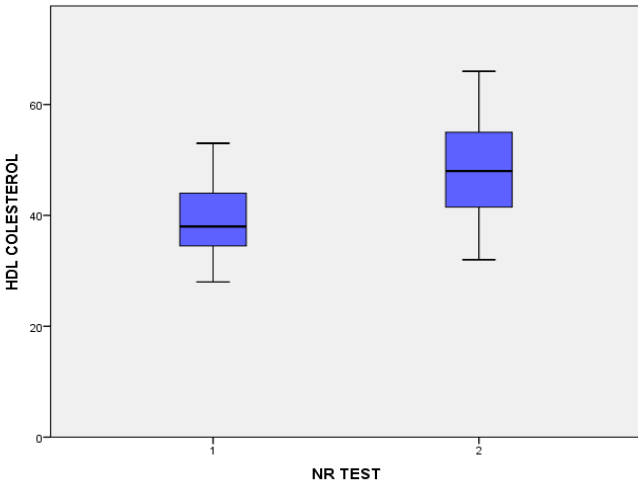


Figure 18. HDL-cholesterol at initial and second evaluation

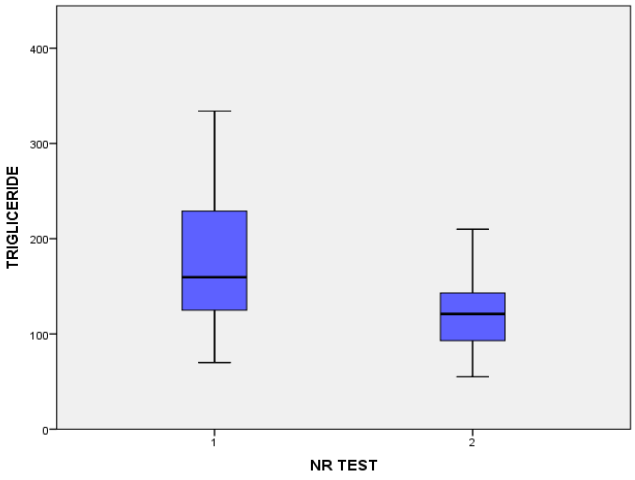


Figure 19. Triglycerides at initial and second second evaluation

The data suggested that patients with CAD that benefit of a 6-month cardiovascular rehabilitation program present a significant decrease in some of the major cardiovascular risk factors, especially lipid profile (table XXXVII). Similar results have been reported in other studies that used a cardiovascular rehabilitation program comparable to ours [Lavie et al., 2008; Lavie et al., 2009].

Table XXXVII. Lipid markers – comparative data after 6 months of rehabilitation

Variables	Mean 1	Std. deviation 1	Mean 2	Std. deviation 2	Sig. (2-tailed)
BMI	30.8	4.55	30.3	4.32	<0.22
Total cholesterol	192.23	47.73	147.90	29.87	<0.02
LDL-Cholesterol	119.50	44.51	76.2	30.07	<0.01
HDL-Cholesterol	40.43	11.19	50.07	11.92	<0.01
Triglycerides	172.73	69.41	124.57	45.81	<0.01

4.3.5. Discussion

Reports concerning cardiopulmonary exercise testing in coronary patients showed an improvement in both respiratory and cardiovascular parameters, after completion of a cardiovascular rehabilitation program, similar to our results [Nixdorff et al., 2009; Popovic et al., 2018]. In our opinion, our study opens future research perspectives. Thus, we intend to enroll more patients in our study and extend the monitoring period to 12 months in order to assess the long-term benefits of cardiovascular rehabilitation.

4.3.5. Conclusions

Our data proved that a 6-month cardiovascular rehabilitation program improves lipid profile, CPET parameters and overall physical condition in subjects with angina pectoris, myocardial infarction or ischemic cardiomyopathy, underlying the significance of such therapeutic plans in the management of these patients.

Găitan A, Stătescu C, Sascau R, Balasanian M, Georgescu CA. Predictors of Positive Response to Resynchronization Therapy in Patients with Recurrent Episodes of Acutely Decompensated Advanced Heart Failure. *Journal of Cardiovascular Emergencies* 2018;4:24-31. https://www.jce.ro/wp-content/uploads/2018/03/jce-2018-0003-1.pdf

4.4. Predictors of Positive Response to Resynchronization Therapy in Advanced Heart Failure

4.4.1. Introduction

Heart failure (HF) accounts for approximately 1-2% of the adult population in developed countries, with a prevalence ≥10% in those aged >70 years, and approximately 4% from the total

number of emergencies admitted to the hospital [Cleland et al., 2005; Arsenescu Georgescu et al., 2011; Brignole et al., 2013; Arsenescu Georgescu et al., 2014; Ponikowski et al., 2016]. The main contributing factors in HF related systolic ventricular dysfunction, are coronary artery disease (CAD), hypertension and diabetes. Approximately 25-50% of these patients present a large QRS complex with duration > 120 msec, associated with a left-bundle block in 15-27% of the cases and with an atrial-ventricular asynchronism in 35% of the cases [Cleland et al., 2005; Arsenescu Georgescu et al., 2011; Brignole et al., 2013; Arsenescu Georgescu et al., 2014; Ponikowski et al., 2016]. Currently, such patients could benefit of cardiac resynchronization therapy (CRT), which selection is based on electrical and electromechanical dyssynchronization criteria: electrocardiographic criteria (duration of the PR interval and morphology of the QRS complex, type of basic rhythm) and echocardiographic parameters (left ventricular ejection fraction [LVEF], size of the ventricles, presence and severity of mitral regurgitation and intra- or inter-ventricular asynchrony) [Cleland et al., 2005; Arsenescu Georgescu et al., 2014]. The concept of CRT is based on synchronous stimulation of the ventricles using several intracardiac leads positioned in different sites in the heart and connected to a pulse generator.

Several randomized multicenter trials underlining the role of CRT in symptoms relief, improving effort-making capacity and decreasing cardiovascular morbidity and mortality were performed. Even though the long-term clinical effects of CRT were evaluated in the last years, and indications for resynchronization therapy are well described, selection parameters are still not well defined. Previous studies showed that up to 30% of patients who benefited from this technique, can be categorized as non-responders, for complex and multifactorial reasons [Cleland et al., 2005; Sipahi et al., 2011; Cheng et al., 2011; Thibault et al., 2013; Florea, Arsenescu, 2013; Rinkuniene et al., 2014]. Also, while the role of CRT has been well established in patients with chronic stable HF, little is known about the effects of CRT in patients with advanced decompensated HF, with severely depressed EF and advanced New York Heart Association (NYHA) stages.

4.4.2. Aim

The purpose of the study was to identify echocardiographic and clinical features that predict a positive response to CRT in patients with advanced HF admitted in an emergency hospital for recurrent episodes of HF decompensation.

4.4.3. Material and methods

We performed a prospective observational study including 42 patients admitted between January 2010 and June 2014 for recurrent episodes of acutely decompensated advanced HF. The subjects were directed to the electrophysiology laboratory of the Cardiology Department from Cardiovascular Disease Institute in Iasi, Romania, for CRT implantation. The inclusion criteria were: patients in NYHA functional class III/IV on optimal pharmacological treatment, with a severely reduced left ventricular systolic function (LVEF ≤ 35%) and a QRS complex duration of

>120 msec, in sinus rhythm. The exclusion criteria were: patients with a previously implanted pacemaker or defibrillator, recent myocardial infarction (< 3 month), or recent coronary artery bypass surgery (<6 month).

Clinical evaluation included assessment of NYHA functional class before and at the six-month follow-up after biventricular pacing. Echocardiographic measurements were done immediately before and six months after CRT device implantation, with all patients at rest, in the lateral decubitus position, at baseline before device implantation and six months later. Also, a standard evaluation of left ventricular volumes was performed in the apical 4-chamber plane using the Simpson method. The severity of mitral regurgitation was determined as the ratio between the maximum area of regurgitation flow in color Doppler testing and the area of the left atrium, being classified as having mild (ratio <20%), moderate (20-40%) or severe (>40%) mitral regurgitation.

CRT device was implanted through the left subclavian and cephalic vein. Coronary sinus morphology was assessed prior to the procedure by angiography or angio-computed tomography. The left ventricular lead was inserted into the posterolateral vein with acceptable threshold stimulation in the absence of phrenic stimulation; the atrial lead was placed in the right atrial appendage, and the right ventricular lead was positioned in the right ventricular apex or ventricular septum. The device was programmed in DDDR stimulation mode and the atrioventricular and inter-ventricular intervals were individually optimized after implantation.

Definitions: Within the study we considered patients as *responders* if they exhibited an improvement of at least one NYHA functional class, an increase in LVEF of ≥5% or a decrease of left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) of ≥15% at the six-month follow-up; *double responders* if both clinical and echocardiographic improvement was noted; *non-responders* if none of these criteria was fulfilled; *super-responders* if they presented an improvement of more than one NYHA class and an increase of LVEF with more than 10% at follow-up.

Statistical analysis was performed using statistical functions in SPSS 18.0 at the significance threshold set at 95%. Data were presented as average values (average arithmetic mean, median, module, minimum and maximum values) and dispersion indicators (standard deviation, coefficient of variation). The t-Student test was used for comparison of the average values recorded in 2 groups with normal distributions, and F test (ANOVA) was used when comparing 3 or more groups with normal distributions. Correlation coefficient "Pearson" (r) was used for linear regression analysis, representing the correlation of 2 variables in the same group, the direct / indirect correlation being given by the coefficient sign. ROC analysis was used for analysis of the sensitivity / specificity balance of the tests.

4.4.4. Results

Our study group included 36 males (85,71%) and 6 females (14,28%), with a mean age of 61,33±10.4 years. Base line characteristics of the study subjects are summarized in Table XXXVIII. Baseline ECG analysis showed that the QRS complex had a mean duration of 178,8±18 msec, with a left bundle brunch block (LBBB) morphology in most of the cases (95,24%), while

only 4,76% of the cases presented a right bundle brunch block (RBBB) morphology. Ischemic cardiomyopathy was responsible for HF in 23,81% of the cases. CRT-D implantation was indicated in 19,04% of the patients for associated paroxysmal monomorphic ventricular tachycardia, while the rest of the subjects received a CRT–P type. Within the study population, a significant number of individuals presented associated comorbidities. Diabetes mellitus was identified in 28.6% of all patients and hypertension was present in 31% of the total cases, 22.2% from those with ischemic etiology and 37.5% of those with non-ischemic etiology had a history of hypertension (p=0.284); moreover, 40.9% of patients in NYHA III class and 20% of those in NYHA IV class had a history of hypertension (p=0.139). Chronic renal disease was present in 38.1% of the cases and obesity was present in 28.7%.

Table XXXVIII. Patients characteristics of the study population

Patients characteristics	**Baseline (n= 42)**
Age (years)	61,33±10,4
Gender (male %)	85,71
DCM - ichemic n (%)	10 (23,81)
NYHA class IV n (%)	15 (36,42)
QRS duration (ms)	178,8±18
CRT-D n (%)	8 (19,04)
LVEF (%)	20,85±6,5
LVEDD (mm)	68,4±6,5
LVESD (mm)	60,5±4,2
LVEDV (ml)	236± 65,8
LVESV (ml)	185± 59,5
LAV (ml)	95,8±16,5
ACE-I n (%)	36 (85,71)
ARB n (%)	6 (14,28)
Beta blockers n (%)	40 (95,23)
Diuretics n (%)	42 (100)
Aspirin n (%)	10 (23,81)
Warfarin n (%)	36 (85,71)

**DCM = dilated cardiomyopathy; CRT-D = cardiac resynchronization therapy – defibrillator; LVEF = left ventricular ejection fraction; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; LVEDV – left ventricular end-diastolic volume; LVESV – left ventricular end-systolic volume; LAV – left atrial volume; ACE-I = Angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers*

Baseline echocardiographic characteristics of the study groups

Left Ventricular Ejection Fraction

The results showed that baseline ejection fraction ranged from 10 to 30%, averaging 22.40 ± 5.61%, close to the median value obtained for the entire study group which was 22%, highlighting the homogeneity of the value series. Evaluation of intragroup characteristics in relation to LVEF at baseline showed no significant differences in LVEF in relation to gender (20.33% for females versus 22.75% for males, p=0.335), age groups (22.82% for younger than 60 years of age vs. 22.12% for older than 60 years of age, p=0.695), type of cardiomyopathy (22.11 for ischemic % vs. 22.63% for non-ischemic, p=0.773) and time recorded since symptom onset (p=0.630). Still, patients in the NYHA IV functional class had significantly lower values of EF than those seen in NYHA III patients (18.65% vs. 25.82%, p=0.001).

Left ventricular volumes

The measurements of left ventricular volumes in relation to subgroup characteristics at baseline are presented in table XXXIX. The results showed no significant differences of left ventricular end-diastolic volume (LVEDV) or end-systolic volume (LVESV) between different subgroups of gender, age or type of cardiomyopathy. Yet, the mean LVEDV was significantly higher in patients less than 6 months after the onset of symptoms (274.32 vs 262.20 ml; p=0.05) while the mean LVESV was significantly higher in NYHA IV functional class as compared to NYHA III (188.30 vs 181.73 ml; p=0.027).

Left atrial volume (LAV)

The results showed that baseline LAV ranged from 72 to 187 ml, averaging 137.17 ± 30.33 ml. Equally to the data documented for ventricular volumes, there were no significant differences in the LAV in relation to gender (134.72 vs 151.83 ml, p=0.205), age groups (141.94 vs 133.92 ml, p=0.407) or etiology of DCM (139.17 vs. 135.67 ml, p=0.716), while the mean LAV level was significantly lower in patients in NYHA III functional class (128.45 vs. 146.75 ml, p=0.05) and in those with a time interval greater than 6 months from the onset of symptoms to acute decompensation (145.55 vs. 127.95 ml, p=0.05) (Table XXXIX).

Duration of QRS complex

The duration of the QRS complex varied from 120 to 240 msec, averaging 160.48 ± 19.62 ms before the procedure. We noticed no significant differences in the mean QRS in relation to gender (161.39 msec for males vs 155 msec for females, p=0.467), age groups (155.29 msec for younger than 60 years vs 164 msec for older than 60 years, p=0.161) etiology (162.78 msec for ischemic vs 158.75 msec for non-ischemic, p=0.517), NYHA functional class (157.73 msec for NYHA III vs 163.50 msec for NYHA IV, p=0.347) or time from onset of symptoms to acute decompensation (163.64 msec for shorter than 6 months vs. 157 msec for longer than 6 months, p=0.279).

Regarding CRT type, 83.3% of the patients were treated with CRT-P and only 16.7% CRT-D (figure 20). Both CRT-P and CRT-D were more frequent in males (82.9% vs. 100%, p=0.123), in those over 60 years (60% vs 57.1%, p=0.888) and in those leaving in urban area (6% vs 57.1%, p=0.564).

Table XXXIX. Ventricular and atrial volumes in patients undergoing CRT

Parameter	N (%)	LVEDV (ml)			LVESV (ml)		
		Average±SD	95% CI	p	Average±SD	95% CI	p
All patients	42	268.55±20.37	262.20-274.90	-	184.86±9.72	181.83-187.89	-
Gender Males	36 (85.71%	269.17±19.83	262.46-275.88	0.635	185.06±10.03	181.66-188.45	0.750
Females	6 (14.28%)	264.83±25.13	238.46-291.20		183.67±8.29	174.97-192.36	
Age							
<60 years	17 (40.47%)	266.65±21.58	255.55-277.74	0.624	181.59±8.18	177.38-185.79	0.072
≥60 years	25 (59.52%)	269.84±19.86	261.64-278-04		187.08±10.21	182.87-191.29	
Etiology Ischemic	18 (42.85%)	271.11±20.56	260.89-281.33	0.487	185.67±10.32	180.53-190.80	0.646
Non-ischemic	24 (57.14%)	266.63±20.46	257.98-275.27		184.25±9.43	180.27-188.23	
NYHA class							
III	22 (52.38%)	265.41±18.54	257.19-273.63	0.301	181.73±9.10	177.69-185.76	0.027
IV	20 (47.61%)	272.00±22.18	261.62-282.38		188.30±9.42	183.89-192.71	
Duration from onset of symptoms to CRT							
<6 months	22 (52.38%)	274.32±18.62	266.06-282.57	0.050	186.36±10.63	181.65-191.07	0.298
≥6 months	20 (47.61%)	262.20±20.78	252.48-271.92		183.20±8.59	179.18-1887.22	

** LVEDV – left ventricular end-diastolic volume; LVESV – left ventricular end-systolic volume; LAV – left atrial volume*

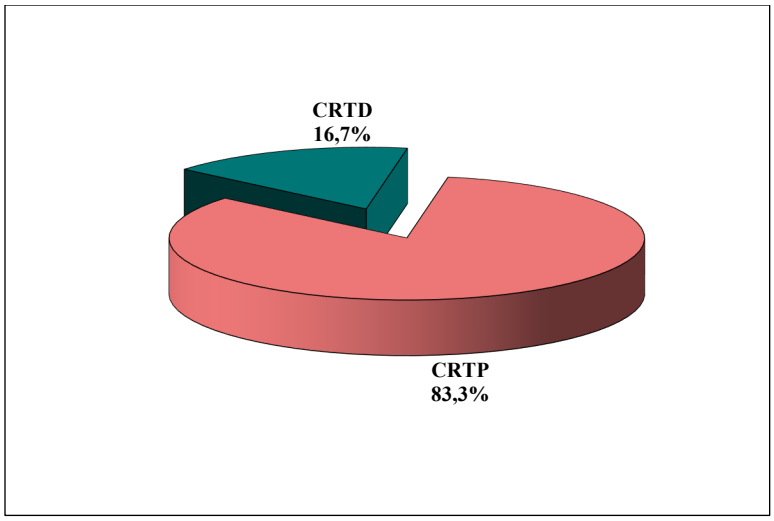


Figure 20. CRT type in the study population

Follow-up after CRT for advanced decompensated HF

When analyzing the functional capacity after CRT, most patients showed a significant improvement with at least one functional NYHA class at the one month follow up (table XL).

In patients with ischemic cardiomyopathy, 55.6% recorded a decrease with one NYHA class and 11.1% with two NYHA classes, while 33.3% of them maintained the initial classification. From the subgroup with non-ischemic cardiomyopathy, 45.8% had a decrease with one NYHA class and 25% with two NYHA classes, while 25% retained their classification.

Tabel XL. Evolution of NYHA functional class post CRT

NYHA class post CRT	NYHA class before CRT			
	NYHA III		NYHA IV	
	N	%	N	%
NYHA I	4	18,2	0	0,0
NYHA II	11	50,0	4	20,0
NYHA III	6	27,3	10	50,0
NYHA IV	1	4,5	6	30,0

Left ventricular function and volumes at follow-up post CRT

We noticed that average LVEF recorded a significant increase from 22.40% to 29.98% (p=0.001) at the 6 months' follow-up (Figure 21)

. Our data proved that in 76.2% of the patients LVEF increased by at least 5%, with no significant differences between gender (36.68% for males vs 42.32% for females, p=0.699), age groups (34.68% for <60 years of age vs. 39.39% for >60 years of age, p=0.6) or etiology (39.52% for ischemic HF vs 35.96% for non-ischemic HF, p = 0.699).

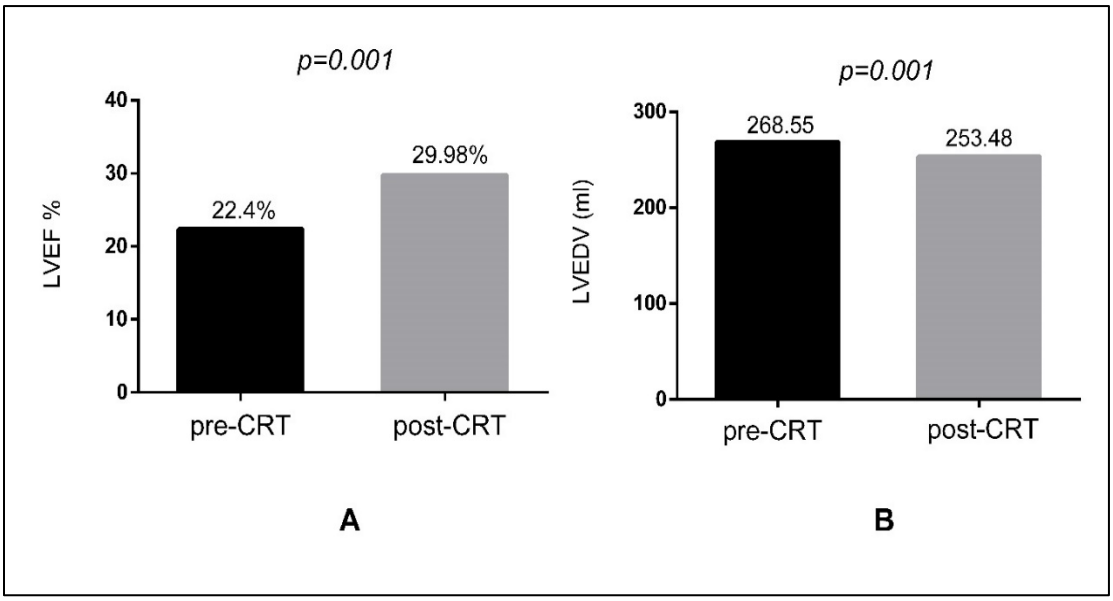


Figure 21. Hemodynamic improvement post CRT; A – improvement in left ventricular ejection fraction (LVEF); B – improvement in left ventricular end-diastolic volume (LVEDV)

Values of left ventricular volumes significantly decreased after CRT implantation from 268.55 ml to 253.48 ml, p=0.001 for LVEDV and from 184.86 ml to 168.24 ml, p=0.001 for LVESV (figure 21). The mean LVEDV decrease was slightly higher in females than in males (16.03 ml vs 20.17 ml; p = 0.350), and a slightly higher average level was observed in the subgroup with over 60 years of age (14.53 ml vs 18.04 ml, p=0.265). However, there were no significant differences of LVESV in relation to gender (p=0.237), age groups (p=0.901) or duration from symptoms onset to presentation with decompensated HF (p=0.293).

Evolution of QRS duration post CRT

On surface electrocardiogram, QRS duration decreased from an average value of 160.48 msec at baseline to 140.4 msec at follow-up, indicating a statistically significant correlation between the narrowing of QRS complex and the increase of the LVEF (p=0.001).

Type of responder pattern following CRT

According to CRT response, 6 patients (14.3%) were classified as clinical responders, showing improvement in NYHA functional class after CRT without any improvement in echocardiographic parameters, and 10 patients (23.8%) were classified as echocardiographic responders, demonstrating a significant improvement of LVEF, LVEDV and LVESV post CRT without a significant clinical improvement. Nevertheless, the most frequently observed response type in this study was the double response, encountered in 23 out of 42 patients (54.8%) who showed both clinical and echocardiographic improvement. Only 3 patients were classified as non-responders as they did not show any positive changes in either the NYHA functional class or the echocardiographic parameters (figure 22).

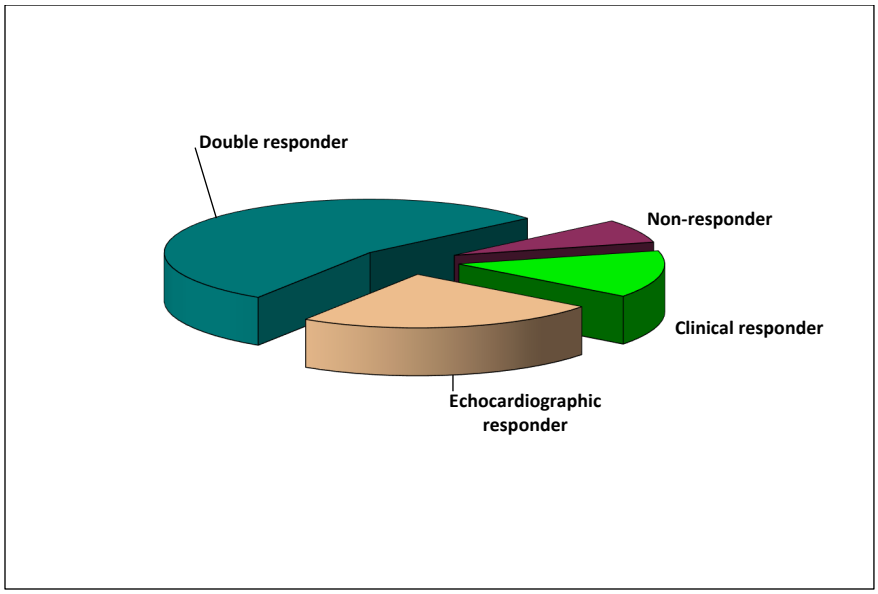


Figure 22. Type of response to CRT

ROC analysis for prediction of clinical response to CRT

According to the ROC analysis, good predictors for clinical improvement after CRT were the absence of chronic renal disease and duration from onset of symptoms to CRT implantation (AUC=0.625, 95%CI: 0.400-0.850 for absence of renal failure and AUC=0.516; 95%CI: 0.369-0.853 for symptoms duration) (Figure 23A). Yet, gender, age, duration from symptom onset, and comorbidities were not good predictors for the echocardiographic response (AUC <0.600) (figure 23B).

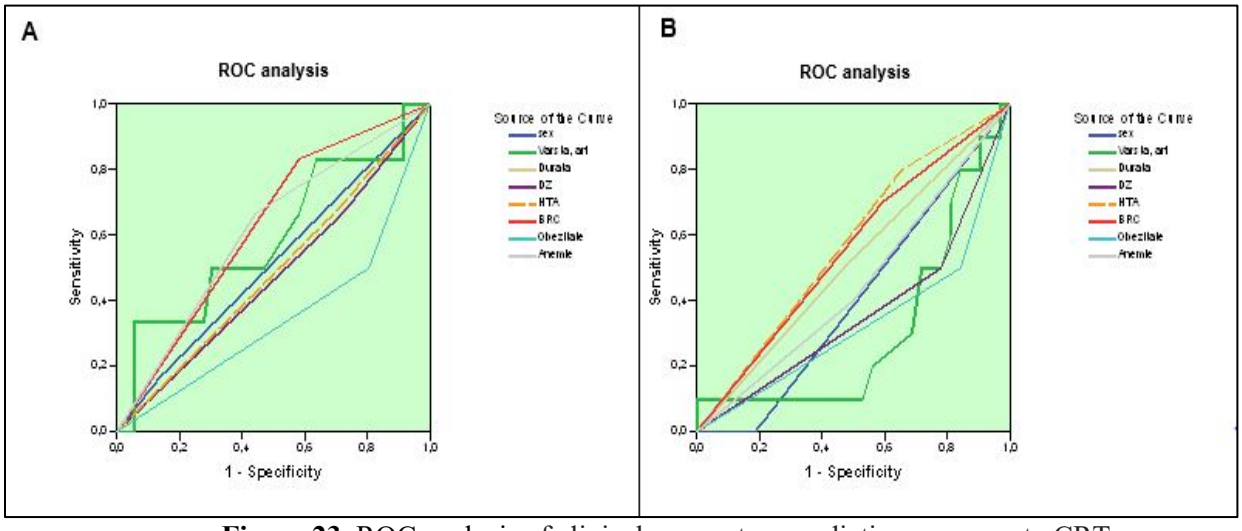


Figure 23. ROC analysis of clinical parameters predicting response to CRT

A – Clinical parameters predicting clinical response (AUC = 0.406 for gender; AUC = 0.311 for age; AUC = 0.516 for duration; AUC = 0.359 for presence of diabetes; AUC = 0.572 for hypertension; AUC = 0.625 for chronic renal disease; AUC = 0.328 for obesity; AUC = 0.833 for anemia); B – Clinical parameters predicting echocardiographic response

4.4.5. Discussion

The scientific research, ever since the early 1990s, mentions cardiac stimulation as a complementary therapy for heart failure [Cleland et al., 2005; Sipahi et al., 2011; Cheng et al., 2011; Arsenescu et al., 2011; Santangeli et al., 2011; Thibault et al., 2013; Arsenescu Georgescu et al., 2014; Rinkuniene et al., 2014]. During the last years, numerous randomized multicenter trials such as MUSTIC-SR (Multisite Stimulation in Cardiomyopathy Study), MIRACLE (Multicenter InSync Randomized Clinical Evaluation Trial), COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure trial) or CARE-HF (The Cardiac Resynchronization Heart Failure trial) proved the role of CRT in symptoms relief, improvement of effort capacity and decrease of morbidity and mortality in patients with HF [Linde et al., 2002; Pires et al., 2005; Cleland et al., 2005; Anand et al., 2009].

Although indications for resynchronization therapy are well described, selection parameters are not well defined and therefore a significant number of patients who benefited from this technique are non-responders [Luderitz et al., 2002; Sawhney et al., 2004; García-Seara et al., 2008; Teh et al., 2009; Stătescu et al., 2011; Thibault et al., 2011; Stătescu et al., 2014]. Consequently, more studies to investigate new options to reduce the frequency of non-response to CRT and to improve selection of patients for CRT are required.

In our study, we emphasized that patients with advanced HF who present to an emergency department for recurrent episodes of decompensated HF and very low EF have a particular pattern of CRT response. Our subjects presented with a very low EF, with a mean value of 22.4%, indicating a severely ill group of advanced HF. Importantly, we identified 4 types of CRT response in this critically ill group, and 38.1% of our study population showed a discordant clinical-echocardiographic response to CRT. Within the study, we found a subgroup of patients with clinical improvement in the absence of hemodynamic improvement (14.3%), as well as a subgroup with hemodynamic improvement in the absence of clinical improvement (23.8%).

Patients with acute heart failure are not commonly included in major CRT trials, due to the potential risks associated with the implantation procedure in these critical cases and the high in-hospital mortality rates. By analyzing the profile of our patient population, one can conclude that is similar to that of critically decompensated HF.

More exactly, our patients presented very compromised ventricular function with very low LVEF, as shown by echocardiography. It is important to acknowledge that the multitude of compensatory mechanisms activated in different stages of disease could be reflected in the variety of response to CRT therapy recorded in our study. Yet, the substrate that leads to the incomplete superposition of the clinical and echocardiographic responses to CRT has not been elucidated so far and needs further research.

The main limitations of the study were related to the relatively small number of patients and the length of follow-up. For this reason, further research is needed to provide information on the predictive features for CRT response in advanced HF on a longer perspective.

4.4.6. Conclusion

CRT represents an important therapeutic option for selected patients with advanced decompensated HF and prolonged QRS interval; still, only some of the commonly used criteria can predict a favorable outcome in patients undergoing CRT.

Butcovan D, Mocanu V, Timofte DV, Costan VV, Danila R, Veselin AP, Ciuntu BM, Haliga RE, Sascau RA, Ghiga G, **Statescu C**. Macrophage Accumulation and Angiogenesis in Epicardial Adipose Tissue in Cardiac Patients with or without Chronic Heart Failure. *Appl Sci* 2020; 10: 5871. **IF: 2.474** https://www.mdpi.com/2076-3417/10/17/5871/htm

4.5. Epicardial Macrophage and Angiogenesis in Cardiac Patients with or without Chronic Heart Failure

4.4.7. Introduction

Epicardial adipose tissue (EAT) is evident on the free wall of the right ventricle, on the left ventricular apex, around the atria, as well as around the two appendages [Matloch et al., 2016; Iacobellis, Barbaro, 2019], being mainly composed of adipocytes, nerves, inflammatory cells, and small blood vessels [Iacobellis, Barbaro, 2019; Butcovan et al., 2017].

Recent studies proved that the extent of epicardial adipocytes is linked with the upregulation of pro-inflammatory factors and inflammatory cell infiltration [Ansaldo et al., 2019]. Moreover, EAT thickness is closely related to coronary artery disease (CAD) [Bachar et al., 2012], atrial fibrillation [Tinica et al., 2015], and heart failure [Iacobellis et al., 2004], in particular.

Previous research showed that heart fat depots are an independent risk predictor for cardiovascular dysfunction in CAD patients [Ding et al., 2008]. Also, EAT size increases in patients with CAD [Mahabadi et al., 2009], including those with thoracic obesity [Bala et al., 2016; Khawaja et al., 2011].

In 2014, Fitzgibbons et al. stated that increased EAT thickness was the strongest determinant of left ventricular (LV) mass [Fitzgibbons et al., 2014]. Other studies revealed that patients with heart failure (HF) have decreased EAT volume compared with normal controls [Doesch et al., 2010; Khawaja et al., 2011].

There are authors who support that the amount of inflammation and angiogenesis in fat tissue may be important indicators of “abnormal” adipose tissues [Rosito et al., 2008; Matloch et al., 2018].

Thus, the macrophages number infiltrating the fat tissue increases in obesity-related cardiovascular disease and angiogenesis is involved in adipose tissue remodeling and expansion.

4.4.8. Aim

The present study aims to underline the role of EAT as a biomarker of CAD. More specific, using EAT biopsies from CAD patients undergoing cardiac surgery, we analyzed the link between some cardiovascular (CV) risk factors and EAT morphology (thickness, inflammation, and angiogenesis), in patients diagnosed with CAD with or without concomitant CHF.

4.4.9. Material and methods

The study population was represented by 15 patients with documented CAD, 9 males, and 6 females, aged between 50 to 66 years old. The patients underwent right atrial appendages (RAA) excision during coronary artery bypass graft (CABG) surgery in 2017. The exclusion criteria were: other associated CV pathologies, inflammatory disease, connective tissue disease, active malignancy, and thyroid disease. The subjects were divided in two groups: with or without concomitant chronic heart failure (CHF), based on cardiac dysfunction on echocardiography (left ventricular ejection fraction ≤50%) and symptoms of heart failure (NYHA functional class II or III). The protocol of the study was approved by the Ethics Committee of the Institute of Cardiovascular Diseases and all patient signed an informed consent to participate in the study before cardiopulmonary bypass.

Study Procedures We evaluated body mass index (BMI), the presence of arterial hypertension (medical-record review and the requirement of antihypertensive drugs), dyslipidemia (established by the clinical medical history, by current treatment with hypolipidemic drugs, or by of plasma low-density lipoprotein (LDL)-cholesterol ≥115 mg/dL or plasma triglycerides ≥150 mg/dL), diabetes mellitus (confirmed by clinical history, or by fasting plasma glucose ≥126 mg/dL) and smoking status [Parisi et al., 2018]. LV ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD) were assessed via echocardiography. Subsequently to CABG surgery, EAT samples of the RAA of the CAD patients with CHF were compared with samples from CAD patients without CHF.We further analyzed associations between EAT thickness, inflammation, and angiogenesis, and the number of CV risk factors. All data were expressed as mean values or frequencies.

We examined the RAA epicardial adipose tissue thickness and area by using usual hematoxylin-eosin staining in optical microscopy [Timofte et al., 2019]. EAT thickness was expressed as a mean value of ten EAT thickness area from the entire histological section. Furthermore, epicardial inflammatory foci and angiogenesis required immunohistochemical (IHC) confirmation. Thus, IHC was performed according to standard protocols on formalin-fixed, and paraffin-embedded sections. We used CD68 and CD34 markers. Assessment of immunohistochemistry stained sections was made by the presence of positive brown staining.

Morphometry was performed by the assessment of the macrophages and microvessel density. We analyzed five histological fields at 200× magnification for each case. The results were expressed as percentages or mean values of the number of positive cells or vessels related to the

studied area. The semi-quantitative evaluation was made by using a manually-driven evaluation method.

Statistical analysis was performed using SPSS Statistics 21 Software (IBM SPSS, Chicago, IL, USA). The Mann–Whitney test and Pearson chi-square test were used for parametrical (non-normal distribution due to small size data) and non-parametrical data, respectively. Numerical data were presented as means ± SD and categorical data were presented as percentages. A $p < 0.05$ was considered statistical significant.

4.4.10. Results

The demographic, clinical, hemodynamic, and biochemical characteristics of CAD patients are presented in table XLI. We noticed that the mean age in CAD cases without HF (58 years) was lower than in CAD cases with HF (63 years). All patients showed well-known CV risk factors for CAD. CAD patients with CHF showed a higher prevalence of male sex, obesity, and dyslipidemia ($p < 0.05$) compared to those without CHF.

Table XLI. Demographic, clinical, hemodynamic, and biochemical characteristics of CAD patients

Variable	**Patients without CHF (n = 9)**	**Patients with CHF (n = 6)**
Age (y)	58.3 ± 14.7	63.4 ± 11.2
Male sex (%)	33.3	100*
Weight (kg)	78.3 ± 14.5	88.0 ± 22.1
BMI (kg/m^2)	27.6 ± 5.6	32.3 ± 7.1*
Obesity (%)	0	100*
History		
Dyslipidemia (%)	33.3	100
Arterial hypertension (%)	66.6	50
DM type 2 (%)	66.6	50
Smoking (%)	33.3	0
Echocardiography		
LVEDD (cm)	5.0 ± 0.5	6.9 ± 1.2*
LVESD (cm)	3.3± 0.6	5.6 ± 1.3*
LVEF (%)	54.1 ± 3.3	28.5 ± 7.2*
Biochemical values		
Total cholesterol (mg/dL)	212 ± 42	206 ± 38*
Triglycerides (mg/dL)	161 ± 12	175 ±54*

Variable	Patients without CHF (n = 9)	Patients with CHF (n = 6)
LDL cholesterol (mg/dL)	124 ± 9	135 ± 11*
HDL cholesterol (mg/dL)	57 ± 4	45 ± 3*

*p-value ≤ 0.05 was considered significant; CAD, coronary artery disease; CHF, chronic heart failure, DM, diabetes mellitus, LVEF, left ventricular ejection fraction, LVEDD, left ventricular end-diastolic diameter, LVESD, left ventricular end-systolic diameter.

EAT thickness, macrophage infiltration (figure 24 a, b), and capillary network (figure 25 a, b) were identified within RAA specimens. The EAT thickness (185.8 μm) was non-significantly lower (p = 0.07) in CAD patients with CHF, as compared to those without CHF (217.2 μm). Regarding EAT macrophage infiltration, it was more extensive in CAD patients with CHF than in those without CHF (figure 24a,b).

The mean value of CD68 positive cells in CAD patients with CHF (325.78/μm2) was significantly higher (p < 0.001) than in CAD patients without CHF (244.9/μm2). EAT angiogenesis was less extensive in patients with CHF than in those without CHF (Figure 25a,b). The mean value of CD34 positive count in CAD patients with CHF (22.83/μm2) was significantly lower (p < 0.001) than in CAD patients without CHF (65.2/μm2).

The link between the number of risk factors and EAT IHC labels is shown in Table XLII.

Table XLII. Mean EAT thickness and IHC markers of macrophages accumulation and angiogenesis in peri-atrial EAT samples from CAD patients

Patients	EAT thickness (μm)	CD68 (No/μm^2)	CD34 (No/μm^2)
Without CHF	217.1 ± 21.3	244.9 ± 5.5	65.2 ± 1.7
With CHF	185.8 ± 27.9	325.7 ± 16.1	22.7 ± 3.8
p-value	0.07	<0.001	<0.001

p-value < 0.05 was considered significant, CAD, coronary artery disease; CHF, chronic heart failure.

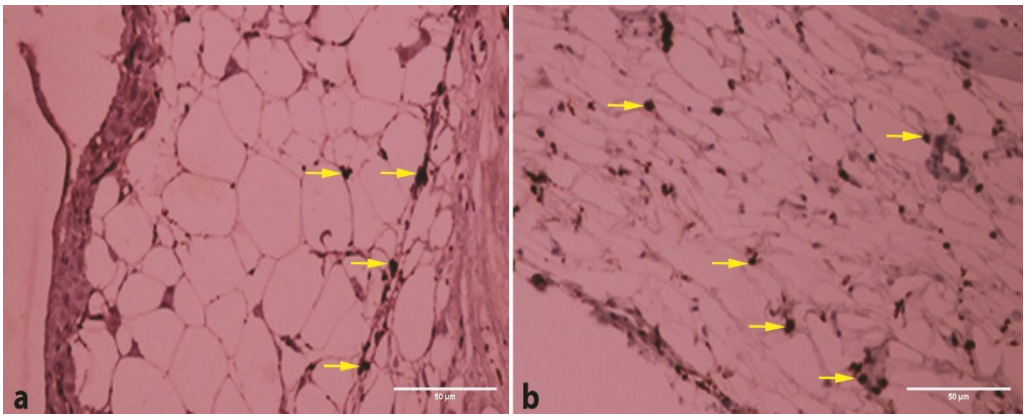


Figure 24. Immunohistochemical EAT analysis of the macrophages (CD68 200×) in CAD patients without CHF (**a**) and CAD patients with CHF (**b**).

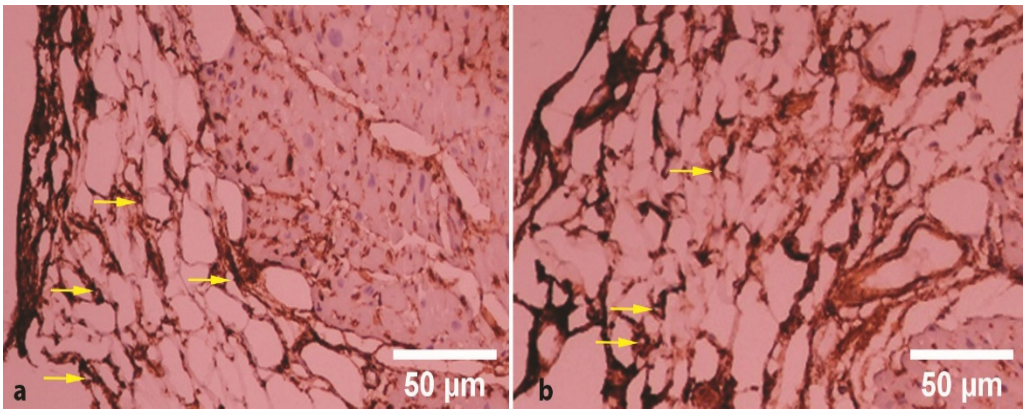


Figure 25. Immunohistochemical EAT analysis of the vessels (CD34 200×) in CAD patients without CHF (**a**) and CAD patients with CHF (**b**).

4.4.11. Discussion

Our research analyzes the link between known CV risk factors and EAT features on RAA samples following open-heart surgery. We identified that the following risk factors are likely to be significant predictors of CAD progression: male sex, obesity, and dyslipidemia. Previous studies stated that EAT thickness is a CV risk factor in patients with or without preoperative heart failure, receiving standard CABG technique [Kitagawa et al., 2015; Nagy et al., 2017]. Rare data regarding EAT size and the association of EAT with the severity of cardiac ischemia in CAD patients who underwent CABG surgery are available. Several evidence supported the fact that the severity of CAD was related to EAT thickness [Eroglu et al., 2009; Mahabadi et al., 2013] and that epicardial fat was associated with lower ejection fraction [Mookadam et al., 2010]. Other reports have proposed that EAT could serve as a predictor of CAD, and EAT values >2.4 mm can predict the presence of significant CAD (>50% diameter) [Iacobellis et al., 2004; Ahn et al., 2008]. Within our study, we found a non-significant decrease of EAT thickness in patients with CHF compared to those without CHF, associated to EAT fibrous tissue remodeling. Studies of Nagy et al. revealed that EAT amount is an independent CAD risk factor, being related to other CV risk factors [Nagy et al., 2017]. Similar to previous reports [Fitzgibbons et al., 2014; Salazar et al., 2016], we consider that EAT thickness, measured by imaging techniques, may serve as a tool in the follow-up assessment of the CAD patients. In previous research, we observed extracellular matrix alterations in EAT of CAD patients due to a great number of collagen deposits [Tinica et al., 2015] and also, that fibrosis could limit the adipocyte expandability, similar to other studies [Jiang et al., 2017]. Our data revealed no significant difference between adipocyte size in EAT of non-CAD individuals and CAD patients [Butovan et al., 2017]. Similar to other authors, we stated that the increased EAT thickness in CAD patients may be due to fibrosis which restrict the extension of EAT by limiting adipocyte hypertrophy [Aitken-Buck et al., 2019]. Another significant result of our study was the presence of EAT inflammatory foci, which may stimulate angiogenesis at this level. Previous studies consider that epicardial fat is a source of inflammatory cells in CAD [Hirata

et al., 2011; Matloch et al., 2018]. A particularity of our CABG patient is that those with CHF were obese. Therefore, the morphological exam revealed that in obese cardiac patients with CHF, EAT presented increased inflammation and decreased thickness compared to non-obese patients without CHF. It was shown that EAT thickness measured post-mortem [Schejbal et al., 1989] or clinically by echocardiography, computed tomography (CT), or magnetic resonance imaging (MRI) was lower in patients with CHF [Doesch et al., 2010; Khawaja et al., 2011; Fitzgibbons et al., 2014]. The reduced epicardial fat could explain the increased inflammation by a reduction in the local secretion of protective anti-inflammatory adipokines [Fitzgibbons et al., 2014; Fosshaug et al., 2015]. Our data revealed angiogenesis as another morphological hallmark of the EAT in CAD patients, consistent with previous studies [Dozio et al., 2015; Matloch et al., 2016]. Within our study, angiogenesis was of about three times greater in our CAD patients without CHF (of about 65 microvessels/μm^2) than in CAD patients with CHF (23 microvessels/μm^2) on coronary arteries as reported by other authors [Iacobellis et al., 2009; Salazar et al., 2016; Butcovan et al., 2017]. The limitations of our study were the small number of participants and that IHC can only measure one or two markers per sample, and it may not completely reflect the complex mechanisms involved in epicardial adipose tissue thickening.

4.5.6. Conclusions

Our study performed on epicardial fat samples of the RAA demonstrated that the abundance of CD68-macrophages appeared to be associated with CHF in CAD patients. Also, the individuals referred for CABG, in whom systolic heart dysfunction was confirmed by echocardiography, had decreased angiogenesis. Histologically, the increased EAT thickness in CAD patients was related to the connective tissue repair process.

Siriopol D, Popa R, Mihaila M, Rusu F, Sascau R, **Statescu C**, Cătălina Z, Vasiliu V, Bucur A, Neamtu A, Siriopol I, Cianga P, Kanbay M, Covic A. Application of survival classification and regression tree analysis for identification of subgroups of risk in patients with heart failure and reduced left ventricular ejection fraction. *Int J Cardiovasc Imaging* 2021 Jan 16. **IF: 1.969**
https://pubmed.ncbi.nlm.nih.gov/33454896/

4.6. Survival classification and regression tree analysis for identification of subgroups of risk in some patients with heart failure

4.6.1. Introduction

Data regarding heart failure (HF) are not entirely reliable due to the lack of case reports in underdeveloped countries and the inconsistency of methods in evaluating the occurrence rate of this disorder. However, epidemiological studies showed that there are approximately 26 million cases of HF worldwide [Ponikowski et al., 2014]. As the population ages, the incidence increases [Dunlay, Roger, 2014], along with health-related costs [Lesyuk et al., 2018]. Various therapeutic opportunities were conceived during the last years: β-blockers, mineralocorticoid receptor

antagonists, ivabradine, and more recently sacubitril/valsartan and SGLT-2 inhibitors. Cardiac device therapy, such as implantable defibrillators, is also recommended by current guidelines. Yet, the mortality rates in patients with HF did not significantly change over time, being about 50% at 5 years and 70% at 10 years, comparable to those reported in early 2000's [Taylor et al., 2017; Gerber et al., 2015]. Researchers have always pursued to design some risk prediction models in order to statistically prefigure the risk of HF-related complications. However, in clinical practice, the use of these models is limited, considering the difficulty of individualization for each patient [Howlett, 2013].

4.6.2. Aim

Within the present study, we aimed to identify by classification and regression tree (CART) analysis, groups of patients with different survival patterns in a population with heart failure and reduced left ventricular ejection fraction (HFrEF). In order to achieve our goal, we used standard procedures of heart function assessment and also non-traditional methods for determining hydration and nutritional status in HF patients, namely lung ultrasonography (LUS) and bioimpedance spectroscopy (BIS) analysis. Finally, we compared the prognostic value of this novel methods with that of conventional Cox survival analysis.

4.6.3. Material and methods

We performed a prospective observational study of outpatient adults referred for clinically indicated transthoracic echocardiograms in our hospital between 2016 and 2018. Information regarding this study were previously reported [Siriopol et al., 2020]. We included in the study patients with a left ventricular ejection fraction (LVEF) below 45% measured by echocardiography. The total number of eligible patients was 321. 153 subjects were excluded from the study due to limb amputation, metallic joint prostheses, cardiac pacemakers or stents, decompensated cirrhosis, prior diagnosis of pulmonary fibrosis, pneumectomy, massive pleural effusion, end-stage renal disease, active systemic infections and terminal illnesses. Other 17 patients didn't sign the informed consent. Consequently, 151 patients were included in the final investigation. All the procedures were done in accordance with the principles outlined in the Declaration of Helsinki [Rickham, 1964]. The protocol was approved by the Research Ethics Committee of the "Grigore T. Popa" University of Medicine and Pharmacy Iasi.

The demographic parameters recorded at baseline were age, gender, weight, height, comorbidities (diabetes, coronary artery disease, hypertension, atrial fibrillation, chronic kidney disease) and smoking status. The arterial blood pressure values were registered in the morning in all patients by three consecutive evaluations, after a 15-min resting period, with the mean values calculated for systolic (SBP) and diastolic blood pressure (DBP) [Mancia et al., 2013]. According to current guidelines, hypertension was defined as a SBP of at least 140 mmHg and/or DBP of at least 90 mmHg or previously diagnosed hypertension under treatment during the previous 2 weeks, irrespective to BP values. A medical history of coronary artery/heart disease, angina or angina

pectoris, or myocardial infarction was considered as coronary artery disease. The diuresis, the presence of peripheral edema (slight pitting of at least 2 mm depth with no visible distortion) [Seidel et al., 1995], the NYHA functional class, and the medication were also evaluated. Biochemical analysis of serum creatinine, hemoglobin, glucose, total cholesterol, triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol, C-reactive protein (CRP), uric acid and sodium levels were done. We assessed the estimated glomerular filtration rate (eGFR) by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [Levey et al., 2009]. Echocardiograpy was performed before LUS and BIS evaluations by two trained echocardiographers according to the recommendations of the American Society of Echocardiography [Lang et al., 2015]. As previously described by Jambrik et al., LUS was done with patients in the supine position, for a total of 28 sites per complete examination [Jambrik et al., 2004]; the total number of B-lines was noted for each zone (from a minimum of 0 to a maximum of 10) and the extent of lung congestion was obtained by summing the scores from all the 28 zones - as seen in Figure 26 - with two assessments performed from two different investigators from our study.

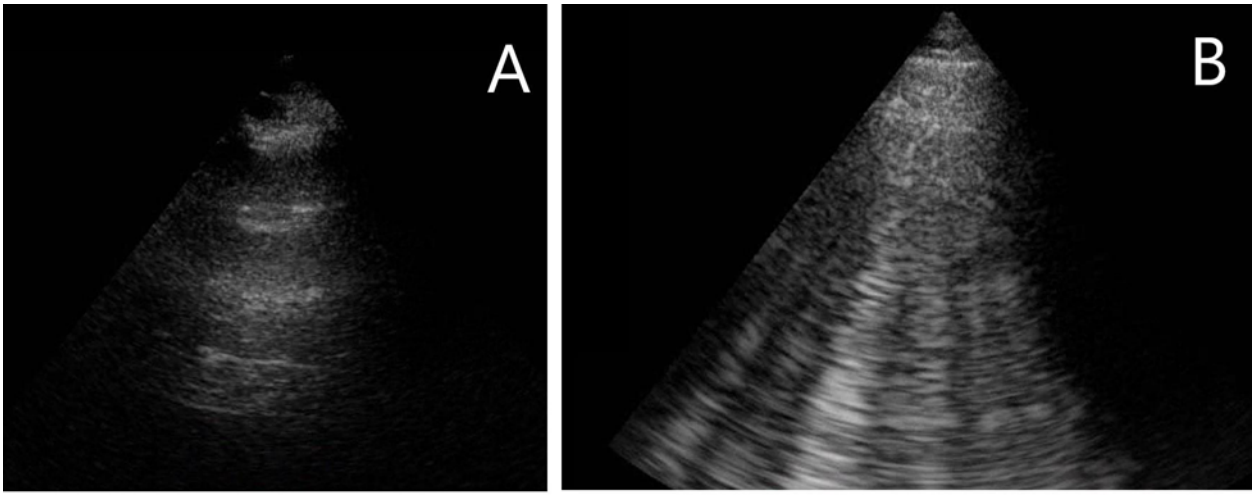


Figure 26. Images from the lung ultrasound from two different sites from patients from our study, showing 0 (A) and 10 B-lines (B).

Bioimpedance analysis

After performing LUS measurement, we assessed the hydration state and the body composition [https://www.fmc-au.com/therapy-systems-and-services/analysis-systems/bcm]).

We determined the extracellular water (ECW), intracellular water (ICW) and TBW as previously described [Moissl et al., 2006]. The device expresses body composition as a three-compartment model, being able to provide information about overhydration, lean and tissue mass. Absolute fluid overload (AFO), defined as the difference between the expected patient's ECW under normal physiological conditions and the actual ECW, and relative fluid overload (RFO), defined as the AFO to ECW ratio, were used in order to describe the hydration status. The lean tissue index (LTI) and fat tissue index (FTI) were also evaluated, where LTI and FTI are the respective tissue masses

normalized to height squared. Because in patients with limb amputation, metallic joint prostheses, cardiac pacemakers or stents, or decompensated cirrhosis, this method could provide unreliable results [Wizemann et al., 2009], these subjecrs were excluded from the study as previously stated.

Outcome: The major outcome was all-cause mortality. Deaths were confirmed through patient follow-up phone calls, hospital's electronic medical records or the social security death index.Within the study, the *statistical analysis* was done using Stata SE software, version 13 (StatCorp, College Station, TX, USA). A p value <0.05 was considered to be statistically significant. Variables were expressed as median with interquartile range (IQR), mean ± standard deviation (SD), or as percentage of frequency, as appropriate. The between-group comparisons were performed using the Chi-square test for categorical variables, and Mann-Whitney U test or the independent T-test, for continuous variables. The Shapiro-Wilk test helped us to assess the normality of the distribution and logarithmic conversion was performed for non-normally distributed variables. CART analysis was valuable to categorize subgroups of risk for all-cause mortality, as well as cut-off values for the factors identified as significant risk predictors [Lofaro et al., 2016]. The analysis begins by dividing data into smaller sections to provide a clearer view of interactions among variables. We further compared the results of two Cox proportional hazard models in order to assess whether the use of CART analysis offers higher predictive performance over conventional Cox survival analysis: the first one a conventional Cox model and the second one using only the subgroups identified by the CART analysis. For the CART analysis, all the available variables were included in the initial step. All data were offered in the form of Hazard ratios (HR) and 95% confidence intervals (CI). We achieved bootstrapping validation when needed in order to avoid the problem of overfitting due to the low number of incident outcomes. We compared the two Cox models using the concordance index (c-index), a measure equivalent to the area under the receiver operating characteristic curve in logistic regression. The Bayesian information criterion (BIC) and the Akaike information criterion (AIC) were also calculated for each Cox model; there is no statistical test that compares different BIC or AIC estimations, and a lower value indicates a better fitted model.

4.6.4. Results

Our 151 patients had a mean age of 67.1±12.1 years. Regarding sex distribution, 69.2% of them were males. 56 (37.1%) and 47 (31.1%) patients had dilated and ischemic cardiomyopathy respectively, these two conditions being the most common causes of HF. Demographic, biological, bioimpedance, echocardiographic and treatment features of the study group are offered in Tables XLIII and XLIV and Supplementary Table XLIII. Patients who died through the follow-up (35.1%/53 reported deaths), had a higher prevalence of peripheral edema and severe baseline NYHA class. Compared to the survivors, they also had a significantly higher number of B-lines (median 21 vs. median 7.5, p<0.001) and urea, CRP, soluble ST2 and galectin-3 levels (see Table XLIII). Nevertheless, these patients displayed significantly lower eGFR (61.1±25.3 vs. 69.4±23.7 ml/min/1.73 m^2, p=0.04), hemoglobin (12.6±2.1 vs. 13.8±2.0 g/dL, p=0.001), serum sodium

(135.5±5.3 vs. 138.2±4.3, p<0.001) and leptin (median 13.5 vs. median 24.8 ng/mL, p=0.01) values.

Table XLIII. Baseline demographic, clinical and biological characteristics of the study population.

	All (N=151)	All-cause death NO (N=98)	All-cause death YES (N=53)	P value
Age, years	67.1±12.1	65.6±12.1	69.8±11.7	**0.03**
BMI, kg/m^2	28.9±4.7	29.2±4.6	28.4±4.8	0.33
Male, n (%)	105 (69.5)	70 (71.4)	35 (66.0)	0.49
SBP, mmHg	124.6±18.3	124.5±16.9	124.8±20.8	0.90
DBP, mmHg	75.4±11.3	76.1±10.5	74.0±12.6	0.28
Smoking, n (%)	60 (39.7)	37 (37.8)	23 (43.4)	0.49
Diuresis, L/day	1.4±0.5	1.4±0.5	1.5±0.5	0.09
Edema, n (%)	75 (49.7)	36 (36.7)	39 (73.6)	**<0.001**
III/IV NYHA class, n (%)	73 (48.3)	41 (41.8)	32 (60.4)	**0.03**
B-lines	12.0 (3.0-32.0)	7.5 (2.0-26.0)	21.0 (10.0-48.0)	**<0.001**
Comorbidities				
Diabetes, n (%)	53 (35.1)	31 (31.6)	22 (41.5)	0.23
CAD, n (%)	89 (58.9)	63 (64.3)	26 (49.1)	0.07
Hypertension, n (%)	93 (61.6)	57 (58.2)	36 (67.9)	0.24
Atrial fibrillation, n (%)	80 (53.3)	50 (51.6)	30 (56.6)	0.55
Biological parameters				
Serum creatinine, mg/dL	1.1 (0.9-1.4)	1.1 (0.9-1.3)	1.2 (0.9-1.4)	0.12
eGFR, ml/min/1.73m^2	66.5±24.5	69.4±23.7	61.1±25.3	**0.04**
Urea, mg/dL	47.0 (35.0-69.0)	43.5 (33.0-62.0)	58.0 (41.0-80.0)	**<0.001**
Hemoglobin, g/dL	13.4±2.1	13.8±2.0	12.6±2.1	**0.001**
Serum glucose, mg/dL	107.0 (96.0-131.0)	107.5 (95.0-131.0)	106.0 (98.0-128.0)	0.52
Total Cholesterol, mg/dL	151.0 (127.0-187.0)	153.0 (132.1-187.0)	144.0 (123.0-184.0)	0.32
LDL Cholesterol, mg/dL	91.0 (75.0-117.4)	93.5 (77.0-116.0)	87.0 (74.0-124.0)	0.68
HDL Cholesterol, mg/dL	38.0 (30.0-46.0)	37.0 (31.0-47.0)	40.0 (30.0-45.0)	0.84
Serum Triglycerides, mg/dL	121.0 (96.0-148.0)	121.0 (97.0-148.0)	123.0 (81.0-147.0)	0.35
CRP, mg/L	25.6 (9.0-56.4)	19.9 (7.8-46.9)	35.1 (15.8-89.7)	**0.01**
Uric acid, mg/dL	7.5 (6.2-8.8)	7.5 (6.1-8.4)	7.8 (6.5-9.1)	0.29
Serum sodium, mmol/L	137.2±4.9	138.2±4.3	135.5±5.3	**<0.001**
Soluble CD146, ng/mL	236.00 (189.60-329.20)	221.4 (190.2-338.0)	236.8 (188.8-314.0)	0.48
NT-proBNP, pg/mL	800.0 (400.0-1500.0)	795.0 (300.0-1500.0)	910.0 (500.0-1320.0)	0.26
ST2, pg/mL	8.17	6.47	10.32	**0.02**

	(4.61-14.35)	(3.67-11.93)	(5.77-14.85)	
Galectin-3, ng/mL	26.40 (18.30-35.80)	24.3 (17.0-35.4)	29.2 (22.4-37.0)	**0.04**
CT-1, pg/mL	1.40 (0.30-10.20)	2.7 (0.4-10.9)	1.2 (0.3-6.7)	0.26
Acylated ghrelin, pg/mL	10.30 (1.30-41.5)	11.6 (2.0-41.6)	6.1 (1.0-40.9)	0.32
Leptin, ng/mL	21.90 (7.70-49.10)	24.8 (10.8-49.7)	13.5 (6.2-29.7)	**0.01**

Data are expressed as mean±SD, or median with IR, or percent frequency, as appropriate. Significant values are indicated in bold. Abbreviations: BMI – body mass index; CAD – coronary artery disease; CKD – chronic kidney disease; CRP – C-reactive protein; CD146 – cluster of differentiation 146; CT-1 – cardiotrophin-1; DBP – diastolic blood pressure; eGFR – estimated glomerular filtration rate; HDL – high-density lipoprotein; LDL – low-density lipoprotein; NT-proBNP – N-terminal brain natriuretic peptide; SBP – systolic blood pressure; ST2 – soluble suppression of tumorigenesis 2

Within the study, we noticed that those patients who died had higher values for ECW (19.1±2.7 vs. 17.4±3.4 L, p=0.001), AFO (2.0±2.3 vs. 0.6±2.9 L, p=0.002) and RFO (10.2±11.9 vs. 1.9±13.6%, p<0.001), but lower values for ICW (17.4±3.3 vs. 18.7±3.6 L, p=0.04) and LTI (10.5±2.3 vs. 11.6±2.6 Kg/m^2, p=0.01) than those who survived. However, there were no differences between these patients in regard to TBW and FTI (see Table XLIV).

Table XLIV. Echocardiographic and bioimpedance characteristics of the study population

	All (N=151)	**All-cause death NO(N=98)**	**All-cause death YES (N=53)**	**P value**
Echocardiography				
LV EDVi, mL/m^2	85.1 (70.3-107.8)	81.3 (68.2-103.8)	97.8 (79.4-111.1)	**0.01**
LV ESVi, mL/m^2	54.2 (31.3-80.8)	46.6 (29.5-79.9)	61.9 (38.1-82.9)	0.13
Septal wall thickness, mm	12.5±2.2	12.5±2.1	12.5±2.5	0.99
Posterior wall thickness, mm	11.8±1.8	11.7±1.7	11.9±1.9	0.53
LVMI, g/m^2	152.9 (126.9-187.3)	144.7 (121.1-179.3)	168.0 (139.4-200.8)	**0.004**
LAVI, mL/m^2	40.7 (32.4-62.9)	36.4 (27.6-50.9)	57.3 (41.0-74.0)	**<0.001**
LVEF, %	32.5±10.2	32.7±10.5	32.0±9.8	0.68
Bioimpedance				
TBW, L	36.5±5.8	36.4±5.9	36.6±5.8	0.85
ECW, L	18.3±2.9	17.4±3.0	19.1±2.7	**0.001**

ICW, L	18.0±3.4	18.7±3.6	17.4±3.3	**0.04**
AFO, L	1.1±2.8	0.6±2.9	2.0±2.3	**0.002**
RFO, %	4.8±13.5	1.9±13.6	10.2±11.9	**<0.001**
LTI, Kg/m^2	11.2±2.6	11.6±2.6	10.5±2.3	**0.01**
FTI, Kg/m^2	16.8±5.2	17.0±5.3	16.5±4.9	0.52

Data are expressed as mean±SD, or median with IQR, as appropriate. Significant values are indicated in bold.

Abbreviations: AFO – absolute fluid overload; ECW – extracellular water; FTI – fat tissue index; ICW – intracellular water; LAVI – Left atrial volume index; LVEF – Left ventricular ejection fraction; LV EDD – LV end diastolic diameter; LV EDVi – left ventricular end diastolic volume index; LV ESD – LV end systolic diameter; LV ESVi – left ventricular end systolic volume index; LVMI – left ventricular mass index; LTI – lean tissue index; RFO – relative fluid overload; TBW – total body water

Supplementary Table XLIII. Medications

	All (N=151)	All-cause death NO (N=98)	All-cause death YES (N=53)	P value
ACEIs/ARBs, n (%)	68 (45.0)	46 (46.9)	22 (41.5)	0.52
Beta-blockers, n (%)	116 (76.8)	76 (77.6)	40 (75.5)	0.77
Diuretics, n (%)	109 (72.2)	67 (68.4)	42 (79.3)	0.16
Spironolactone, n (%)	90 (59.6)	54 (55.1)	36 (67.9)	0.13
Antiplatelet agents, n (%)	74 (49.0)	46 (46.9)	28 (52.8)	0.49
Anticoagulation, n (%)	105 (69.5)	74 (75.5)	31 (58.5)	**0.03**
Statins, n (%)	70 (46.4)	52 (53.1)	18 (33.9)	**0.03**
Nitrate, n (%)	55 (36.4)	39 (39.8)	16 (30.2)	0.24
Digoxin, n (%)	33 (21.9)	16 (16.3)	17 (32.1)	**0.03**
Amiodarone, n (%)	38 (25.2)	25 (25.5)	13 (24.5)	0.89

Data are expressed as percent frequency. Significant values are indicated in bold. Abbreviations: ACEI - Angiotensin-converting enzyme inhibitors; ARB - Angiotensin II receptor blockers.

Survival and prognostic analysis

The follow-up included a mean and median time of 18.8 and 20.4 months, respectively. The severity of NYHA class, the number of B-lines and urea, CRP, NT-proBNP, LVMI, LAVI, AFO and RFO values were positively associated with all-cause mortality, while hemoglobin, serum sodium, leptin, ICW and LTI levels were negatively related with the outcome as seen in Table XLV. An essential point of our analysis was to determine if CART analysis could provide a superior predictive performance over conventional Cox survival analysis.

Table XLV. Univariable Cox survival analysis.

	HR	IC 95%	P value
Age, years	1.03	1.00-1.05	**0.03**
NYHA Class, (reference Class I-II)	3.27	1.78-6.01	**<0.001**
Log B-lines	1.50	1.18-1.92	**0.001**
Hemoglobin, g/dL	0.82	0.72-0.93	**0.002**
Log Urea, mg/dL	1.84	1.06-3.20	**0.03**
Log CRP, mg/L	1.27	1.05-1.53	**0.01**
Serum sodium, mmol/L	0.92	0.88-0.96	**<0.001**
Log NT-proBNP, pg/mL	1.26	1.01-1.59	**0.04**
Log Leptin, ng/mL	0.76	0.62-0.94	**0.01**
Log LVMI, g/m^2, g/m^2	2.58	1.02-6.55	**0.04**
Log LAVI, mL/m^2	2.49	1.29-4.79	**0.006**
ICW, L	0.92	0.85-0.99	**0.04**
AFO, L	1.11	1.02-1.19	**0.01**
RFO, %	1.02	1.01-1.04	**0.004**
LTI, Kg/m^2	0.88	0.78-0.98	**0.03**

Abbreviations: AFO – absolute fluid overload; CI – confidence interval; CRP – C-reactive protein; HR – hazard ratio; ICW – intracellular water; LAVI – Left atrial volume index; LVMI – left ventricular mass index; LTI – lean tissue index; NT-proBNP – N-terminal brain natriuretic peptide; RFO – relative fluid overload.

By using a backward stepwise Cox survival analysis, and including all the univariable associates of the outcome, we noticed that only age, the severity of NYHA class, hemoglobin, serum sodium and LTI were retained in the final model (see Supplementary Table XLIV).

Supplementary Table XLIV. Multivariable Cox survival analysis (stepwise backward method)

	HR	IC 95%	p
Age, years	1.03	1.00-1.05	**0.04**
NYHA class, (reference class I-II)	2.53	1.35-4.74	**0.004**
Hemoglobin, g/dL	0.84	0.73-0.97	**0.02**
Serum sodium, mmol/L	0.93	0.89-0.97	**0.002**
LTI, Kg/m^2	0.89	0.78-0.99	**0.03**

Abbreviations: CI – confidence interval; HR – hazard ratio; LTI – lean tissue index.

Within the study, we used the CART algorithm, and we included all the available variables in the initial step. Consequently, we identified five groups based on serum sodium, the severity of NYHA class, serum urea and systolic blood pressure (as seen in Figure 27 and Supplementary XLV). Patients with a serum sodium of at least 136 mmol/L and NYHA class I or II (Group 1 in Figure 27 and Supplementary XLV) had the best survival, while a noteworthy worse prognosis

was seen in patients with serum sodium ≥ 136 mmol/L, NYHA class III or IV and serum urea ≥ 70 mg/dL (Group 3 in Figure 27 and Supplementary XLV), in those with serum sodium<136 mmol/L and SBP<120 mmHg (Group 4 in Figure 27 and Supplementary XLV) and in those with serum sodium < 136 mmol/L and SBP ≥ 120 mmHg (Group 5 in Figure 27 and Supplementary XLV). A trend towards a worse survival was also observed in patients with serum sodium ≥ 136 mmol/L, NYHA class III or IV and serum urea < 70 mg/dL; (Group 2 in Figure 27 and Supplementary XLV), but no statistical significance was noticed.

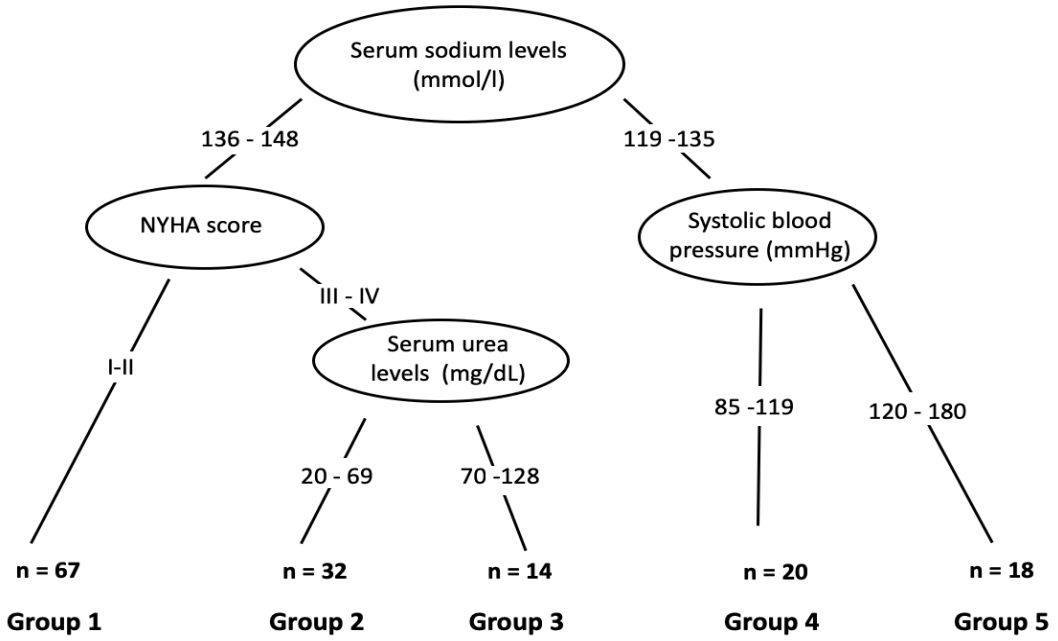


Figure 27. Tree for classification of survival subgroups

Supplementary XLV. Cox survival analysis using the categories defined by CART

	Patients	HR	CI 95%	P value
Group 1	67		Reference	
Group 2	32	2.23	0.86-5.81	0.09
Group 3	14	10.59	4.15-27.08	**<0.001**
Group 4	20	5.48	2.24-13.42	**<0.001**
Group 5	18	20.93	8.43-51.97	**<0.001**

Group 1: Serum sodium≥136 mmol/L, NYHA class I/II; **Group 2**: Serum sodium≥136 mmol/L, NYHA class III/IV, Serum urea<70 mg/dL; **Group 3**: Serum sodium≥136 mmol/L, NYHA class III/IV, Serum urea≥70 mg/dL; **Group 4**: Serum sodium<136 mmol/L, SBP<120 mmHg; **Group 5**: Serum sodium<136

mmol/L, SBP≥120 mmHg. Abbreviations: CI – confidence interval; HR – hazard ratio; SBP – systolic blood pressure.

We further compared the two models. We concluded that the model derived from the CART analysis showed better predictive power than the conventional Cox model (c-index 0.790, 95% CI 0.723-0.857 vs. 0.736, 95%CI 0.664-0.807, p<0.05 – see Table XLVI).

Table XLVI. Performance comparison of Cox models using only patient data and only CART subgroups

	c-index (95% CI)	AIC	BIC
Conventional model[a]	0.736 (0.664-0.807)	447.81	462.89
CART model[b]	0.790 (0.723-0.857)*	428.59	440.66

[a]Conventional model includes age, NYHA Class, hemoglobin, serum sodium and LTI.
[b]CART model includes the 5 groups identified by CART analysis.
*P<0.05 versus conventional model
Abbreviations: AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; CART – Classification and Regression Tree; LTI – lean tissue index.

4.6.5. Discussion

In our study, we identified different groups of risk for all-cause mortality in patients with HFrEF by using CART analysis that showed improved prediction abilities compared to more conventional statistical methods. For a long time, prediction of future outcomes in HF was made by prognostic stratification. However, it is difficult to introduce these models in clinical practice [Howlett, 2013], most likely because of the low reliability at patient level, the variety of methods to choose from or the complexity of the used statistical approaches [Canepa et al., 2018]. A systematic review performed in 2020 identified 40 studies with 58 risk prediction models and 105 distinct predictors [Di Tanna et al., 2020], highlighting the complex physiopathological mechanisms that render HF as a major clinical and public health condition. The authors used conventional statistical prognosis analysis and concluded that the most frequent variables included in the prognostic models were NT-proBNP, age, diabetes and sex, but also sodium and NYHA class [Di Tanna et al., 2020]. By comparison, in our analysis (model from Supplementary Table XLIV), NT-proBNP levels were not retained in the final model, but age, the severity of NYHA class and serum sodium were included. According to our conventional Cox analysis, hemoglobin and LTI were also independently associated with all-cause mortality. Previous studies have suggested that hemoglobin levels could be a substitute of fluid control/a marker of extracellular water [Hung et al., 2015]; Therefore, the association of hemoglobin with the major outcome was expected. Other studies showed that an increase in BMI is a risk factor for HF development, and a higher BMI in those with recognized HF is linked with better outcomes [Horwich et al., 2001; Sharma et al., 2015]. Our newly identified negative association between LTI and the outcome of

interest could explain, at least in part, the above-mentioned "obesity paradox" (eg. a higher BMI with an increase in LTI, and not FTI, could be protective). CART analysis has significant benefits taking into account its capability to identify predictive cut-off values for continuous, and even related, variables. Published reports have used arbitrary cut-off values based on subjective evaluations or on the distribution of data in their sample [Levy et al., 2006; Agostoni et al., 2013]. CART algorithm allows an investigative subgrouping of patients based only on the outcome and its prognosis.

In addition, another main feature of the phenotypes identified by the CART analysis is related to its straightforwardness and simplicity. Even though serum sodium, NYHA class, SBP and even serum urea levels could be used as indirect markers of fluid status/overhydration, it is important to notice that these variables were retained in the final model, while other, more related to body fluid compartments (like LUS and BIS related characteristics), were not. Moreover, LUS, through the B-lines assessment, is a well-established diagnostical and prognostic method used in acute and chronic HF patients even though BIS is not a validated tool in HF patients (as opposed to hemodialysis patients) [Wizemann et al., 2009; Onofriescu et al., 2014; Onofriescu et al., 2015; Siriopol et al., 2019]), [Platz et al., 2016; Gustafsson et al., 2015; Platz et al., 2017; Coiro et al., 2020; Buessler et al., 2020]. We noticed that in our study group of chronic HF patients, the number of B-lines was not retained as a prognostic variable in neither of the two prognostic models. This aspect could be linked to the variances in the included subjects (without pacemakers or stents, all patients with a LVEF below 45%), in the LUS protocol, but also to the differences in the adjusting factors as we included both serum sodium and serum urea levels, while in the other studies these variables were not [Gustafsson et al., 2015; Platz et al., 2016]. As a final point, the use of the tree classification, helped us to identify combined effects between different factors, stating also the significance of such factors in the context of others. For instance, in our CART analysis, the significance of SBP values is limited only in patient who are hyponatremic and, similarly, serum urea levels only in the context of severe HF. In HF patients, a lower serum sodium level generally suggests poor water excretion or the use of diuretics.

The present study has *limitations and strengths*. First, we included a relatively small sample size of selected HF patients from a single-center unit and we weren't able to provide the exact cause of death. Yet, we used a special automated survival tree algorithm that has provided different advantages over conventional statistical approach. Our HF population was a particular one, as we excluded those patients with different comorbidities that could interfere with our volume assessment techniques, and as such, the generalizability of the results to the entire HF population could be limited. Additionally, since we didn't have a validation cohort, these results should be validated in other HF populations, including larger samples.

4.6.6. Conclusions

CART analysis allowed us to identify different groups of risk for all-cause mortality in patients with HFrEF. The use of this type of modelling indicated an improved prediction capability over that of using more conventional statistical methods.

Section III. Future directions in professional, academic and scientific

By excellence, the teaching profession requires a permanent training as well as the continuous acquisition of new knowledge. Additionally, medical practitioners have the responsibility to periodically grow in their careers, until the end of it. Professional development is essential for the teacher in order to to provide an image of the contemporary scientific world and to learn effective methods of interacting with students.

III.1. Developments in academic and professional activity

Perspectives, objectives in academic field

- The continuous professional and didactic self-improvement, through permanent individual study, participation in national and international courses, congresses, conferences;
- A constant upgrade of teaching materials and courses, in accordance with the national and international guidelines and protocols; integration of novelties along with the classic, fundamental and essential elements of medical training; the permanent updation of the teaching materials uploaded on the university platform;
- Implementing internships and interactive courses, for students and residents, as part of the teaching process;
- Improving the evaluation methods, with the elaboration of tests, multistage case discussions, and images – for a correct and objective assessment of individual performances; to address the standardization of the practical examination for a correct evaluation and equality of opportunity;
- Refining the teaching act, both during courses and internships, basend on the personality and skills of each recipient (student/resident physician);
- Creation of monographs that centralize the current state of knowledge for my area of interest;
- Guidance of at least 4 graduation thesis and student papers annually;
- Engaging students in volunteer work, and educational actions for patients with cardiovascular diseases;
- Increasing the enthusiasm for postgraduate education, by involving as many residents as possible in practical and research activities and by increasing the quality of the courses in accordance with the novelties in the field;
- Creating a core working group, consisting of students and resident physicians with an interest for cardiology research and practice; the outlined themes could be used later for the elaboration of graduation or doctoral theses and could represent a selection method for the future university staff;
- Attending personal development modules ("public speaking", "teach to teach" etc.) as a means to improve my teaching skills;

- Increasing collaboration with colleagues from other disciplines and organizing interdisciplinary clinical evenings for students and resident physicians;
- Positive and prompt response to all projects, events, tasks launched by the Discipline, Department, Faculty or University.

Perspectives, objectives in clinical activity and professional competences

- Continuous self-improvement through individual study, participation in national and international conferences;
- Improving cardiology and internal medicine knowledge in order to provide my patients with the best medical care;
- Strengthen my skills in the field of cardiac implantable electronic devices;
- Oversight of all clinical programs and medical equipment as well as supervision of the clinical staff that I am in charge of;
- Intensifying the collaboration with my colleagues from other specialties, holding interdisciplinary sessions for students and resident physicians;

III.2. Developments in research activity

In the upcoming period, I plan to continue with the research direction that I have settled in the cardiology field after I completed my Ph.D. thesis but, also, to start new ones, as follows:

III.2.1. Prevalence of pacing-induced cardiomyopathy as assessed by cardiac magnetic resonance imaging

It is estimated that annually, more than 1 000 000 pacemakers are implanted worldwide, almost half of them for high-degree atrioventricular block diagnosis [Mond, Proclemer, 2011]. The majority of the subjects tolerate the high burden of RV pacing without developing any adverse event.

However, it is essential to acknowledge that in a minority of cases, chronic RV pacing leads to left ventricular dysfunction and symptomatic heart failure. Pacing-induced cardiomyopathy (PICM) is the term used to describe the phenomenon when there is a decline in left ventricle ejection fraction (LVEF) in the context of chronic right ventricle (RV) pacing [Merchant, Mittal, 2018]. Except for the decrease in LVEF, other complications can emerge in long-term RV pacing, such as ventricular remodeling, atrial fibrillation, and higher mortality.

Over time, different definitions have been used in order to define PICM. As listed below, three of them were the most frequent employed in research studies: (a) LVEF ≤ 40% when the baseline LVEF was ≥ 50% or a reduction in LVEF ≥ 5% if baseline LVEF was < 50%; (b) LVEF ≤ 40% when the baseline LVEF was ≥ 50% or a decrease in LVEF ≥ 10% if baseline LVEF was ≤ 50%; (c) an absolute decrease in LVEF greater than 10% irrespective of baseline values. Because

of this high variability in terminology, the true prevalence of PICM is still undetermined, largely ranging from 5.9% to 39%, according to these definitions [Kaye et al., 2019].

Safak et al. aimed to assess the prevalence of PICM on 170 subjects with no structural heart disease and preserved LVEF (≥45%) before pacemaker implantation on mid-term follow-up. PICM was defined by a LVEF ≤ 45% with dyskinesia, in the absence of other potential cause for cardiomyopathy. They have highlighted that, in subjects with no evidence of structural heart disease and preserved ejection fraction at the time of the implantation, the occurrence rate of PICM is not insignificant as 6% of the entire study cohort developed PICM during 24.5 months of follow up [Sfak, 2019]

The mechanisms responsible for the emergence of LV systolic dysfunction are not completely understood, interventricular dyssynchrony and individual susceptibility being major triggers [Merchant, Mittal, 2020]. Also, the data regarding the onset of PICM after pacemaker implantation is discordant. Traditionally, it was considered that almost 20% of subjects develop PICM after 3-4 years of RV pacing [Merchant, Mittal, 2018].

Conversely, Tayal et al. retrospectively analyzed the Danish nationwide registry and identified a cohort of 27 704 individuals who underwent pacemaker implantation from 2000 to 2014. Patients with pacemakers and without heart failure were age- and gender-matched in a 1.5 ratio to subjects without pacemaker and without a history of heart failure. At two years' follow up 10.6% of the study population developed overt heart failure compared to 6.7% of the group control. Notably, the risk of developing new-onset heart failure was the highest among the first six months [Tayal et al., 2019].

As mentioned above, RV pacing determines an impairment in LV systolic function by generating electrical and mechanical dyssynchrony. In order to prolong the preservation of LV systolic function, alternative pacing sites have been conceived, such as mid-septal or outflow RV pacing. The idea behind placing the leads in unconventional sites, rather than at RV apex, came as a modality to reduce QRS duration and thus of decreasing dyssynchrony. However, as stated by Bansal R et al., non-apical RV pacing does not seem to reduce the incidence of PICM when compared to apical lead position [Bansal et al., 2019].

This evidence was also supported by the findings of Kim JH et al., who performed a multicenter, retrospective analysis over a 15-year period in South Korea. From December 2001 to August 2015, 900 patients benefited from pacemaker implantation. The final study population consisted of 130 subjects with complete atrioventricular block, with pacing dependent-rhythm, electrocardiographically and echocardiographically followed up for 4.5 years. Pacemaker data were also collected at regular intervals. The authors have shown that in individuals implanted for complete atrioventricular block, the occurrence of PICM is not influenced by the pacing site but rather of the paced QRS duration. A cut-off value of above 140 msec of paced QRS duration had a 95% sensitivity in identifying PICM, while a cut-off value of above 167 msec had a specificity of 90% for PICM [Kim et al., 2018].

According to Chow SW et al.'s analysis on 1418 implanted subjects, baseline left bundle branch block, paced QRS duration ≥ 155 msec and ventricular pacing percentage ≥ 86% were

independent predictors of PICM. Subjects with PICM portrayed a poorer prognosis than those without [Cho et al., 2019].

Regarding the available therapeutic options, various studies have illustrated that cardiac resynchronization therapy (CRT) or biventricular pacing can potentially reverse PICM [Nazeri et al., 2010]. Khurshid et al. retrospectively studied 1279 subjects that underwent CRT procedures between 2003 and 2016, including those with CRT upgrade from a dual-chamber or single-chamber ventricular pacemaker as a means to treat PICM. The authors aimed to evaluate the extent and time course of improvement in LVEF after CRT upgrade for PICM as well as to analyze the predictors for amelioration of LV systolic function. They have emphasized that CRT is a powerful therapeutic tool in PICM, 72 % of severe PICM subjects, defined as pre-upgrade LVEF ≤ 35% had an improvement in LVEF within one year. Into what concerns, the elements that predicted the degree of response in the univariate analysis, age, body mass index, loop diuretic use, upgrade to CRT-defibrillator, and shorter native QRS duration were significantly linked to a positive response [Khurshid et al., 2018].

The management of sudden cardiac death (SCD) in PICM is another aspect of paramount importance. Khurshid et al. also brought to attention that, even though the number of subjects that experienced malignant ventricular arrhythmias in their study was small, in PICM, there is a permanent myocardial substrate for monomorphic ventricular tachycardia, warranting more attention [Faddis et al., 2018].

Thereafter, Barra et al. sought to evaluate if a defibrillator back-up at the time of the CRT upgrade provides any additional benefit in subject with PICM. A retrospective analysis of 199 patients with PICM and no sustained ventricular arrhythmia was performed. The study population was further divided into 109 individuals with CRT-Pacemaker upgrade (CRT-P) and 95 with CRT-Defibrillator upgrade. The study population was followed-up for 66 ± 24 months. No improvement in survival rate was achieved when CRT-D upgradation was performed in subjects at low-risk of SCD, with no history of life-threatening ventricular arrhythmias [Barra et al., 2018].

Despite significant progress in understanding the pathophysiology of pacing-induced cardiomyopathy and in implementing proper medical care, there are still a lot of unanswered questions. Except for abnormal electrical and mechanical activation of the ventricles, numerous experimental studies have pointed that, at a microscopical level, myofibrillar disarray and extensive interstitial fibrosis are among the common findings in chronic RV pacing [Adomian, Beazell, 1996; Karpawich et al., 1999; Merchant FM, Mittal , 2018].

Even though late gadolinium enhancement (LGE) by cardiac magnetic resonance imaging (CMR) is valuable in evaluating myocardial fibrosis, CMR imaging's potency to predict PICM development and its predictive value in comparison to that of transthoracic echocardiography have not been reviewed ever before.

In the light of the above-mentioned shortcomings, I plan to perform a single-center, prospective, observational study on subjects implanted with dual-chamber pacemakers for complete atrioventricular block within the Electrophysiology Laboratory of the Institute of Cardiovascular Diseases “Prof. Dr. George I.M Georgescu” from Iasi, Romania.

After implantation, during the same hospitalization, the echocardiographic assessment will mainly focus on:

- the evaluation of LV systolic function: LVEF ejection fraction via biplane Simpson method; mitral annular plane systolic excursion (MAPSE) via M-mode echocardiography; peak myocardial systolic velocity (S') via Tissue Doppler Imaging; global longitudinal strain (GLS) via speckle-tracking echocardiography;
- the assessment of RV systolic function: tricuspid annular plane systolic excursion (TAPSE) via M-mode echocardiography; peak myocardial systolic velocity (S') via Tissue Doppler Imaging; right ventricular fractional area change (RVFAC) via 2-dimensional transthoracic echocardiography.

Of note, only subjects with preserved LVEF (≥ 50%) and unimpaired RV systolic function will be included for further analysis. Additionally, within 40 days after pacemaker implantation, all patients will be referred for CMR imaging. LV and RV systolic functions will be measured, and the amount of baseline myocardial fibrosis will be detected with LGE- CMR imaging technique.

At three months, six months, one year, and two years after implantation, clinical, electrocardiographic, pacemaker-related data and echocardiographic measurements will be collected. A drop greater than 5% in LVEF will be used to define the emergence of PICM.

Additionally, at two years after implantation, an LGE-CMR imaging reappraisal will be performed in all subjects that completed the follow-up period.

My research's main objectives will be to assess the percentage of the final study cohort that developed PICM, the correspondence between echocardiographic and CMR findings with regard to RV and LV systolic functions and the capability of increased baseline LGE by CMR imaging to predict the appearance of PICM.

III.2.2. The potency of novel biomarkers to predict chronic heart failure development following an acute myocardial infarction

Heart failure (HF) is a major public health issue accounting for substantial morbidity and mortality worldwide. Despite remarkable diagnostic and therapeutic progress, HF persists in having significant social and economic implications [Ponikowski et al., 2016]. The number of subjects diagnosed with HF in the USA increased from about 5.7 million between 2009-2012 to about 6.5 million between 2011-2014. Much more important, it is estimated that the number of people living with HF in the USA will increase by 46% from 2012 to 2030 [Benjamin et al., 2017]. Thus, it is being emphasized the value of interfering with the progress of heart failure, the influence of a timely diagnosis, and the impact of prompt therapeutic intervention.

In the past decades, research has focused on novel biomarkers' clinical utility in diagnosing HF, stratifying the risk, and guiding therapy [Sarhene et al, 2019]. It is estimated that biomarker-guided HF care can lead to a 20-30% mortality reduction compared to standard treatment [Troughton et al., 2014].

The natriuretic peptides are the most exhaustively investigated and used biomarkers in HF, particularly useful in evaluating the prognosis and ruling out the diagnosis, both in the acute and chronic setting [Nadar et al., 2019]. According to both American and European guidelines is recommended to measure natriuretic peptides in all subjects with HF (class I, level of evidence A) [Yancy et al., 2013; Ponikowski et al., 2016].

The plasmatic release of B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) is directly related to myocardial stretch, and these two biomarkers act by down-regulating the sympathetic system, promoting diuresis, lowering peripheral vascular resistance, and enhancing smooth muscle relaxation. Baseline increased levels of BNP and NT-proBNP in 3346 asymptomatic subjects of the Framingham OffSpring study anticipated the risk of adverse cardiovascular events, including HF [Wang et al., 2004]. Importantly, natriuretic peptides guided HF therapy did not improve clinical outcomes, but serial assessments of BNP and NT-proBNP levels can help decide between ambulatory or in-hospital medical care [Berezin, 2018].

Nevertheless, other biomarkers' role, such as troponin, soluble suppression of tumorigenesis-2 (sST2), and galectin-3, has been considered by recent guidelines updates.

Increased levels of high-sensitivity troponin (hsTn) were noticed in patients with chronic and acute HF, even in the absence of coronary artery disease. Several studies have highlighted that an elevated concentration of hsTn is an independent indicator of poor outcomes in HF [Ibrahim, Januzzi, 2009].

In an analysis conducted by Parissis et al. on 113 subjects with acute decompensated HF, high concentrations of hs-TnT were an independent predictor of death, even after adjusting for age, gender, and ejection fraction, and creatinine levels [Parissis et al., 2013]. Additionally, in the ADHERE-HF registry, almost 6.2% of subjects with acute decompensated HF with high concentrations of hsTn were subsequently linked to adverse in-hospital mortality [Peacock, 2008; Sarhene et al., 2019].

sST2 is an IL-1 receptor class member and a well-known marker of inflammation, hemodynamic stress, and cardiomyocyte strain. sST2 inhibits the antifibrotic and antihypertrophic effects of IL-33. sST2 has not a diagnostic, but rather a predictive value, in chronic and acute HF, being a powerful tool in grading disease severity and stratifying the risk. Data from the PRIDE study have shown that subjects with higher sST2 levels are more likely to die within one year [Januzzi et al., 2007; Sarhene et al., 2019].

Galectin-3 is released by activated macrophages and mediates myocardial fibrosis and cardiac remodeling. As depicted by different studies, plasmatic levels of Galectin-3 are considerably greater in subjects with HF, augment proportionally with the NYHA functional class, correlate negatively with left ventricular ejection fraction and with cardiac chambers dimensions [Chen et al., 2013; Paul, Harshaw-Ellis, 2019].

Except for natriuretic peptides, cardiac troponins, galectin-3, and sST2, myriads of other biomarkers have been linked to HF pathogenesis, treatment, and prognosis. All these biomarkers can be further classified as follows:

- Neurohumoral activation biomarkers – adrenomedullin, urocortin-1, arginine vasopressin;
- Oxidative stress biomarkers – myeloperoxidase;
- Biomarkers of myocardial stretch – BNP, NT-proBNP, atrial natriuretic peptide (ANP);
- Mediators of inflammation and fibrosis – TNFα, IL-6, sST2, Galectin-3, PTX3;
- Biomarkers of myocyte injury and apoptosis – hsTn;
- Markers indicative of extracellular matrix remodeling – C-terminal propeptide and C-terminal telopeptide of type 1 collagen, N-terminal peptide of procollagen type III, matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs);
- Renal function biomarkers – cystatin C, β-trace protein (BTP), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), *N*-acetyl-(D)-glucosaminidase;
- Markers of malnutrition and inflammation – albumin and transthyretin [Correale et al., 2015].

Circulating adiponectin has emerged as a novel biomarker in HF, with undetermined function. It is mainly produced in the adipose tissue, but it can be released from the cardiomyocytes as well. Animal studies have proven a cardioprotective effect of adiponectin, which acts by reducing the extent of myocardial hypertrophy and the burden of interstitial collagen by suppressing apoptosis and oxidative stress. Despite these beneficial actions in acute settings, evidence has pointed that increased circulating adiponectin levels over time promotes cardiac remodeling and progression to HF. Furthermore, adiponectin seems to have a better diagnostic value for patients with acute heart failure and renal insufficiency, to be a prognostic factor and a therapeutic target in HF [Dai et al., 2018; Pourafkari et al., 2019].

TNFα, IL-1 and IL-6 are commonly known, useful biomarkers in HF. Rauchhaus et al. performed a study on 152 subjects with chronic HF and demonstrated that high concentrations of TNFα and IL-6 are independent risk factors of mortality, even after adjustments for conventional risk factors [Rauchhaus et al., 2000; Ibrahim, Januzzi, 2018].

In patients with acute myocardial infarction (AMI), elevated levels of IL-6 act upon stimulating liver production of C-reactive protein (CRP), exerting anti-apoptotic effects and therefore limiting the infarct size [Hage et al. 2017]. Nevertheless, elevated levels of IL-6 in acute coronary syndromes are independent predictors of adverse cardiac events, thus antagonizing its effects via pharmacotherapy might be appropriate [Wang et al., 2020].

Most research has focused on the predictive power of cardiac biomarkers in chronic HF, and thus their suitability in acute presentations has yet to be assessed through the aid of observational studies. On these grounds, I aim to conduct a prospective study on patients with AMI treated by percutaneous coronary angioplasty within the Cardiology Clinic of the Institute of Cardiovascular Diseases "Prof. Dr. George I.M. Georgescu", Iasi, Romania that will aim to evaluate the potency of IL-1β, IL-6, TNFα, adiponectin and CRP to predict the development of adverse cardiac remodeling and chronic HF.

During the index hospitalization, an comprehensive cardiovascular evaluation will be performed, focusing however on laboratory investigations and echocardiogram.

Apart from standard laboratory tests, IL-1β, IL-6, TNFα, CRP, and adiponectin will be drawn in all subjects within seven days from the acute presentation.

Echocardiographic measurements will be performed according to the recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging and will mostly include:

- the evaluation of left ventricular systolic function - ejection fraction via biplane Simpson method; mitral annular plane systolic excursion (MAPSE) via M-mode echocardiography; tricuspid annular plane systolic excursion (TAPSE) via M-mode echocardiography; peak myocardial systolic velocity (S') via Tissue Doppler Imaging; global longitudinal strain (GLS) via speckle-tracking echocardiography;
- the left ventricular diastolic function assessment - peak E wave velocity, E/A ratio, tricuspid regurgitant jet velocity, left atrial volume index, and E/e' ratio.

Of note, patients with severe pulmonary hypertension, severe valvular heart disease, and those planned for coronary artery bypass grafting will be excluded from further analysis.

After that, the study participants will be clinically, biologically, and echocardiographically evaluated at three months, six months, 12 months, and two years after the acute event.

The primary objective will be to judge the predictive value of high baseline concentrations of IL-1β, IL-6, TNFα, CRP, and adiponectin into what concerns chronic HF development after an acute AMI.

The secondary objectives will be to evaluate sequential changes in LV size, ejection fraction, and diastolic function and compare the results with those obtained during the index hospitalization; to assess the potency of the above-mentioned biomarkers to anticipate reinfarction; to analyze the prognostic significance of biomarkers versus echocardiography.

III.2.3. Iron deficiency and response to cardiac resynchronization therapy

Based on left ventricular ejection fraction (LVEF), heart failure (HF) can be generally grouped into three major categories: HF with reduced LVEF (LVEF ≤ 40%), HF with mid-range ejection fraction (LVEF 41-49%), HF with preserved LVEF (LVEF ≥ 50%) [Murphy et al., 2020].

Cardiac device therapy has emerged as a powerful treatment tool in HF with reduced ejection fraction management [Angel et al., 2017]. Implantable cardioverter defibrillators (ICD), used for either primary or secondary prevention, are of tremendous benefit in those at high risk of sudden cardiac death. Cardiac resynchronization therapy (CRT) or biventricular pacing is recommended in symptomatic HF subjects, despite three months of optimal medical treatment with severely impaired LVEF ≤ 35% and QRS duration ≥ 120 msec [Breitenstein, Steffel, 2019]. Its major advantage mainly consists of an improvement in biventricular simultaneous contractility that further leads to reduced QRS duration and increased LVEF.

Despite proven benefits, both ICD and CRT therapies persist in being under-exploited. Importantly, not all individuals respond to CRT, highlighting, therefore, the need for a proper selection. Patients with wide QRS complex (>150 milliseconds), with left bundle-branch block morphology (LBBB) and normal sinus rhythm, seems to benefit the most. Nevertheless, evidence has shown that a favorable therapeutic response can also be attained in subjects with a QRS duration of 120 – 149 milliseconds or non-LBBB morphology, one the ground of other conditions such as LVEF, HF etiology, and NYHA functional class [Yancy et al., 2013].

Research has lately focused on the amount of LV remodeling on CRT clinical outcomes. LV remodeling is characterized by changes in the normal elliptical LV architecture, with increased volumes, determined at a microscopical level by cardiomyocytes hypertrophy, apoptosis, and enhanced interstitial fibrosis [Konstam et al., 2011]. LV remodeling not only promotes HF progression, but it also represents an independent prognostic factor. Adverse cardiac remodeling may result from numerous heart muscle disease, but it is strongly related to myocardial infarction.

Classically, it was considered that LV remodeling is associated with a poor prognosis. However, Shamoun et al. retrospectively analyzed the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart failure) trial data in order to assess if the extent of LV remodeling influences all-cause mortality and heart-failure hospitalization rate. Larger left ventricular end-diastolic diameters were significantly linked to a reduction in all-cause mortality in those assigned to device therapy versus standard medical treatment [Shamoun et al., 2019].

Advances in medical and device therapy have led to the advent of a relatively new concept, namely reverse remodeling, which traduces a decrease in LV volumes and an improvement in systolic function [Waring, Litwin, 2016].

It is estimated that the incidence of LV reverse remodeling among subjects with HF with reduced ejection fraction varies from 26-46%. Duration of HF, demographics, comorbid medical conditions, and the implemented type of treatment are independent predictors of reverse remodeling. Besides, subjects with nonischemic cardiomyopathies, such as tachycardiomyopathy, ethanolic cardiomyopathy, peripartum cardiomyopathy, and drug-induced cardiomyopathy, are more prone to reverse remodeling [Aimo et al., 2019].

A variety of treatment methods can determine a decrease in LV volumes and mass, recovery of regular LV geometry, and enhancement of LV ejection fraction, including CRT, which has been shown to reduce mortality and morbidity by favoring LV reverse remodeling [Kim et al., 2018]. By fostering LV reverse remodeling, CRT decreases the burden of ventricular arrhythmias and the risk of sudden cardiac death afferent to heart failure [Galand et al, 2019].

According to the CARE-HF study results (Cardiac Resynchronization in Heart Failure), CRT determines persistent LV reverse remodeling, with the most pronounced effects seen within 3-9 months [Ghio et al., 2009]. In the MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy), CRT-D subjects with LBBB and complete left-sided reverse remodeling, defined as concordant reverse remodeling of the LV and the left atrium, had a considerable lower risk of HF and death, HF alone and death alone on the long-term follow up when compared to patients with discordant reverse remodeling [Mathias et

al., 2016]. Of note, CRT-D has no proven benefit, and, on the contrary, it may even be unsafe in individuals without LBBB [Naqvi et al., 2019].

As stated by van der Bijl et al., LV reverse remodeling can be defined by either a reduction of ≥ 15% in LV end-systolic volume (LVESV) or a ≥ 5% absolute improvement in LV global longitudinal strain (GLS) [van der Bijl] et al., 2019]. Consistent with the PREDICT-CRT trial results, the presence of apical rocking and septal flash before the implementation of CRT is associated with lower all-cause mortality. Also, it has an incremental prognostic value [Stankovic et al., 2016].

The MARC (Markers and Response to CRT) study was primarily designed to identify CRT response predictive markers. It prospectively studied the ability of 11 clinical elements, 11 electrocardiographic criteria, four echocardiographic parameters, and 16 humoral biomarkers to predict therapeutic response post-CRT. Two hundred forty patients were enrolled in the study. In the univariate analysis, only 17 parameters were significantly associated with LVESV reduction. These findings led to the development of the CAVIAR score, which estimates the rate of reverse remodeling after CRT and therefore improves patient selection [Maass et al., 2018].

Emerging data indicate that iron deficiency negatively impacts CRT efficacy and that iron substitution might enhance LV contractility in subjects with incomplete LV reverse remodeling following CRT [Lacour et al., 2020; Martens et al., 2019]. Additionally, it has been emphasized that serially persistent reductions in natriuretic peptides concentrations are related to the extent of LV reverse remodeling [Aimo et al., 2019].

However, the magnitude of LV reverse remodeling and brain natriuretic peptides levels reduction at one year after CRT has not been evaluated in subjects with baseline iron deficiency that benefit from proper iron repletion.

Thereby, I intend to conduct a single-center, prospective, interventional study on subjects with HF with reduced ejection fraction treated by CRT within the Cardiology Clinic of the Institute of Cardiovascular Diseases „Prof. Dr. George I.M Georgescu" Iasi, Romania. Subjects fulfilling the criteria for CRT, but also with concomitant iron deficiency and elevated concentrations of brain natriuretic peptides will represent the study group. In the control group will be recruited the candidates to CRT, with high concentrations of natriuretic peptides, but with normal ranges of serum iron.

Therefore, during the index hospitalization, all subjects enrolled in the analysis will be assessed for iron levels, B-type natriuretic peptide (BNP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

The echocardiographic assessment of the study population will mainly consist of the:

- evaluation of LV ejection fraction and volumes;
- assessment of atrioventricular dyssynchrony – the ratio between diastolic filling time and RR interval duration;
- evaluation of interventricular dyssynchrony – the difference between left ventricular and right ventricular pre-ejection time;

- appraisal of intraventricular dyssynchrony – septal to posterior wall motion delay in M-mode echocardiography;
- the presence of apical rocking and septal flash;
- assessment of GLS with speckle tracking echocardiography.

Candidates for CRT, in sinus rhythm, will be implanted in the Electrophysiology Laboratory of Institute of Cardiovascular Diseases „Prof. Dr. George I.M Georgescu" Iasi, Romania. Iron substitution therapy will be initiated during the same visit. Subjects will benefit of clinical, biological, and echocardiographic evaluation at one month, three months, six months, and one year after implantation. At each site visit, serum iron will be evaluated and patients will be treated until normalization. The reduction in the BNP and NT-proBNP will be judged at every presentation the site.

Transthoracic echocardiography will pursue the appreciation of the number of CRT responders. Response to CRT will be defined as a reduction in LVESV ≥ 15%, and/or an increase in LVEF ≥ 5%, and/or an improvement in GLS ≥ 5%.

The study's main objective will be to compare if proper iron substitution therapy significantly improves the rate of CRT responders and leads to comparable results to those noticed in the control group.

The second objective of the study will be to assess the impact of iron repletion on BNP levels, heart failure hospitalization rate, and all-cause mortality.

III.3. Final remarks

In my opinion, no matter how many qualities you have as a researcher, you will never succeed if you do not understand what teamwork means, if you do not respect others activity, if you are not able to subordinate your personal goals to the general ones. Moreover, beyond work, study, dedication, competence, and personal ambition, a career is also built upon teamwork skills, when the desire of individual affirmation and constructive competition is intertwining with collaboration and common belonging.

This habilitation thesis presents my professional, academic and scientific achievements during the postdoctoral period (2012-2020) and few of the projects I have for future development on professional, academic/teaching and scientific fields. Attaining the habilitation certificate would represent an important step for my academic career, a recognition of my entire activity, an honor and, at the same time, an open door to professional ascent. It will offer me the opportunity to train the young teaching staff of our university, and to promote scientific connections in Romania and abroad.

Last but not least, I feel privileged to be part of the family of the University of Medicine and Pharmacy "Grigore T. Popa" Iasi and the Institute of Cardiovascular Diseases "Prof. George Georgescu ". I hope that my entire future activity will lead not only to personal fulfillment but also will add value to the discipline, department and university of which I am a member.

SECTION IV. REFERENCES

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