UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE
GRIGORE T. POPA IAȘI

FROM ANATOMOCLINICAL REASONING TO MEDICAL AND SURGICAL PRACTICE

Habilitation thesis

CRISTINA FURNICĂ M.D., Ph.D.

Iași, 2020

CONTENTS

ABBREVIATIONS

ACC - aortic cross clamp
AcM - acute marginal
ACo - aortic coarctation
ACS - acute coronary syndrome
AF - atrial fibrillation
AHT - arterial hypertension
AKI - acute kidney injury
AMI - acute myocardial infarction
AP – aorto-pulmonary
ASD – atrial septal defect
AUC - area under the curve
AVSD – atrioventricular septal defect
BA - Broadman area
BT – Blalock-Taussig
CABG - coronary artery bypass grafting
CAD - coronary artery disease
CCTA - coronary computed tomography angiography
CHD – congenital heart diseases
CKD - chronic kidney disease
COPD - chronic obstructive pulmonary disease
CPR - curved planar reconstructions
CVD - cardiovascular disease
CX - circumflex artery
DILV – double inlet left ventricle
DM - Diabetes mellitus
DORV – double outlet right ventricle
DSM - Diagnostic and Statistical Manual
DTI - diffusion tensor imaging
DWMH - deep white matter hyperintensities
ECC - extracorporeal circulation
HLHS – hypoplastic left heart syndrome
IABP - intra-aortic balloon pump
ICD – International Classification of Diseases
ICU - intensive care unit
ITA - internal thoracic artery
IVC – inferior vena cava
LA - left atrium
LAA - left atrial appendage
LAD - left anterior descending artery
LITA - left internal thoracic artery
LV – left ventricle
LVEF - left ventricular ejection fraction
MACE - major adverse cardiovascular events
MDCT - Multidetector Computed Tomography
MO - marginal oblique
MRI - magnetic resonance imaging
MV – mitral valve
MVD - multivascular disease
MVD - multivascular disease
OR - odds ratio

OV - oblique vein
PA – pulmonary artery
PAPVR (partially anomalous pulmonary venous retur
PDA – patent ductus arteriosus
PDA - posterior descending artery
PeWMH - periventricular white matter hyperintensities
PFO – patent foramen ovale
PV – pulmonary valve
PV - pulmonary vein
RA - radial artery
RA – right atrium
RCA - right coronary artery
RFCA - radiofrequency catheter ablation
RITA - right internal thoracic artery
ROC - receiver operating characteristic
RV – right ventricle
RVOT – right ventricular outflow tract
SR - sinus rhythm
SVB - saphenous vein bridge
SVC – superior vena cava
SVG - saphenous vein graft
TAR - total arterial revascularisation
TGA – transposition of great arteries,
TOF – tetralogy of Fallot
TV – tricuspid valve
VR - volume rendering
VSD – ventricular septal defect
WHO - World Health Organization
WMH - white matter hyperintensities

REZUMAT

Sintagma *teză de abilitare* rezumă sincretic firul Ariadnei desfășurat prin labirintul unei cariere mature, multivalente, ajunse la apogeu. Dincolo de planuri, obiective, evaluări sau analize, medicina este un demers vocațional, unic și irepetabil.

Prezenta teză de abilitare prezintă parcursul meu profesional, rezultatul principalelor cercetări desfășurate în perioada postdoctorală (după 2003), precum și proiectele de viitor pe linie academică, didactică și profesională medicală, direcții intricate, indisolubile, care se vor aduna timpului ce va să vină.

Teza este structurată în manieră clasică, în concordanță cu indicațiile Consiliul Naţional de Atestare a Titlurilor, Diplomelor și Certificatelor Universitare.

Lucrarea debutează prin prezentarea a două rezumate, în limba română și engleză, urmate de punctarea realizărilor ştiinţifice şi profesionale şi a planurilor de evoluţie şi dezvoltare a carierei, pe toate cele patru paliere: academic, de cercetare științifică, didactic și medical.

Prima parte a lucrării detaliază *realizările ştiinţifice şi profesionale din perioada postdoctorală*. Cronologic, sunt menționate reperele profesionale, realizările științifice și publicațiile rezultate (articole și cărți) precum și proiectele de cercetare sau formare în care am fost implicată în calitate de membru sau coordonator.

Dintre acestea, menționez proiectul de suflet, „***100 de inimi pentru 100 de copiii***” care a vizat tratarea copiilor cu malformații cardiace congenitale și formarea de specialiști în domeniu, proiect pe care intenționez să îl continui și extind în viitorul apropiat cu formarea unei rețele multinaționale de îngrijire cardiovasculară.

În continuitatea aceleiași secvențe sunt prezentate rezultatele activității de cercetare, structurate pe trei direcții majore: *Neuroanatomia – bază a psihiatriei, Bazele anatomice și embriologice ale terapiilor cardiovasculare* și *Bazele anatomice ale practicii medicale ginecologice, neurologice și medico-legale.*

Capitolul *Neuroanatomia – bază a psihiatriei* relevă una din preocupările mele majore și constante care rezidă din tripla formare, anatomist, medic psihiatru și medic legist.

În opinia mea, anomaliile morfologice și funcționale ale structurilor cerebrale reprezintă substratul majorității afecțiunilor psihiatrice și se pot constitui în potențiale ținte terapeutice doar secundar înțelegerii evoluției substratului morfologic.

În acest capitol sunt rezumate studii de cercetare derulate pe parcursul anilor, complementare prin rezultatele obținute, și care vizează identificarea unei corelații între leziunile substanței albe cerebrale, exprimate imagistic prin hiperintensități T2 pe imaginile de rezonanță magnetică, variațiile de grosime a scoarței în diferite arii corticale și ideația suicidară caracteristică tulburărilor bipolare și/sau sindroamelor de tip schizoid. Rezultatele obținute certifică substratul alterărilor morfologice survenite în contextul acestor patologii și se constituie în premize pentru o cercetare ulterioară detaliată în domeniu, așa cum se descrie ulterior, în capitolul privind perspectivele de cercetare științifică.

Capitolul următor, *Bazele anatomice și embriologice ale terapiilor cardiovasculare*, este rezultat al unei colaborări durabile între Disciplina de Anatomie și colectivul Institutului de Boli Cardiovasculare „Prof. Dr. George I.M. Georgescu” din Iași.

Împreună cu membrii acestui colectiv electiv de cercetare medicală am derulat o serie de studii privind analiza substratului morfologic al leziunilor cardiovasculare și a modalității

efective prin care recreerea anatomiei normale și respectarea principiilor anatomice asigură succesul și durabilitatea manevrelor diagnostice și terapeutice cardiovasculare, intervenționale sau chirurgicale.

Seria de studii științifice desfășurate împreună cu membrii colectivului Institutului de Boli Cardiovasculare din Iași a debutat cu analiza aplicării abordării morfologice secvențiale în diagnosticul malformațiilor cardiace congenitale, în concordanță cu etapele dezvoltării cordului, urmată de studiul implicării anomaliilor anatomice ale atriului stâng, auriculului stâng și venelor pulmonare în geneza și recidiva fibrilației atriale.

Ulterior, membrii colectivului de cercetare s-au aplecat asupra studiul eficienței recreerii geometriei rădăcinii aortei în tratarea durabilă a dilatației de aortă ascendentă și regurgitării valvulare, fără a recurge la protezare.

O altă direcție de cercetare a vizat analiza semnificației și impactului prognostic al morfologiei arterelor coronare, leziunilor coronariene și bypass-urilor aorto-coronariene în severitatea bolii cardiace ischemice și evoluția pe termen mediu și lung a pacienților cu bypass aorto-coronarian.

Ultimul studiu a evaluat în premieră mondială de altfel, valoarea prognostică a factorilor morfologici (tipul, lungimea și calibrul graftului), fiziopatologici (fluxul competitiv, modificările degenerative de la nivelul graftului) și chirurgicali (tip de anastomoză, unghi de anastomoză) asupra permeabilității pe termen lung a grafturilor și, implicit, a pacienților care au beneficiat de bypass aorto-coronarian.

Caracterul de noutate și importanța studiului au fost apreciate de comunitatea științifică internațională, articolele ISI și lucrările derivate din cercetare făcând obiectul a numeroase citări și invitații spre a susține prelegeri pe acest subiect primite de membrii grupului de cercetare.

Capitolul *Baze anatomice ale practicii medicale* prezintă rezultatele studiilor de anatomie clinică în domenii medicale conexe respectiv ginecologie, neurologie și medicină legală.

Cele 2 studii de anatomie clinică ginecologică analizează modificările anatomiei loco-regionale decelate în cazul endometriozei și chistadenofibroamelor tubare prin metode imagistice moderne, rezonanța magnetică și ecografia tridimensională.

Un alt studiu vizează traiectul intracranian al nervului trigemen cu identificarea situsurilor potențiale și a mecanismelor de compresie folosind imagistica prin rezonanță magnetică, iar cel de al 4-lea studiu analizează modificările asociate patologiilor psihiatrice pornind de la un caz clinic.

Ultima parte a tezei rezumă *planurile de cercetare științifică viitoare*, strâns intricate celor educaționale, academice și profesionale și care vizează constituirea unei Rețele multinaționale de diagnostic și tratament a copiilor cu malformații cardiace congenitale și Studiul îmbătrânirii normale a creierului uman din punct de vedere morfologic și funcțional prin utilizarea drept metodă de investigare a imagisticii prin rezonanță magnetică.

Teza se încheie cu detalierea referințelor bibliografice aferente studiilor prezentate și sumarizarea idelor prin o serie de concluzii.

SUMMARY

The very object represented by the habilitation thesis is somehow an Ariadna's thread that must be woven and unwind in the labyrinth of one's research. It is both the present and the future of an already mature academic career as the postulant must prove the success of prior research, but also the prospects and future proposals.

Medical profession has been my vocation, beyond personal plans, objectives and analyses. I consider myself lucky as I have always known that Medicine is both in my heart and soul.

Tackling the drafting of such a document is not easy. Classically, a researcher can be attached to a single disciplinary field if successive choices and opportunities have not decided otherwise. The current thesis is a transversal and multidisciplinary reflection over a single dominant, *knowledge*, acquiring and sharing, a continuous process with multiple "human" variables – students, fellows, patients.

The thesis presents, briefly and synthetically, my professional career, the result of the main researches carried out during the postdoctoral period (after 2003) as well as my future plans from an academicals, didactical and medical perspective, three strictly intricate directions that cannot be dissociated from each other.

The thesis is structured in a classical manner in accordance with the indications of the National Council for the Certification of Titles, Diplomas and University Certificates. Thus, the thesis begins with the presentation of the two summaries, in Romanian and English, followed by the main scientific and professional achievements and career development plans.

The first part details the scientific and professional achievements of the postdoctoral period and includes as an introductory part a brief overview of the professional path pointing out the main elements that marked my career from an academic, medical and scientific point of view.

Thus, there are mentioned in a chronological order the main research studies, the books and articles resulting from it, as well as the projects in which I was involved as a member or coordinator.

Of these, I mention my soul project, "100 hearts for 100 children" which aimed at treating children with congenital heart diseases and training specialists in the field, a project that I intend to continue and expand in the near future with the formation of a multinational cardiovascular care network.

Later, within the same part, are presented the results of the research activity structured in 3 major directions, *Neuroanatomical basis of psychiatry*, *Developmental and anatomical basis of cardiovascular therapies* and A*natomical basis in different clinical approaches.*

The chapter *Neuroanatomical basis of psychiatry*, reveals one of my major and constant concerns that resides in my triple formation as an anatomist, psychiatrist and forensic pathologist. Thus, I consider that the morphological and functional abnormalities of the brain represent the substrate of many psychiatric disorders and may represent potential therapeutic targets after a thorough understanding.

In this chapter I present the results of 2 studies that complement each other and aim to identify a correlation between the occurrence of cerebral white matter lesions, translated by T2 hyper intensities on the magnetic resonance images; cortical thickness variations in different

areas and the suicidal ideation that occurs in bipolar disorders and schizophrenia. The results demonstrate the existence of this correlation and represent the premises for further research detailed in the future perspectives chapter.

The next chapter, *Developmental and anatomical basis of cardiovascular therapies*, is the result of a multidisciplinary collaboration between the Anatomy Discipline and the team of the "Prof. Dr. George I.M. Georgescu" Cardiovascular Diseases Institute from Iași.

Together with this team, we started a series of studies that aimed at analysing the morphological substrate of cardiovascular lesions and how recreating the normal anatomy and respecting anatomical principles ensures the success and the sustainability of cardiovascular therapeutic manoeuvres.

The series of studies began with the analysis of the application of the sequential morphological approach in the diagnosis of congenital heart diseases in accordance with the normal stages of heart development and was followed by the study of the involvement of the anatomical abnormalities of the left atrium, left auricle and pulmonary veins in the genesis and recurrence of atrial fibrillation; the study of the efficiency of recreating the normal geometry of the aortic root in the treatment of ascending aortic dilatation and valvular regurgitation without replacing the valve; and analysis of the significance and prognostic impact of the morphology of coronary arteries, coronary lesions and aorto-coronary bypasses in the severity of ischemic heart disease and the long-term prognosis of patients with coronary artery bypass grafts.

The last study represented a world premiere and evaluated the prognostic impact of morphological (type, length and size of the graft), pathophysiological (competitive flow, degenerative changes of the graft) and surgical factors (type of anastomosis, angle of anastomosis) on the long-term patency of coronary grafts and, implicitly, on the prognosis (life expectancy and quality of life) of patients who benefited from coronary artery bypass grafting.

The novelty and importance of the study were appreciated by the international scientific community, ISI articles and papers derived from research being the subject of numerous citations and invitations to give lectures on this topic.

Another chapter, A*natomical basis in different clinical approaches* presents the results of a series of clinical anatomy studies in connected medical domains like gynaecology, neurology and legal medicine.

The 2 studies in clinical gynecologic anatomy analyse the changes of local and regional anatomy in case of endometriosis and cystadenofibromas of the uterine tube through modern medical imaging methods like magnetic resonance and 3D ultrasound.

Another study investigates the intracranial course of the trigeminal nerve and identifies the potential locations and compression mechanisms using magnetic resonance imaging and the 4th study analyses the changes associated with psychiatric pathologies starting from a clinical case.

The last part of the thesis presents the future research plans strictly correlated to the previously established educational, academic and professional directions and aiming to form a multinational congenital cardiac care network and study the normal aging process of the human brain from a morphological and functional point of view by using magnetic resonance imaging.

The thesis ends with the detailed bibliographic references related to the presented studies and conclusions.

SECTION I. ACADEMIC, PROFESSIONAL AND SCIENTIFIC ACHIEVEMENTS

PERSONAL BACKGROUND

The very object represented by the habilitation thesis is somehow an Ariadna's thread that must be woven and unwind in the labyrinth of one's research. It is both the present and the future of an already mature academic career as the postulant must prove the success of prior research but also the prospects and future proposals. It is equally a paradox, dilemma or sophism of the ***Menon*** of Plato, as the researcher must know or not know what he wants to find, "*one thing I am ready to fight for as long as I can, in word and act—that is, that we shall be better, braver, and more active men if we believe it right to look for what we don't know than if we believe there is no point in looking because what we don't know we can never discover*".

Tackling the drafting of a habilitation thesis is not easy. Classically, a researcher can be attached to a single disciplinary field if successive choices and opportunities have not decided otherwise.

The current paper is a transversal and multidisciplinary reflection over a single dominant, *knowledge through research*, acquiring and sharing, a continuous process with multiple "*human*" variables – students, fellows, patients. As Associate Professor of Anatomy at the "*Grigore T. Popa*" University of Medicine and Pharmacy from Iasi, forensic pathologist and psychiatrist I have been interested in creating a bridge between anatomy and clinical practice by finding a morphological substrate of various diseases.

Professional activity

The professional career started as general practitioner 25 years ago, being followed by training in surgery, forensic pathology and psychiatry under the supervision of elites in the field. Professional expertise was steadily acquired through continuous education in connected domains such as criminalistics (master's degree), addictology, professional liability, psychiatric medico-legal expertise and management skills in mental services.

Functional neuroanatomy, a constant topic of the research activity, is strictly interrelated to the professional interest, thus ensuring a double formation in forensic pathology and psychiatry.

Research activity

The postdoctoral research activity focused on 2 major domains of morphofunctional sciences: neuroanatomy and anatomy of the cardiovascular system, namely their applications in daily medical and surgical practice. This activity resulted in several textbooks and original papers in collaboration with experts in the field. The interest in neuroanatomy was stimulated by a one-year internship at the Universita degli Studi di Torino in 2004 and continued with a series of studies analysing the morphological substrate of psychiatric diseases such as bipolar disorders and schizophrenia.

Considering that cardiovascular morphology holds the answer to effective surgical repair of various diseases, together with the team of the "Prof. Dr. George I.M. Georgescu" Cardiovascular Diseases Institute, we performed several studies regarding the impact of morphological factors on long term coronary artery bypass grafts, the surgical restoration of aortic root geometry for treating aortic valve regurgitation and morphological correction of

congenital heart defects. The research activities resulted in drafting 16 ISI articles as main author and 7 ISI articles as co-author together with 28 articles in indexed journals. The studies have also been disseminated through over 65 papers presented at scientific meetings as participant or guest lecturer. The novelty of the research was appreciated by the scientific international community; the articles being cited 51 times which resulted in a Hirsch index of 6. In the same time, there was coordinated the editing of 5 textbooks and wrote, together or in collaboration with other authors, 9 books including 3 manuals for students.

The scientific activity was directed towards a morphological, surgical, forensic and neuropsychiatric perspective, considering that modern medicine evolves paradigmatically towards multidisciplinarity. In our opinion, a unilateral approach, from a single perspective, morphological or clinical, is not licit as it does not correspond to the requirements and tendencies of modern medicine inclining towards a holistic clinical, diagnostic and therapeutic approach for a general improvement of the quality of life and stable results on the mid and long term. Coordinating the research activity of the project „*Morphoanatomical and Pathophysiological Aspects of Coronary Artery Bypass Grafting in Terms of Long-Term Outcome (CABOT)*" (internal grant of "Grigore T. Popa" University of Medicine and Pharmacy) was a step towards improving the efficiency of aorto-coronary bypass grafting by adjusting the surgical strategy according to the anatomical and clinical profile of the individual patient. The results have been disseminated through 2 articles published in ISI journals from abroad, a world premiere as the study was the first to analyse morphological pathophysiological and surgical factors conditioning long-term graft patency.

Academic activity

The academic career started in 1999 with the admission as Assistant Professor of Anatomy under the guidance of world-class anatomists such as professor Ion Petrovanu, professor Dan Stefan Antohe, professor Mircea Chiriac, professor Mircea Zamfir and associate professor Horatiu Varlam, mentors to whom it is owed the anatomical knowledge and teaching abilities acquired during long training years. Gradually all the stages of the academic career have been completed. Under the guidance of mentors, the expertise was extended from practical training of first and second-year students of the Romanian programme to trilingual seminars and lectures. Once the English programme was initiated, I participated to curriculum elaboration, gave lectures and coordinated practical training, a circumstance that would repeat after almost 9 years with the French programme. Formation activity covered various areas and educational levels, from undergraduates to postgraduates and included extracurricular practices such as coordinating the "***Andreas Vesalius***" Anatomy Circle and students' research.

As an expert for organizing practical training and planning surgical interventions I was responsible for the formation of specialists in paediatric cardiology for a quality medical act with the purpose of improving the quality of life within the project "*100 hearts for 100 children*". The project was appreciated and awarded a special prize by the European Union and managed to transcend the goals originally set by starting an efficient programme for screening, diagnosis and treatment of children suffering from congenital heart diseases.

As a result of this project, there was formed a group of specialists capable of providing complete medical care, at European standards, to these children, a group that currently operates at the Cardiovascular Institute from Iasi. I also participated as expert for remedial courses in the project "*Learning center – support mechanism for students at risk*" carried out by the "*Grigore T. Popa*" University of Medicine and Pharmacy. The project aimed to facilitate the study of anatomy for students that encounter difficulties in passing their anatomy exam. Given the current qualification as forensic pathologist, we participate in coordinating the training of forensic autopsy technicians, the first educational programme of this type in Romania. Medicine, in all its forms, is the purpose of my life, the current medical practice completing this triangle together with the academic and research activity.

CHAPTER 1. NEUROANATOMICAL BASIS OF PSYCHIATRY

1.1. Introduction

Affective instability, neurovegetative disorders, impulsivity and psychotic productions are the main symptoms associated with schizophrenia and bipolar disorder and pleads for an organic or functional dysfunction of the anterior limbic system (amygdala, hippocampus and fronto-striato-thalamic circuits) involved in the control of cognitive and emotional processes. During centuries of medical history, all we knew about the brain was its gross anatomy; concerning psychiatric disorders, our knowledge was limited to symptoms. Modern medical imaging techniques such as magnetic resonance imaging (MRI) provided remarkable insights into the brain's normal and pathological functioning. Every year we gain new knowledge on the functional neuroanatomy and neurobiology of psychiatric disorders. Due to this line, psychiatry defines a medical specialty subjected to continuous and inevitable remodelling. Nowadays, psychiatric disorders are conceptualized and treated differently than 10 and 20 years ago due to the new concepts in understanding of the underlying mechanisms.

In this chapter, there will be reviewed the state of art on the neuroanatomical substrate of psychiatric disorders and our contribution to the field.

The prefrontal cortex has been particularly debated in psychiatric research because of its involvement in the regulation of the expression of emotional states. Recent studies revealed a decrease in grey matter volume in the upper and middle parts of the left hemisphere significantly associated with the duration of the disease. Similar changes were identified in the middle and lower parts of the right hemisphere, mostly in the inferior frontal gyrus (BA 47) and the precentral gyrus (BA 44), which could be associated with the number of manic episodes. Increases in volume and density of the grey matter have also been reported in the left insular and frontoparietal cortex. As for white matter volume, it has been found to be either identical to that of healthy subjects or locally decreased in the right frontal region. Disorganization of white matter bundles, particularly affecting the Brodmann areas 9 and 10 as well as the superior longitudinal and fronto-occipital fasciculi, has also been reported by studies using diffusion tensor imaging (DTI) (136,149)**.**

The cingulate cortex has been incriminated in bipolar disorders, as it plays a major role in regulating cognitive and emotional processes. The Broadman areas that compose it (24, 25 and 33) are closely interconnected with other regions involved in the regulation of emotions, such as amygdala, insula, thalamus, periaqueductal grey matter and orbitofrontal cortex. In bipolar disorders, the volume of the cingulate cortex was reported to be decreased in the subgenual portion of both hemispheres, particularly in patients with familial aggregates. In addition, a decrease in volume of the left anterior cingulate cortex has been signalled in untreated patients compared to patients treated with lithium, who registered no such anomaly. It would appear that the decrease of grey matter density in this region is associated with an unfavourable outcome (115).

The temporal lobe, especially the superior gyrus, plays a major role in all language associated processes. Early MRI studies showed bilateral atrophy of the temporal cortex in bipolar patients, later found to be restricted to the left hemisphere. More recently (28), a volume increase of the right temporal lobe has been found, more specifically of the right superior temporal gyrus.

The hippocampus, along with the amygdala, the orbitofrontal cortex and the cingulate cortex, are part of the Papez neuronal circuit involved in information processing and in memory,

particularly declarative and emotional one. Most studies report no significant hippocampal volume abnormality in bipolar patients. Nevertheless, Velakoulis (263) indicates a global volume decrease of the hippocampus during a first psychotic episode. *During our research we analysed a patient with early onset schizophrenia and noted hippocampal atrophy*.

The amygdala receives afferences from the frontal and temporal lobes, plays a major role in generating responses to emotional stimuli and is responsible for projections to the limbic areas, particularly the hippocampus, the entorinal cortex, the thalamus and the neocortex. Its enlargement has been frequently observed in bipolar disorder and, according to some authors, this volume increase is correlated with the number of manic episodes. However, other studies have reported a decrease in volume. Chen et al. (58) have shown a correlation between the increase in amygdala volume and age.

Basal ganglia are connected to the cortex and the limbic system through two parallel circuits, the integrity of which conditioning the regulation of mood and affect. Several studies report no significant difference in the volume of these structures between bipolar patients and control groups. Nevertheless, a bilateral volume increase of the striatum has been observed (106) simultaneously in adolescent bipolar patients and during the first manic episode.

The thalamus is a relay structure between cortical and subcortical regions essential for coordination of both cognitive and motor processes. The size of thalamic nuclei is usually similar in bipolar patients and normal subjects, but an increase in thalamic grey matter density has been reported in female patients (56).

In addition to its involvement in motor, vestibular and ocular activity, the cerebellum plays an elective role in the integration of cognitive processes and the regulation of mood. There are two main pathways connecting this structure with the rest of the brain: the one that connects the red nucleus of the mesencephalon to the associative cortical areas, and the cerebello-thalamic tract, which establishes a connection with associative areas, both cortical and limbic and, in particular, with the dorsolateral and medial prefrontal cortex, the anterior cingulate cortex and the posterior hypothalamus. A volume reduction of the cerebellar vermis has been reported in bipolar patients, particularly in those with many manic episodes. In addition, a similar decrease of the volume of cerebellar hemispheres and vermis has been demonstrated in patients presenting a familial form of bipolar disorder (115).

DTI allows mapping of nervous tissue microstructure and describes its organization *in vivo*. It offers the possibility of detecting and quantifying white matter abnormalities otherwise not visible in conventional imaging. Diffusion tensor imaging is based on the random displacement of water molecules in all directions that can be quantified by a "*diffusion coefficient*" expressing motion amplitude. At cerebral level, this displacement is dependent on the organization of tissues and cellular elements, such as the axons. This technique makes it possible to visualize the direction of white matter tracts and offers functional data in addition to the morphological one. Abnormalities in axonal orientation, particularly in case of the connections between the frontal cortex, the striatum and the corpus callosum have been detected in bipolar patients. Using this technique, Haznedar et al. (117) observed alterations in the fasciculi of the internal capsule adjacent to the striatum and thalamus and mainly in the orbitofrontal cortex.

White matter hyper intensities signalled on MRI images are typical for unequal and diffuse changes of the cerebral white matter and indicative of various disorders such as dilatation and demyelination of perivascular spaces, possibly consecutive to cerebral ischemia and oedema or to impaired cerebrospinal fluid circulation.

Several studies (8,92) on bipolar disorders signal a higher prevalence of white matter hyper intensities (WMH) in bipolar patients (22-46%) than in healthy subjects (0-22%) a finding that was not confirmed by all authors and *was the subject of a personal study in patients with suicidal behaviour*. It appears that WMH observed in bipolar patients are related to the

severity and duration of the disorder.

Schizophrenia, one of the most devastating mental disorders, is characterised by intrusive voices (auditory hallucinations) that may determine the patient to form false beliefs (delusions) which could trigger a perceptual anomaly of the reality towards manifest suicidal behaviour. Several researches (149,271) focus on identifying the signs that could predict the early onset of the disease while others tried to establish a connection between brain regional functional and morphological anomalies, and the positive or negative outcome of this still enigmatic disease.

Studies worldwide (209) tried to identify a neurobiological and biochemical basis of suicidality, and recent researches showed an association between the presence of WMH, neuronal biochemical anomalies, suicidal ideation and suicidal attempts. WMH are classically divided into periventricular (PeWMH) and deep white matter hyper intensities (DWMH) and indicate myelin pallor, mild gliosis and tissue rarefaction. Several clinical features in depression such as anxiety, panic disorders, sleep disturbances, poor concentration, drug addiction seem to be linked to suicide, being highly associated with early death within one year of initial assessment.

My interest in this field is reflected by the following published papers and books:

Articles:

1. **Furnica C**, Chistol RO, Leon Constantin MM, Perianu L, Rusu AC, Alexa AI, Tinica G. Biochemical correlates of MRI white matter hyperintensities. Rev. Chim (Bucharest) 2016; 67 (6): 1210-1213.

Books:

1. **Furnica C**, Varlam H, Minea R, Antohe DSt. Peripheral Nervous System: The Cranial Nerves. Junimea Publishing House, Iași, 2011.

1.2. Aims

In my opinion the many psychiatric disorders have an organic substrate, morphological and functional changes being frequently encountered. One of the main directions of my research activity consisted in identifying the subjacent anomalies associated with bipolar disorders and schizophrenia. Given the potentially fatal outcome of suicidal ideation occurring in patients diagnosed with these diseases, together with my team we performed a study that aimed to investigate and quantify potential cerebral anomalies in these patients using magnetic resonance imaging (MRI), a potential screening method for recognizing those at risk of committing suicide.

1.3. Materials and methods

Between April 2010-october 2012 we performed a cohort retrospective study at the University Psychiatric Hospital “Socola” from Iasi, Romania.

The sample population consisted of two groups defined as follows:

- Group 1–40 psychiatric patients (21 males, 19 females), aged 18-51 years, with a history of suicidal attempt who underwent cerebral MRI after the suicidal attempt;
- Group 2 - 45 psychiatric patients (24 males, 21 females), aged between 18-55 years, without a declarative suicidal ideation who underwent cerebral MRI after the psychiatric examination.

Inclusion and exclusion criteria are listed in table I.

Table I. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
-age ≥ 18 years; -informed consent for inclusion in the study; -MRI examination images in DICOM format; -available blood test results; -DSM IV diagnosis of major affective disorder (unipolar major depressive disorder, bipolar disorders type 1 and 2); -previous suicidal attempt for inclusion in group 1; -no history of psychiatric disorders for inclusion in group 2.	-other neurological or psychiatric disorders; - history of head trauma; -different degrees of mental retardation; -congenital anomalies; -MRI contraindications.

The psychiatric diagnosis was established by a psychiatrist blind to the results of the MRI examination or blood tests. Magnetic resonance imaging examinations were performed in various medical imaging departments from public or private services located in different towns from the region of Moldavia. All examinations contained axial and sagittal FLAIR sequences, axial and coronal T2 sequences, axial T1 sequences pre and post-Gadolinium injection and were provided in DICOM format by the patient and re-analysed by the same radiologist with no knowledge of the written result provided by the originator medical imaging department.

The presence of WMH was evaluated according to the Fazekas scale and graded 0 to 3 (0 – absence of WMH, 1 - multiple punctate WMH, 2 - beginning confluency of WMH, 3 - large confluent WMH) for both periventricular and deep white matter hyperintensities (92).

Blood samples were collected from all patients and were tested for the lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), total proteins and fractions, complete blood count (CBC), and platelet serotonin level (spectrofluorimetric method).

Chi-squared test, Student t-test, and logistic regression were applied in order to estimate the association between suicidal attempts, suicidal ideation, white matter hyperintensities and blood parameters.

The hippocampus and amygdala were delineated on the magnified 3D coronal post-contrast T1 sequence according to the Joint EADC-ADNI Harmonized Protocol (http://www.hippocampal-protocol.net/SOPs/LINK_PAGE/Groups_Protocol/convit-protocol.pdf). Hippocampal and amygdalian areas were added and multiplied by section thickness in order to calculate their volume (Fig. 1).

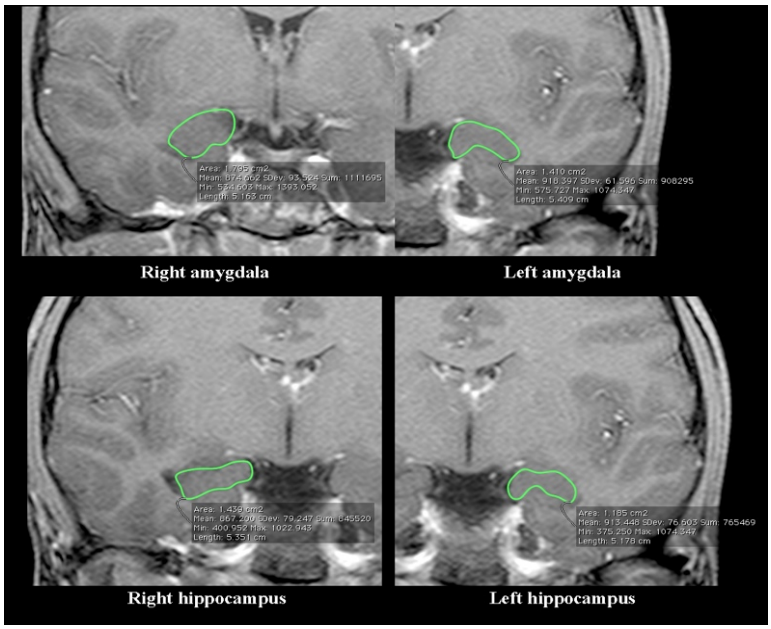


Fig. 1. Area measurements for amygdala and hippocampus (personal data)

1.4. Results

The demographic and clinical features of the study groups are listed in table II.

Table II. Sociodemographic and clinical characteristics of the study groups

Variable	Group 1	Group 2	Significance
Sex (M)	52.5	53.33	n.a.
Age	42.4	39.5	0.01
Addictive behaviour (%)	5	4.44	0.003
Comorbidities (cancer, heart diseases, diabetes) (%)	7.5	6.67	0.002

Most patients (22 cases) in group 1 were diagnosed with type I bipolar disorder (55%) compared to group 2 patients who mainly had a major depressive disorder (57.78%) (Table III).

Table III. Psychiatric diagnosis in studied groups

	Group 1	Group 2
Type I bipolar disorder	22 (55%)	20 (44.44%)
Type II bipolar disorder	11 (27.5%)	23 (51.11%)
Major depressive disorder	15 (37.5%)	26 (57.78%)

The prevalence of both DWMH and PeWMH was significantly higher in group 1, compared to group 2 (Chi-squared $p = 0.02$ and respectively 0.007) (Table IV).

Table IV. Incidence of WMH in the studied groups and according to pathology

	DWMH	PeWMH
Group 1	18 (45%)	16 (40%)
Group 2	15 (33.33%)	13 (28.89%)
Type I bipolar disorder	15 (35.72%)	14 (33.33%)
Type II bipolar disorder	9 (26.47%)	7 (20.59%)
Major depressive disorder	9 (21.95%)	8 (19.51%)

Analysis of the incidence of WMH according to the clinical diagnosis revealed a higher prevalence of DWMH and PeWMH in type I bipolar disorder (chi-squared $p = 0.01$) and no statistically significant difference between patients diagnosed with type II bipolar disorder and major depressive disorder.

Concerning the particular forms of WMH, one patient from group 1 and one patient from group 2 had type 3 DWMH and PeWMH. For the usual forms, there was no significant difference between the prevalence of type 1 and type 2 DWMH and PeWMH between the two groups (Table V).

Table V. Distribution of white matter hyperintensities according to Fazekas scale

	Group 1	Group 2
DWMH 0	22 (55%)	30 (66.67%)
DWMH 1	10 (25%)	9 (20%)
DWMH 2	7 (17.5%)	5 (11.11%)
DWMH 3	1 (2.5%)	1 (2.22%)
PeWMH 0	24 (60%)	32 (71.11%)
PeWMH 1	9 (22.5%)	8 (17.78%)
PeWMH 2	6 (15%)	5 (11.11%)
PeWMH 3	1 (2.5%)	0

Deep WMH mostly involved the frontal and parietal lobes compared to PeWMH frequently located in the *corona radiata* and trigonal areas with no significant differences between the two groups (Table VI).

Table VI. Location of white matter hyperintensities

	Group 1	Group 2
Location of DWMH		
Frontal	9	8
Parietal	5	4
Temporal	2	2
Occipital	2	1
Location of PeWMH		
Corona radiata	6	5
Trigonal area	8	7
Other	2	1

The correlation between suicidal behaviour and WMH was tested using logistic regression. Both PeWMH and DWMH proved a significant association with suicidal attempts and suicidal ideation after controlling for age, comorbidities and addictive behaviour ($p = 0.002$ for PeWMH and $p = 0.001$ for DWMH).

As for blood test results, patients with suicidal attempts of both sexes registered significantly lower concentrations of cholesterol and platelet serotonin compared to the general population (Table VII).

Table VII. Blood samples results in the study groups

	Group 1		Group 2		p
	Females	Males	Females	Males	
Total cholesterol (mg/dL)	153±41.7	167±53.2	182±27.5	185±30.2	<0.001
Erythrocytes (x10^6/µL)	4.17±0.92	4.27±0.73	4.78±0.65	4.63±0.50	<0.001
Total proteins (g/dL)	6.61±0.85	7.02±0.61	6.87±0.76	6.75±0.77	0.311
Platelet serotonin (nmol/platelet)	4.5±0.7	4.5±0.8	5.1±0.5	4.9±0.4	<0.001

Cholesterol value <165 mg/dL, platelet serotonin <4.5 nmol/platelet, and the presence of WMH increased by 1.81 times the risk of suicide among psychiatric patients (95% CI 0.97-3.37, p=0.02) as quantified at multivariate analysis.

While including cases in the study group, an 18 years old male with early-onset schizophrenia was addressed to the hospital with suicidal ideation. The subject was adopted at the age of 4 years without any knowledge about his biological family medical history and had good scholar performances and normal social adaptive skills until 6 months before onset of symptoms, when his adoptive parents noticed a change of mood, defined as a so called "bad behaviour" with significant decline in school performance. One month prior to diagnosis, the young man attempted suicide by narcotics overdose. His parents found him unconscious and called the national emergency number. He was taken to the emergency room and fully recovered with specific toxicological treatment. Afterwards, he was addressed to Socola Psychiatry Hospital for further psychiatric investigation of this suicidal attempt. At the initial psychiatric interview, the young man confessed having sleep disturbances and auditory mystic hallucinations in the past 6 months. He gradually withdrew himself from social life, with a variation in affect and increasing hostility towards his family (fixation, aversion that announced an ambivalent period of state). During this time, his parents noticed a change of character with

pronounced desire of isolation and bizarre behaviour.

During the psychiatric interview the patient emphasized non-emphatically that for the last 6 months he had been presenting mood disturbances (sadness, etc.), self-depreciation, loneliness, unhappiness; feelings of persecution occurring daily, mainly during daytime, with a loss of interest in almost all activities without a declared suicidal intention.

Teachers complained to the parents about his attitude regarding school, accusing poor concentration and attention, poor motivation and daydreaming. Being questioned by his parents concerning his attitude, the patient described vague complaints of headaches, stomach-aches, for which the family physician could not identify any probable cause.

At the interview, the patient appeared hypo mimic, had a poor eye contact, showed flatness of affect, lack of insight, apathy, slowness of thought and action. According to DSM-IV criteria, the patient was diagnosed with a first episode of schizoid psychosis. Treatment with antipsychotic drugs was started and cognitive behavioural therapy was indicated, the patient being discharged with a good symptomatic evolution.

Due to the recurrence of headaches, the parents addressed him to a neurologist who indicated a brain MRI in order to exclude subjacent organic anomalies before prescribing a symptomatic treatment.

The superior temporal gyrus (STG) was traced on the 3D coronal post-contrast T1 sequence in a craniocaudal plane from the first slice where it was visible to the central fissure. The superior temporal sulcus represented the inferior border, and the circular sulcus the medial border. Volume of the superior temporal gyrus was calculated using the same method as for the hippocampus.

The obtained results were compared to the measurements performed on a subgroup of 14 patients extracted from the main control group, aged 19-25 years (Table VIII).

Table VIII. Measurements of investigated structures in normal individuals compared to our patient

(LH – left hippocampus, RH – right hippocampus, LA – left amygdala, RA – right amygdala, LSTG – left superior temporal gyrus, RSTG – right superior temporal gyrus)

	LH	RH	LA	RA	LSTG	RSTG
Normal individuals	3175 mm3	3427 mm3	1123 mm3	1135 mm3	23811 mm3	24382 mm3
Our patient	2863 mm3	3272 mm3	915 mm3	1183mm3	21185 mm3	24236 mm3

Results of image analysis revealed a left-right asymmetry of superior temporal gyrus, hippocampus and amygdala, with a visible loss of volume on the left side later confirmed by morphometric measurements.

1.5. Discussions

A number of studies performed in the past two decades (8,56) stated that WMH are more frequently encountered in patients with bipolar disorders compared to control subjects. Pompili (209) reported them to be strongly associated with suicidal attempts. Our literature review identified only a few comparisons concerning the presence of WMH and biochemical anomalies between patients with bipolar disorders and suicidal attempt and the ones with no suicidal attempt or ideation. The results of the current study demonstrate that patients with attempted suicide presented a lower cholesterol level.

Deisenhammer et al. (72) reported no relationship between serum cholesterol and the course of depression, but the research did not include a suicide group. Other researchers like Law et al. (160) and Boston et al. (43) stated that low cholesterol is rather a result of reduced appetite and low body weight in depressed individuals and could not demonstrate the causality relation between it and attempted suicide. Kunugi et al. (152) found that low levels of

cholesterol in patients with suicidal attempt are not associated with physiological status (malnutrition).

Patients with suicide attempts associated with low tryptophan levels and diminished serotonin synthesis exhibit impulsive and aggressive behaviour. According to Alvarez (11), reduced platelet serotonin level is the consequence of a decreased uptake mechanism secondary to receptor up-regulation. Also, low cholesterol levels could result in diminished central serotonergic transmission. Our study proves that patients with suicidal ideation or suicidal attempt register a high incidence of WMH (60% cumulated frequency), especially Fazekas type 1 and 2 lesions (Fig. 2).

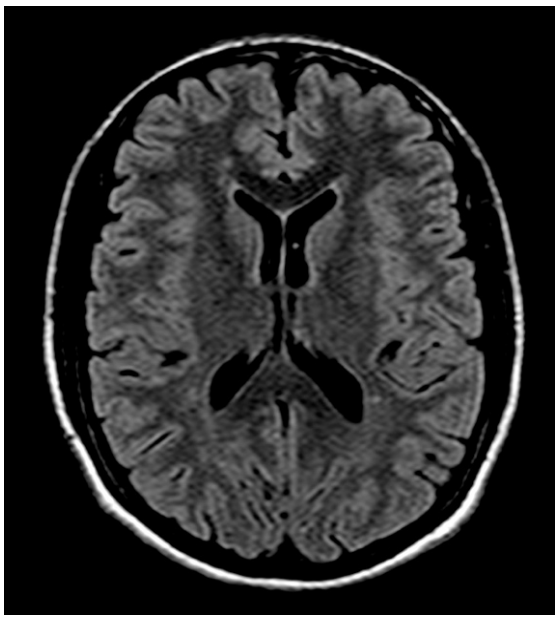


Fig. 2. Type 2 bipolar disorder and grade 1 Fazekas DWMH and PeWMH in a 30 years old female patient (personal data)

We observed no significant difference concerning the location of WMH between the two study groups, but given the small number of patients, the current results are inconsistent.

Pompili et al. (209) concluded in a study performed in 2008 that PeWMH are more likely associated with a history of suicidal attempt, but logistic regression performed in our research after controlling for age, comorbidities and addictive behaviour, showed that both PeWMH and DWMH are significantly associated with suicidal attempts and ideation.

In the current study we did not include patients older than 55 years to reduce the vascular aetiology of WMH after taking into account the hypothesis of "*vascular depression*" as it was proposed by Alexopoulos et al. (9) who suggested that cerebrovascular disease generated WMH and can trigger a secondary depression by affecting white matter pathways involved in mood regulation.

Several studies (85) described the association of WMH and suicidal behaviour but the mechanism predisposing patients with WMH at a high suicidal risk has not been elucidated. Taylor et al. (244) hypothesised that WMH disrupt anatomical pathways involved in mood regulation such as superior longitudinal fasciculus and fronto-occipital fasciculus, critical in cognitive control. These disruptions involve key areas responsible for mood regulation, which include frontal cortex, amygdala-hippocampus complex, thalamus, basal ganglia. Biological alterations combined with mood regulation anomalies and environmental stressors could trigger a suicidal behaviour (81). Anatomically, these regions are interconnected by associative fibres that form the three subdivisions of the superior longitudinal fasciculus. In the frontal lobe, superior longitudinal fasciculus I fibres project to the supplementary motor area and dorsal

Brodmann's areas 6 and 9 and convey information from these areas back to the parietal lobe cortices and probably into the precuneus. Superior longitudinal fasciculus II connections end in Brodmann's areas 6, 8, 9/46, and 44, and superior longitudinal fasciculus III fibers end in ventral Brodmann's areas 6 and 44 (149).

The right extreme capsule is another critical region, lesions in this region leading to an interruption of the dorsolateral prefrontal circuit, responsible for connections between the basal ganglia and dorsolateral prefrontal cortex grey matter. This circuit projects from Brodmann's area 9/46 to the dorsolateral caudate, then to the lateral medio-dorsal *globus pallidus* and rostro-lateral *substantia nigra* (149). The basal ganglia afferentates forwards the ventral anterior and medio-dorsal thalamus and backwards, the dorsolateral prefrontal cortex (136).

Lesions of the uncinate fasciculus interrupt amygdala connections and have important implications in disorders of emotion processing. White matter hyper intensities located in the inferior longitudinal fasciculus adjacent to the para hippocampal gyrus are associated with interruption of connections between V4 in the occipital cortex and the medial temporal structures, amygdala, hippocampus, and para hippocampus. Amygdala has neuromodulatory effects on the extrastriate visual cortex. In suicidal behaviour the affective valence signals could be abnormally transmitted (28,52). The mechanism for this interaction is unclear and could be subject to further investigation.

Our results plead for the regional specificities in patients with affective disorders, if the lesions occur in critical cortical regions for executive and emotional processing. We consider important to anatomically localize the lesions involved in cognitive impairment in order to optimize the psychiatric diagnosis. According to several studies (96,263), patients with suicidal attempts register morphological changes in the prefrontal dorso-lateral and in the orbitofrontal cortical areas. The prefrontal cortex is involved in attention deficits and cognitive dysfunctions while orbito-frontal cortex is involved in depressed mood, hopelessness, inefficient thinking, preoccupation with death, delusions of guilt or worthlessness, loss of self-esteem.

Orbito-frontal cortex anomalies reflect a dysfunction of the serotoninergic system highly associated with vulnerability to suicide act, slightly increased by the association with basal affective disorders (47,106).

MRI studies (106) of people suffering from schizophrenia reveal the following morphological changes of brain structures: increased lateral ventricular volume, a slight decrease in cortical volume (2%) with greater decrements (5%) in hippocampus, amygdala and thalamus and widening of sulci reflecting a reduction of cortical tissue especially in the frontal and temporal lobe.

Prodromal signs that include social isolation and withdrawal, impairment in role function, odd behaviour in ideas, and blunted affect often precede the first psychotic episode of schizophrenia. Patients with ventricular enlargement, even if it is not specific for this disease, present a history of prominent prodromal period with poor social functioning before the onset of psychotic symptoms, suggesting the early onset of schizophrenia, thus being also our subject case (12,91).

The symptoms of the non-psychotic period are defined as residual or negative symptoms because they reflect the absence of normal social and interpersonal function and include social withdrawal, loss of motivation and initiative, apathy, slowness of thought and action, poverty of cognitive process and speech, emotional blunting. These symptoms, in clear contrast with the abnormalities of a psychotic episode are named positive symptoms, because they reflect the presence of distinctive behaviours such as delusions, hallucinations and markedly bizarre or disorganized behaviour. Due to their persistence, the negative symptoms represent the most unmanageable part of the illness, partly being identified in the current case presentation.

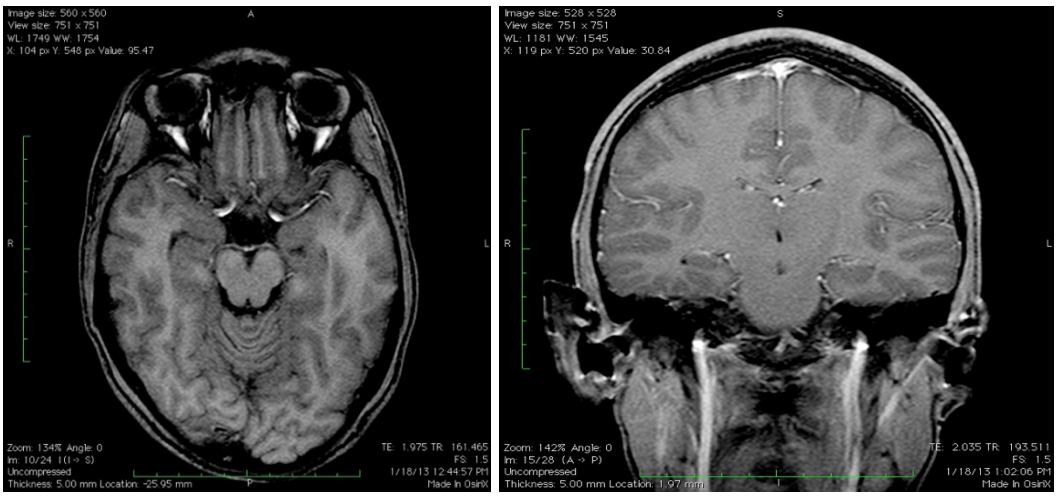
Whole reduction of temporal lobe, especially of the superior temporal gyrus, is a constant MRI volumetric finding in consulted studies (106) being strongly correlated with

positive symptoms and with logical memory impairment. Associations between superior temporal gyrus deficit and auditory hallucinations were reported by Barta and Flaum (28,96). The left superior temporal gyrus of our patient had a volume of 21185 mm^3 compared to 23811 mm^3 in normal patients.

Morphological changings in temporal region are currently reported most frequently on the left side and strictly related with negative symptoms. Superior temporal gyrus contains Broadmann areas 41 and 42, the location of primary auditory cortex where the main auditory pathway project and Wernicke's and Broadmann 22p areas are responsible for integrating the speech process in order to understand the language. The left temporal superior gyrus is responsible for the comprehension of language and social cognition.

Velakoulis et al. (263) compared the volumes of hippocampus and amygdala, and revealed that first episode schizophrenia patient showed left sided hippocampal volume reduction, while those at risk for psychosis had normal hippocampal and amygdala volumes. In the presented case it might be identified a visible asymmetry of hippocampus and amygdala, with a left hippocampal/amygdalian volume of 2863/915 mm3, compared to 3175/1123 mm^3 in normal subjects.

Several functional imaging studies documented the association of early onset of schizophrenia with disruptive pattern and stimulation of the limbic network (Fig. 3). Thus, it clearly appears that some changes demonstrated by functional imaging may predate the onset of schizophrenia itself. Cahn et al. (47) established that grey matter volume decreases in the first year of illness in patients with first episode of schizophrenia, being significantly correlated with the outcome.



a **b**

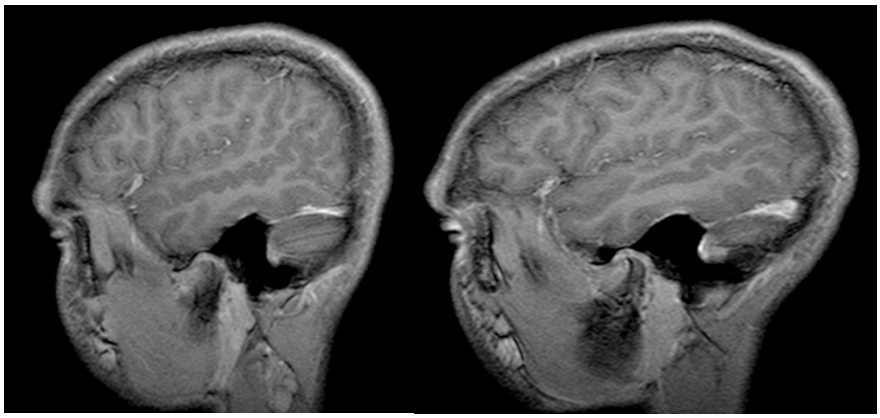
Fig. 3. Visible left-right asymmetry of hippocampus, amygdala (a) and superior temporal gyrus (b) (personal data)

Analysing the current case, we emphasize that psychiatric diagnosis must rely heavily in our days on individual patient's history, on the patient's response to treatment and on finding some reliable criteria (neurobiological, genetic, neuroimaging, etc.) that may predict the outcome of the disease. These limitations have made it difficult in the past to achieve a consensus in the evaluation of psychiatric symptoms, to investigate scientifically psychiatric illnesses and their evolution.

As it is stated in the clinic psychiatry, the evolution of an early onset of schizophrenia is unfavourable as a severe indicative of the illness and because the younger patient has no enough time to build up social and occupational skills in order to aid his rehabilitation. The morphological changes identified in our patient such as a reduced volume of the left superior

temporal gyrus, left hippocampus and left amygdala, together with the antecedents that suggest high vulnerability of the subject during his interactions with the environment, strongly emphasize a negative outcome of this first psychotic episode. It is rather difficult to identify such neuroimaging criteria in patients with early onset of schizophrenia. On the other side, the earlier and acute the onset of schizophrenia appears, the more obvious the precipitants are, and therefore, greater chances of recovery, chronicity tending to predict chronicity.

Taylor (244) demonstrated that the subjects diagnosed with schizophrenia register an elevated risk of premature death due to suicide, as it is the case of our subject, particularly when the suicidal intention develops during the early phase of illness, increasing the risk of mortality and morbidity. The functional maturational changes of the brain during adolescence may increase the disturbances before the symptomatic phase of the illness begins (Fig. 4).



a. **b.**

Fig. 4. Superior temporal gyrus asymmetry in sagittal plane (a – right, b-left) (personal data)

Children destined to develop schizophrenia often present neurobiological development delays with deficits in motor and cognitive functions of the brain. Several studies (81) suggested that there is a high correlation between a premorbid personality and unfavourable outcome.

Actually, suicide is a complex, multi-phase behaviour, and researches are trying to define an explanatory neurobiological model of suicidal behaviour, in order to understand the phenomena, to identify truly high-risk groups and to facilitate development of appropriate treatments. Suicidal behaviour is very changeable from individual to individual and, in our opinion, it is an end-point of a process in which subject's consciousness is balanced between inner disorders and environmental factors, a concept that underlies a vulnerability made up by neurochemical and physiological traits.

The etiopathogenesis of schizophrenia remains unclear and we believe that new modern research designs that include neuroimaging techniques in their protocol might aid in the definition of the limits and understanding of schizophrenia, for which we still consider nowadays the treatment and diagnostic tools to be inadequate. Brain imaging techniques have an important impact on the study of schizophrenia by providing clear evidence of congenital morphological anomalies. In our opinion, a multidisciplinary approach in mental disease may allow a better understanding of their etiopathogenesis and evolution, in order to find most appropriate tools of diagnosis and medical approach.

1.6. Conclusions

The presence of morphological brain alterations and biochemical blood anomalies are strong predictors of future potential suicidal attempt in psychiatric patients. Developing functional imaging studies raised the possibility that early morphological identification of brain changes might enable the prediction of the first episode and the evolution of a future schizophrenic status.

CHAPTER 2. DEVELOPMENTAL AND ANATOMICAL BASIS OF CARDIOVASCULAR INTERVENTIONS

Nature holds the keys for effective medical and surgical correction of cardiovascular anomalies, either congenital or acquired. In order to achieve satisfactory and stable long-term results, the surgeon must recreate normal anatomy or simulate normal structures. Surgical corrections, anastomoses and prosthetic devices that fail to respect nature's law are doomed to failure.

One of our major research projects consisted in analysing morphological and morphometrical factors with prognostic impact in cardiovascular surgery.

Together with my collaborators from "*Prof. Dr. George I.M. Georgescu*" Cardiovascular Diseases Institute, we investigated the impact of cardiac and coronary arteries morphology on the choice of therapeutic procedure and long-term outcome in case of congenital heart diseases (CHD), atrial fibrillation, ascending aorta dilation and coronary arteries disease (CAD).

The endpoint of all these studies consisted in optimising the surgical technique in order to offer patients a normal life expectancy and quality of life according to their age.

2.1. Cardiac morphology in congenital heart diseases

2.1.1. Introduction

Congenital heart diseases (CHD) are the most frequent birth defect occurring in 8.2 per 1,000 live births in Europe (5-10) but studies have shown a higher prevalence rate in premature children (10). They are defined as complex anomalies, often associating extra-cardiac defects, high infantile mortality rate (7 to 26%) and lifetime morbidity for survivors with impact on economy and social life (10,216). Generally, CHD are defined as congruent group of complex pathologies associated with heteromorphic deviations of the cardiac normal development.

To date, the World Health Organization (WHO) identified over 4,000 genetic disorders responsible for more than 44 types of CHD (sporadic and familial forms).

In Romania, approximately 950 children are born with CHD each year and 10-15% require intensive special care in the first month of life (10).

Most children with CHD are diagnosed at birth or during the first two years of life. Sporadic cases are diagnosed later in life secondary to hospital admission for occurring complications.

Diagnosing CHD is simpler nowadays as non-invasive exploration techniques such as echocardiography with Doppler examination, computed tomography (CT) and magnetic resonance imaging (MRI) became widely available.

Therapeutic management has also improved with the emergence of endovascular procedures and minimally invasive techniques. Therefore, the prognosis has significantly improved, and mortality rates decreased by 31% compared to years '80 according to the Canadian Registry (142).

Despite these major improvements, there is still no consensus concerning CHD description and communication dysfunctionalities occur between cardiologists, radiologists, cardiovascular surgeons from different centres and even in the same centre as the used nomenclature is contentious.

My interest in this field is reflected by the following published papers, projects and books:

Articles:
1. **Furnica C,** Chistol RO, Rusu AC, Tinica G. New anatomic and embryologic insights in the surgical approach of congenital heart diseases. Revista Română de Anatomie funcţională şi clinică, macro- şi microscopică şi de Antropologie 2016; XV(2): 167-178.
2. Grigore M, **Furnica C,** Esanu I, Gafitanu D. Pentalogy of Cantrell associated with unilateral anophthalmia (case report and literature review). *Medicine* 2018; 97:31.

Project:
1. Medical formation expert for the project "*100 hearts for 100 children*" (Formation of specialists in pediatric cardiology for a quality medical act with the purpose of improving the quality of life)

Book chapters:
1. **Furnica C**, Rusu AC, Perianu L, Chistol RO. Chapter 3. The anatomy of heart and pericardium in Grigore Tinica ed. congenital heart diseases: principles of diagnosis and treatment. Taida Publishing House, Iasi, 2015.
2. Chistol RO, Tinica G, Anghel D, Rusu AC, **Furnica C**, Gorincour G. Chapter 5. Imaging of congenital heart diseases in Tinica G (ed). Congenital Heart Diseases: Principles of Diagnosis and Treatment. Taida Publishing House, Iasi, 2015.
3. Perianu L, Tinica G, **Furnica C.** Chapter 2. **C**ardiovascular morphogenesis in Tinica G (ed). Congenital Heart Diseases: Principles of Diagnosis and Treatment. Taida Publishing House, Iasi, 2015.

Books:
1. Tinica G, **Furnica C.** The Heart. Clinical and Surgical Anatomy. "Alexandru Ioan Cuza" University Publishing House, 2015.
2. Tinica G, **Furnica C**. The Surgical Anatomy of the Cardiovascular System. "Gr. T. Popa" Publishing House 2017.

2.1.2. Aims

In case of CHD, I consider that the key to an effective treatment are a thorough understanding of the anomaly and a correct and clear diagnosis. Together with the team at the "Prof. Dr. George I.M. Georgescu" Cardiovascular Institute, we decided to perform a study that aimed to systemize CHD description and categorization according to recent developments in cardiac embryology (the segmental approach) and to establish a common communication language between all healthcare professionals involved in diagnosing and treating CHD.

2.1.3. Materials and methods

We performed a retrospective study on a group of 68 patients aged 1 week - 44 years, diagnosed and treated for CHD at the Cardiovascular Diseases Institute (Iasi, Romania) between January 1st – December 31st 2015. Paediatric patients were treated as part of the European project „100 hearts for 100 children".

All 68 patients benefited from complex investigations including echocardiography, cardiac computed tomography angiography (CCTA), and cardiac catheterisation.

In most cases (51 patients - 75%), a surgical or interventional treatment (palliative or corrective) was possible during the same hospitalisation, the rest of 17 cases (25%) benefited from interventional palliation therapy while the surgical treatment was postponed because of inappropriate physical status (malnutrition, infection, other comorbidities).

Perioperative and clinical data was encoded in an Excel database and statistically analysed using SPSS 25.0 for Mac. Medical imaging files were used to illustrate diagnosed

developmental anomalies.

All anomalies were anatomically described using the segmental classification proposed by Van Praagh et al. (260), in order to simplify the nomenclature and facilitate understanding for all the members of the ***Heart Team*** (neonatologist, paediatrician, cardiac surgeon, cardiologist, interventional cardiologist, cardiac electrophysiology specialist, anaesthesiologist, radiologist).

Prior informed consent for data and images usage was obtained in all cases from adult patients or legal caregivers of minor patients.

2.1.4. Results

The 68 patients included in the study presented with the following baseline characteristics (Table IX):

Table IX. Baseline characteristics of CHD patients

Parameter	Number of cases (percentage)
Age (mean)	11,7 ± 11,68 years
Sex ratio M:F	37 : 31 (54%:46%)
Low socioeconomic status	54 (79.41%)
Acyanotic : cyanotic CHD	46:22 (67.65%:32.35%)
CHD part of syndromes	14 (20.59%)
NYHA class (II:III:IV)	14:13:2 (27.45%:25.49%:3.92%)

In 15 cases, CHD were part of syndromes such as Down (6 cases, 8.82%), Noonan (1 case, 1.47%), Di George (4 cases, 5.88%), heterotaxy (2 cases, 2.94%), Williams (1 case, 1.47%).

Most of the 51 patients treated during the study period, associated various CHD complications (Table X).

Table X. Associated cardiovascular complications

Parameter	Number of cases (percentage)
Pulmonary oedema	1 (1.96%)
Atrioventricular block	1 (1.96%)
Right bundle branch block	9 (17.65%)
Pulmonary arterial hypertension	18 (35.29%)
Pulmonary regurgitation	1 (1.96%)
Aortic regurgitation	5 (9.80%)
Mitral regurgitation	3 (5.88%)
Tricuspid regurgitation	4 (7.84%)

The tetralogy of Fallot was the most frequently encountered CHD (13 cases, 19.12%) (Fig. 5).

Of the 68 patients, 38 (55.88%) presented a single anomaly, 23 (33.82%) 2 anomalies, 5 (7.35%) 3 anomalies, and one case (1.47%) had more than 4 anomalies.

In 43 cases (63.24%), *per primam* total surgical correction was possible, 4 patients benefited from secondary correction after a previous surgical palliation (5.88%), 4 cases needed surgical palliation (5.88%) and in 17 cases (25%) surgical or interventional treatment was not possible due to the inappropriate physical status or complex anomalies with no surgical/interventional indication (heterotaxy).

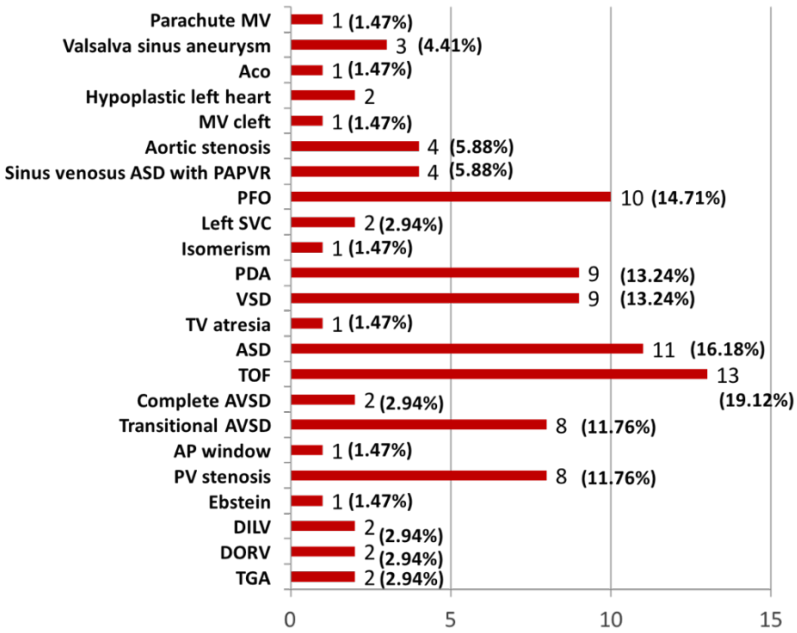


Fig. 5. CHD prevalence in the study group

The surgical procedures performed are detailed in figure 6, most patients (42 cases, 82.35%) benefiting from patch closure of ventricular or atrial septal defects (Fig. 6).

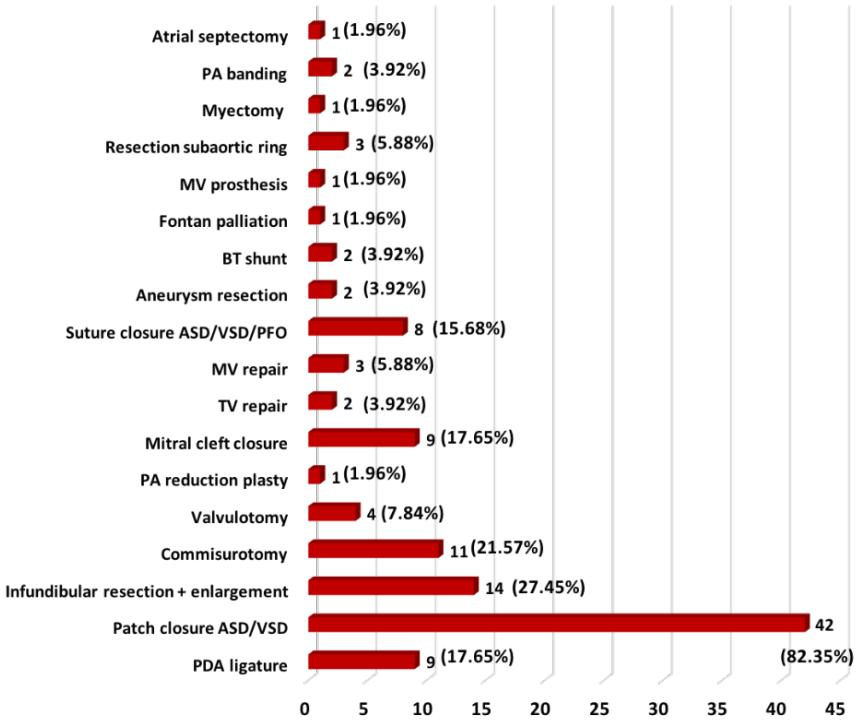


Fig. 6. Surgical procedures performed in the study group

Postoperative complications were registered in only 8 cases (15.69%) and were represented by prolonged thoracic draining in 2 cases (3.92%), postoperative pneumothorax in 2 cases (3.92%), pulmonary complications in one case (1.96%), and important pericardial effusion requiring drainage in another case (1.96%). A single patient (1.96%) developed acute kidney injury and another patient (1.96%) deceased on the 3rd postoperative day because of right ventricular failure. The deceased patient was addressed for the third stage of the Norwood

procedure (Fontan shunt – inferior vena cava – right pulmonary artery anastomosis) for tricuspid atresia as he already benefited from a Blalock-Taussig shunt in the neonatal period and bidirectional Glenn shunt (superior vena cava – right pulmonary artery anastomosis) with pulmonary trunk interruption in early childhood.

A particular case was represented by an *in utero* diagnosis of a severe anomaly, pentalogy of Cantrell, a very rare plurimalformative syndrome that involves 5 different anomalies: a midline supraumbilical wall defect, a diaphragmatic defect, a cleft distal sternum, a defect in the diaphragmatic pericardium, and an intracardiac defect (50). The anomaly was diagnosed in a 14 weeks' foetus of a 42-years-old female who already gave birth to a child with a CHD (pulmonary artery stenosis). Combined abdominal and endovaginal 2D and 3D ultrasound diagnosed a 14 weeks' foetus with a plurimalformative syndrome involving *ectopia cordis* (Fig. 7), large suprambilical anterior abdominal wall defect, omphalocele, anomaly of the shape of the skull, and anomalies of the brain.

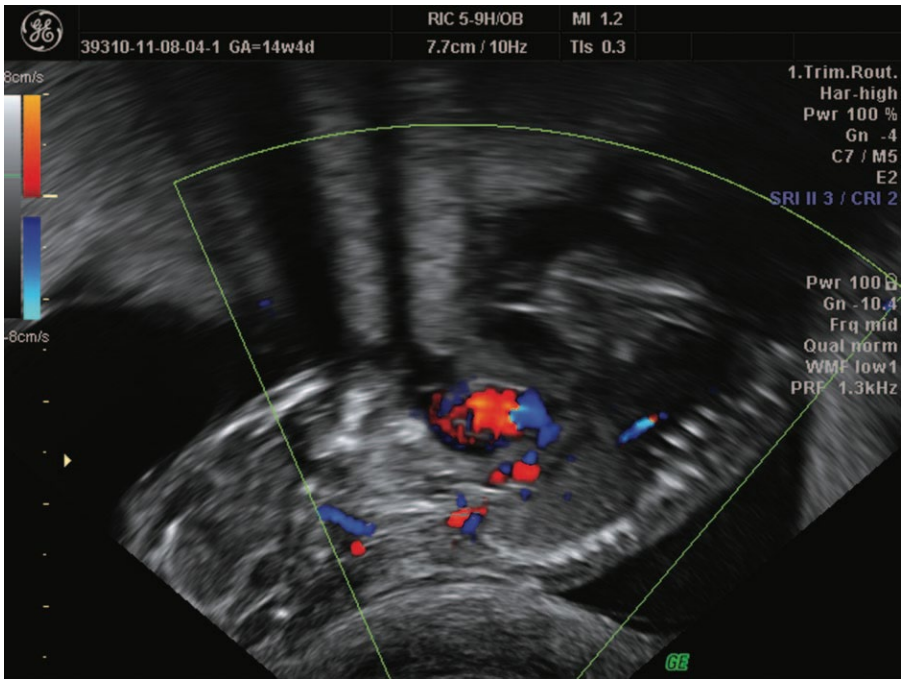


Fig. 7. Ultrasound diagnosis of *ectopia cordis* (personal data)

The diagnosis of pentalogy of Cantrell was established and the parents were advised to interrupt the pregnancy after presenting the potential prognosis of the potential newborn. Therapeutic abortion was performed, and the foetus was submitted for pathological examination that diagnosed an asymmetric head and the pouch of the amniotic membranes near the skull, unilateral anophthalmia a large abdominal wall defect with evisceration of the liver, spleen and most of the gastrointestinal tract. The heart could not be examined given the small size (Fig. 8).

The pentalogy was first described by Cantrell in 1958 (50) and it's incidence was estimated at 5.5 per 1 million live births (51). Generally, the syndrome associates anomalies of the abdominal wall, sternum, diaphragm, pericardium and of the heart. The severity may range from incomplete forms to severe cases like the one presented.

A lack of development of a segment of the lateral mesoderm between days 14-18 was incriminated as a potential cause. The various anomalies associated to this syndrome suggest that multiple factors are involved including teratogens, gene mutation, trisomies 13 and 18, disrupted vessels (59). Only 2 cases reported in the literature were associated with trisomy 18 and they also had other severe anomalies.

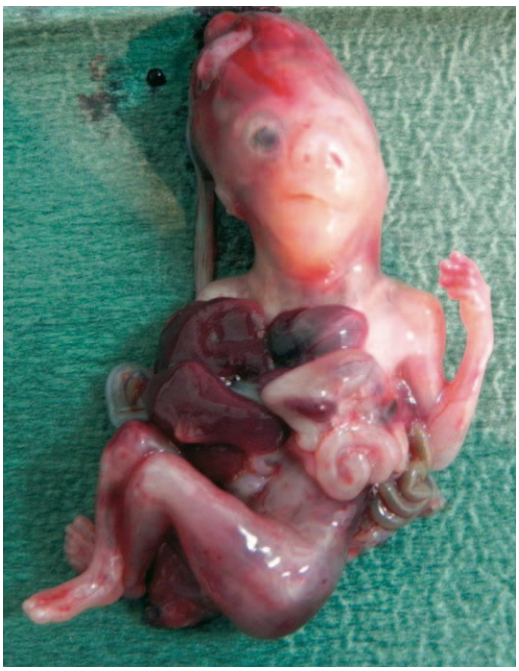


Fig. 8. Macroscopic image of the foetus (personal data)

In our case, the anomaly was severe as it associated the complete absence of the pericardium and diaphragm. Generally, the sternal defect might vary from a notch to agenesis, and abdominal wall defects range from omphalocele to epigastric/umbilical hernia or diastasis recti. Pericardial and diaphragmatic defects are common (37,182).

The particular aspect registered in our case was ectopia cordis, a partial or complete displacement of the heart outside the body. These hearts are usually malformed with ventricular septal defects, atrial septal defects, tetralogy of Fallot, left ventricular diverticulum and hypoplastic left heart. According to Figueroa (94), the most common cardiac anomalies are the double outlet right ventricle and atrial septal defects. Additional anomalies include craniofacial defects, central nervous system anomalies (encephalocele, hydrocephalus, craniorachischisis), imb defects (clubfoot, absence of tibia or radius, hypodactily) abdominal organ defects (gallbladder agenesis and polysplenia), renal anomalies (unilateral kidney evisceration) (20,207,256).

In the presented case, the fetus presented with cranioschisis and unilateral anophthalmia. Along with the asymmetric head a pouch of the amniotic membranes near the skull was present.

Toyama (249) proposed a classification of the anomaly in complete, probable and incomplete depending on the encountered anomalies. The syndrome is considered probable when 4 anomalies are diagnosed in various combinations.

Ultrasound with Doppler examination is very useful in diagnosing the anomaly. The heart was visualised outside the thorax and associated to a giant omphalocele. 3D ultrasound and MRI confirm the diagnosis and provide a complete prenatal view of the anomaly.

Most cases are diagnosed in the 2nd trimester as umbilical hernia is physiologic in the first trimester (110). The prognosis varies and is dictated by the severity of the anomaly. Only a few foetuses survive with a poor quality of life. In complete forms, the prognosis is even poorer with potential *in utero* death.

Ideally, the diagnosis is established *in utero*. An early detection is mandatory to determine prognosis and eventually plan a therapeutic approach. Midline and diapgragmatic defects can be corrected same as several others associated anomalies. In severe cases, early diagnosis allows pregnancy arrest with a reduced psychological effect.

2.1.5. Discussions

Several classifications for CHD have been proposed by various teams over the decades, each with its strengths and pitfalls. The most commonly used is the symptomatic classification (216,245) grouping CHD into cyanotic (right-left shunts) and acyanotic (left-right shunts) which does not contain any morphological information (Table XI).

The symptomatic classification offers no details on the positions of heart chambers and main vessels or the presence of any associated malformations, an essential information for the cardiac surgeon.

In our opinion, an effective CHD classification should fulfil the following criteria's:

- to identify previously unrecognized associations;
- to encode developmental anomalies;
- to link the cause, the mechanism and the final defect;
- to include associated non-cardiac anomalies.

Table XI. Symptomatic classification of CHD (245)

Cyanotic CHD	Acyanotic CHD
Increased pulmonary vascularity	**Increased pulmonary vascularity**
• total anomalous pulmonary venous return (TAPVR) (types I and II)	• ventricular septal defect (VSD)
• transposition of the great arteries	• atrial septal defect (ASD)
• truncus arteriosus	• atrioventricular septal defect (AVSD)
• single ventricle without pulmonary stenosis	• patent ductus arteriosus (PDA)
Decreased pulmonary vascularity	• aortopulmonary window
• tetralogy of Fallot	• ruptured aneurysm of Valsalva
• double outlet right ventricle (DORV) with pulmonary stenosis	• partial anomalous pulmonary venous return (PAPVR)
• single ventricle with pulmonary stenosis	**Normal pulmonary vascularity**
• Ebstein anomaly with atrial septal defect	• aortic valve stenosis
• Uhl anomaly	• aortic coarctation
	• pulmonary stenosis

Derived from the mesoderm, the cardiovascular system of the human embryo develops in the 3rd week of human development, when simple diffusion can no longer meet embryo's nutritional needs. Cardiac development is characterized by a sequence of compartmentalisation and organization of cavities, orifices and great vessels. Cardiovascular development comprises 9 main stages (17,62,66): formation of cardiogenic field; formation and positioning of the heart tube; formation and positioning of the cardiac loop; *sinus venosus* development; pulmonary veins development; atrial septation; ventricular septation; outflow tract septation; valve formation (atrioventricular valves, semilunar valves).

Anomalies may occur in any of these stages and results in CHD. In the early '70s, Richard and Stella Van Praagh, a family of paediatric cardiologists and pathologist from the Children's Hospital Boston, Massachusetts, developed a segmental classification of CHD based on the developmental stages of cardiovascular structures. In 2009, Anderson et al. reviewed their classification and made minor changes to include additional anomalies (258,259,260,14).

The Van Praagh segmental approach (158 is easy to understand, flexible, fast to apply to any diagnostic modality (echocardiography, CCTA, MRI) and particularly useful in the clinical setting as it offers a short encoding of CHD.

In order to encode the CHD, cardiac anatomy must be assessed by dividing the heart into three distinct segments (atria, ventricles and great arteries) based on 10 embryologic regions reunited to define the visceroatrial situs, the ventricular loop orientation and the position of great vessels. These segments are the main building blocks of heart. The morphology and anatomical features specific to each segment are separately evaluated.

Defining the spatial relationships between these blocks at the atrioventricular and ventriculoarterial levels is fundamental for characterising the CHD and any associated anomalies, and for this, the individual segments must be first identified and described.

To encode the identified anomalies into a precise final diagnosis, Van Praagh et al. (158,225) developed a three-part notation system that consists of three letters separated by commas and encompassed by a set of braces. The system succinctly describes the visceroatrial situs, the orientation of the ventricular loop, and the position and relation of the great vessels.

In real life, there is a limited number of possible connections between the three major regions, regardless their spatial orientations. Each region is evaluated independently, following the direction of the blood flow: systemic and pulmonary veins, atria, atrioventricular (AV) valves, ventricles and outflow tracts, semilunar valves and great arteries. Right heart and left heart structures at each level are assessed according to their morphology, relative position, connection to proximal and distal segments, presence and location of shunts and obstruction.

In order to analyse the anomalies, one must correctly identify heart chambers first. "Left" and "right" heart chambers are not defined according to their position but depending on their effective sidedness. Left atrium (LA), left ventricle (LV), right atrium (RA) and right ventricle (RV) have distinctive morphological features easily identifiable with medical imaging (158) (Table XII).

Table XII. Morphological features of heart chambers (158)

Left atrium	**Right atrium**
Tubular appendage with a narrow connection to the chamber Pectinate muscles within the appendage	Flat and triangular appendage with a broad connection to the chamber Pectinate muscle running parallel to the atrium itself and extending outward toward the AV canal Septal surface has superior and inferior limbic bands Myocardial components include the crista terminalis and *tenia sagittalis* Usually receives flow from the coronary sinus, IVC, SVC
Left ventricle	**Right ventricle**
Smooth septal surface Thin, fine trabeculae 2 papillary muscles attached to the free wall only Bicuspid AV valve	Moderator band Coarse trabeculae 3 papillary muscles attached to both the free wall and the interventricular septum Tricuspid AV valve Septal and parietal bands

The morphological evaluation includes several steps:

- **The first step** involves establishing heart's position and visceral sidedness (*visceroatrial situs*). From an embryological perspective, patterning of progenitor heart cells (left or right sided) is concomitant with laterality. Cardiac structures originate by 2 primordia that fuse during development: the RA receives only right-sided cardiogenic area cells and the LA, left-sided cardiogenic area cells. The visceral situs (pattern of asymmetry) is decided at a very early stage of development (62,66).

The visceroatrial situs defines the position of the atria in relation to nearby organs (stomach, liver, spleen, and bronchi) with three possible configurations: the normal *situs solitus* {S,–,–}, *situs inversus* {I,–,–} and *situs ambiguus* {A,–,–}. *Situs ambiguous*, also known as heterotaxy, defines anomalies in the left-right arrangement of the visceral organs and always associates cardiac malformations. The bronchial anatomy, namely the relation between main bronchi and the pulmonary arteries (PAs) is an indicator of the atrial arrangement (19).

In our study group, we encountered a single case of heterotaxy, a patient presenting with left isomerism also known as *polysplenia syndrome* typically reuniting anomalies such as

bilateral left atria, bilateral left lungs (bilobed with hyparterial bronchi), azygos or hemiazygos continuation of the inferior vena cava, midline/transverse liver, multiple splenules without a parent spleen, intestinal malrotation (Fig. 9). The cardiac anomalies associated with polysplenia syndrome are less severe compared to the ones occurring in case of right isomerism. Asplenia syndrome (right isomerism) is characterized by an association of bilateral right lungs (trilobed with eparterial bronchi), absence of the spleen, midline/transverse liver, intestinal malrotation, bilateral right atria and severe cyanotic CHD (19).

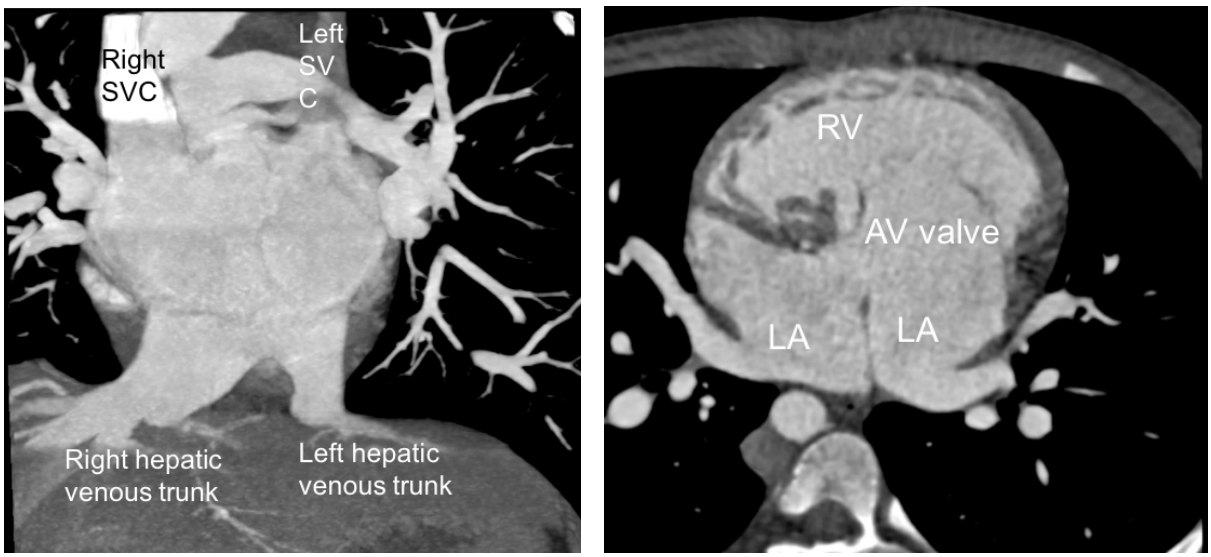


Fig. 9. Patient with left isomerism {A, _,_} and complex CHD characterized by the presence of 2 left atria communicating through a large ASD, bilateral hyparterial bronchi, bilateral bilobed lungs, midline liver draining through 2 suprahepatic venous trunks, 2 superior vena cava, azygos continuation of the inferior vena cava, single atrioventricular valve with an unbalanced flow towards the right ventricle (RV), and polysplenia (IBCV Iasi)

- **The second step** of the segmental evaluation consists in evaluating the ventricular loop. The heart tube grows fast because of continuous cellular migration and multiplication. In order to be accommodated in the limited and inextensible pericardial cavity, it must undergo a series of complex folding, the bulboventricular looping (171). Normally, the cranial part of the loop (*bulbus*) bends anteriorly, caudally and to the right - dextroverted loop (D-loop). The direction of looping defines the relationship between the ventricles (originally situated in series and finally placed side-by-side) and the atrial cavities whose position was determined earlier. The second step is encoded by the second letter of the Van Praagh system {_, D, _} for dextro-loop and {_, L, _} for levo-loop (260). Levo-looping is normal in *situs inversus* and abnormal in *situs solitus*. Congenital heart diseases associated with abnormal looping are the transposition of great arteries and crisscross heart.

In the current series, we identified 2 cases of TGA, one dextro-transposition diagnosed at 1 week of life and one levo-transposition (or congenitally corrected transposition) diagnosed at 27 years old when complications occurred due to the failure of the systemic ventricle (RV morphology) (Fig. 8).

- **The third step** consists in determining and encoding the origin and position of the great vessels. Normally, the myocardial tissue under the aortic valve resorbs, giving rise to the mitro-aortic continuity, whereas the subpulmonary *conus* grows. Two opposite ridges appear and fusion in a spiral manner (62,66) separating independently and simultaneously the *conus* and *truncus* into 2 channels. Anomalies of this process lead to several CHD like tetralogy of Fallot, TGA and double-outlet RV. In the Van Praagh system, positional abnormalities of the great vessels are encoded by the third letter (260) (Fig. 10):

- S –*situs solitus*, normal configuration with the aorta in a posterior and rightward position relative to the pulmonary trunk;
- I – *situs inversus*, inverted position but the aorta and pulmonary trunk maintain normal disposition;
- D-TGA – dextro-transposition, the aorta is in an anterior and rightward position to the pulmonary trunk;

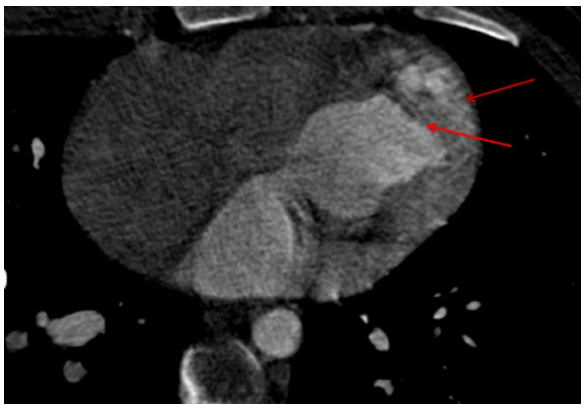


Fig.10. 27-years old male with congenitally corrected transposition. The RV is the systemic ventricle and situated to the left of the ventricle (LV) ejecting blood in the pulmonary trunk. Coarse trabeculations and the moderator band are indicated with arrows (IBCV Iasi)

- L-TGA – levo-transposition, the aorta is in an anterior to and leftward position to the pulmonary trunk;
- D –MGA – dextro-malposition, the aorta is rightward of the pulmonary trunk;
- L-MGA - levo-malposition, the aorta is leftward of the pulmonary trunk.

All the three steps combined define the normal heart as {S, D, S} and CHD as a combination of letters encoding the main anomalies. For example, the levo-transposition presented in figure 10 could be described as {S, L, L-TGA} because of normal visceroatrial situs, levo-loop of the heart tube (the systemic RV to the left of the LV), and aorta originating from the RV anterior and leftward of the pulmonary trunk.

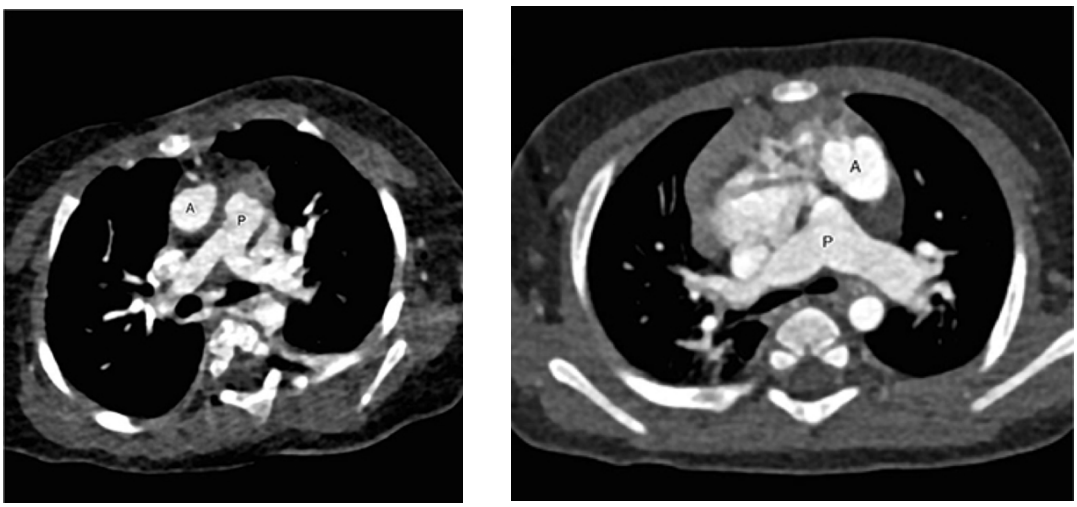


Fig. 11. Dextro {_,_,D-TGA} versus levo-transposition of the great arteries {_,_,L-TGA} (IBCV Iasi)

The system initially described by Van Praagh et al. omitted two aspects, the atrioventricular connection anomalies and double outlet ventricles (ventriculoarterial anomalies), later included by Anderson in 2009 (14) (Fig. 12). Positioning of truncoconal

outlets relative to the two ventricles is concomitant with inlet formation and anomalies involving this process lead to double outlet RV and double inlet LV.

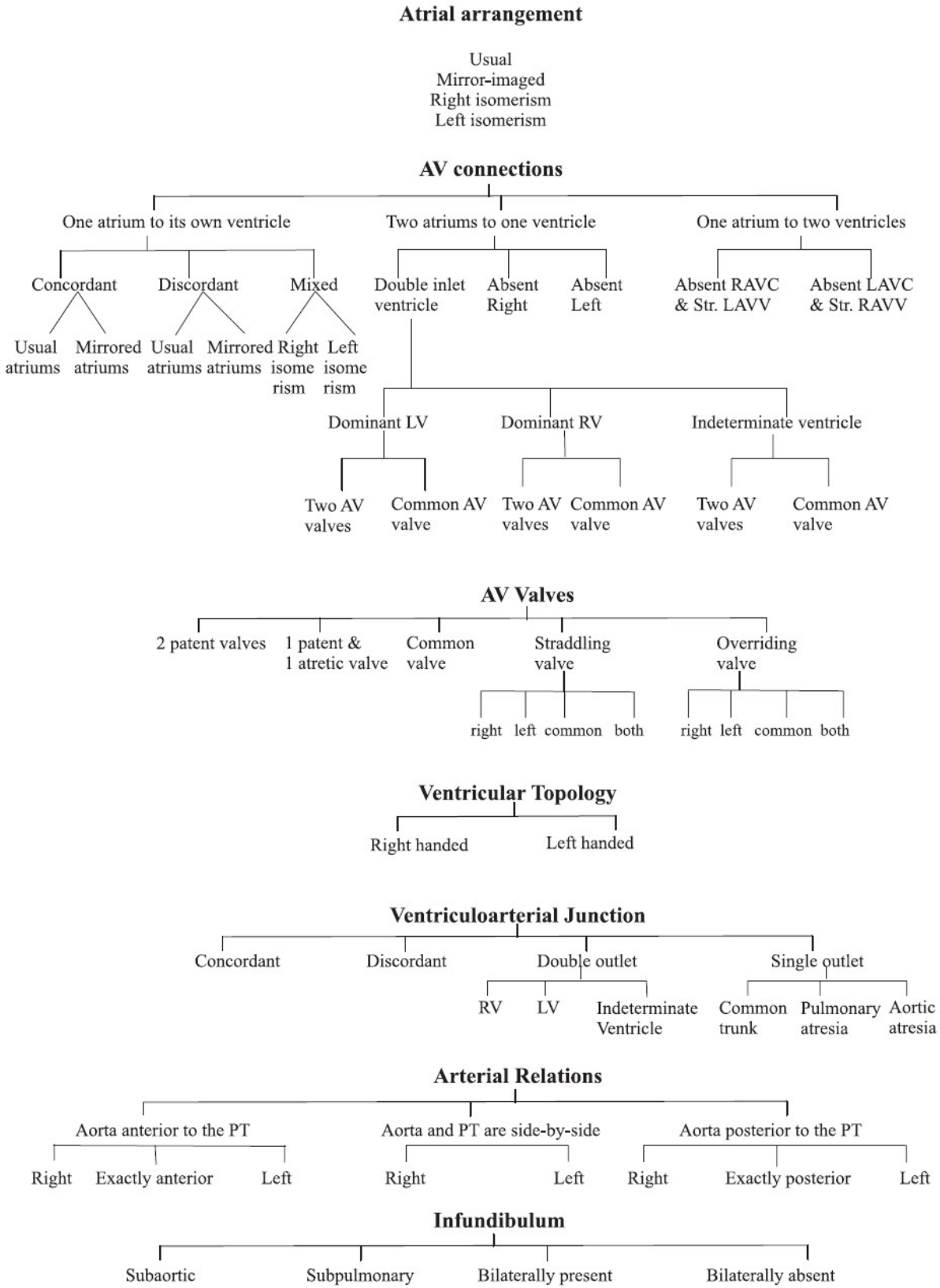


Fig. 12. Anderson systematization of the segmental approach (14)

Total closure of the interventricular septum (IVS) depends on the convergence and fusion of 5 different components (the primitive ventricular septum, the posterior and the anterior AV cushions, and the two conal ridges) (17,62,66).

Lack of coalescence or failure to form of any of these components triggers an abnormal communication between the 2 ventricles, namely ventricular septal defects (membranous, conal, muscular), AV canal defects or the existence of a common ventricle.

According to Anderson (14), there are 5 types of atrioventricular connections:

- Normal (concordant) connection – RA drains into RV, LA into LV;
- Discordant connection – RA drains into LV, and LA into RV;
- Transposition of the great arteries (dextro or levo) - frequently in association with discordant AV connection;
- Ambiguous - in cases of heterotaxy;
- Double inlet or absent right (or left) connection with formation of an univentricular heart.

Atrial septal defects (ASD) are the simplest malformations and omitted from the two segmental classifications as, except for *sinus venosus* ASD, they either occur as single entities (simple anomalies) or are associated to more severe CHD that can be defined using the system. Superior *sinus venosus* ASD is generally associated with partial anomalous pulmonary venous return (PAPVR).

Atrial septation is a complex process involving ingrowths of tissue from different sources; duplication, fusion, and resorption. Anomalies of any of these processes lead to ASD (*ostium primum, ostium secundum, sinus venosus*).

Descriptions of other abnormalities of various segments of the cardiovascular anatomy might also be useful to the surgeon as they have profound physiologic significance: presence, size, and location of atrial and ventricular septal defects; size of the ventricles (hypoplastic or dilated); presence and degree of any ventricular outflow tract stenosis; hypoplastic and stenotic lesions of the aorta or pulmonary arteries; patent ductus arteriosus; additional aorto-pulmonary connections.

In CHD there is no "*one developmental anomaly – one heart disease*" (98,7) association as a single disease (TGA) can be triggered by several anomalies (abnormal looping or trunco-conal septation) and a single anomaly (trunco-conal septation) can lead to several heart diseases (double outlet right ventricle, tetralogy of Fallot).

A complete understanding of CHD requires a thorough understanding of cardiac embryogenesis and all members of "*Heart Teams*" worldwide should use a common language for better communication and transmission of knowledge.

Based on the severity of CHD and underlying embryological anomalies, surgical treatment may involve several procedure types (123) (Table XIII).

Congenital heart defects are responsible for more deaths in the first year of life than any other birth defects. Nowadays, technical progress made foetal cardiac interventions possible.

In 2014 the ***American Heart Association*** (78) issued the first scientific statement on the diagnosis and treatment of foetal cardiac disease recommending percutaneous interventions to be considered in a series of diseases associated with aortic or pulmonary valve obstruction (class IIb recommendation; level of evidence, B/C). These foetal cardiac interventions made survival possible for children diagnosed with previously fatal CHD.

A thorough knowledge of cardiac embryology and anatomy allows an accurate diagnosis and successful management of CHD and is mandatory for all healthcare professionals involved.

The next era of paediatric cardiology will merge the genetic basis of cardiac development with directed therapy and prevention.

Table XIII. Types of surgical procedures in CHD (123)

Temporary palliation for CHD that cannot initially be repaired	• Systemico-pulmonary shunts in tetralogy of Fallot with pulmonary atresia; • Pulmonary banding in CHD associated with left to right shunt and pulmonary overcirculation.
Operations for heart defects that are fully corrected at the first procedure	• Patent ductus arteriosus, • Coarctation of the aorta, • Atrial septal defects, • Ventricular septal defects, • Atrioventricular canal defects, • Total anomalous pulmonary venous drainage.
Heart defects that might require further surgery or intervention after repair	• Transposition of the great arteries - about 10% require repeat surgery or catheter intervention for pulmonary stenosis due to scarring after *arterial switch* • Tetralogy of Fallot - Surgical repair usually comprises patch closure of the VSD and widening of the obstructed RVOT. • RV volume overload will make pulmonary valve replacement necessary in the decades to come because of declining RV function.
Heart defects that will require further surgery after the initial procedure	Pulmonary atresia, truncus arteriosus, transposition of the great arteries with pulmonary stenosis - require reconstruction of the RV outflow tract as part of the surgical correction. This is typically done using a conduit containing a tissue valve.
Long-term palliation of un-correctable lesions: functionally univentricular hearts	The commonest un-correctable lesion is a heart which has only one functional ventricle, or which has two that cannot be separated to form separate systemic and pulmonary circulations. The most frequently used is the three stage Norwood palliation which comprises: • an initial Blalock-Taussig shunt, • SVC-right pulmonary artery anastomosis, • interruption of the pulmonary trunk (Glenn shunt) and IVC – right pulmonary artery anastomosis (Fontan shunt). The single ventricle is maintained as systemic ventricle.

2.1.6. Conclusions

The segmental approach in CHD diagnosis has a double role. On one side, it provides a complete description of the anomaly understandable by any professional involved (a common language worldwide accepted for communication among "*Heart Teams*"), and on the other side, it establishes an order in which a malformed heart should be examined for not lopping any anomalies.

2.2. Left atrial, left atrial appendage and pulmonary veins anatomical variants associated to atrial fibrillation

2.2.1. Introduction

Atrial fibrillation (AF) is a frequent supraventricular arrhythmia with still unclear substrate. The development of the LA involving structures of various embryologic origins has been widely incriminated but the particular involvement of left atrial appendage (LAA) morphology, LA accessory appendages, LA diverticula and anatomical variants of pulmonary veins (PVs) is incompletely elucidated.

Although it is a cavity connected to the left atrium (LA), the LAA is a complex distinct entity, with distinct morpho-anatomical, embryological and pathophysiological features presumed of being involved in the genesis of AF.

The left atrial appendage is considered a vestige of the primitive LA, generally described as a long, narrow, hooked hollow structure opening in the LA on its lateral side, adjacent to the proximal part of the circumflex artery while coursing in the left atrioventricular sulcus. The ostium of the LAA is situated in the proximity of the left superior PV opening, the two ostia being separated only by a ridge of variable width. This area is crossed by the oblique vein of Marshall (OV) that can be enveloped by a myocardial sheath; a hypothetical electrical bridge connected to the myocardium adjacent to the coronary sinus. Functionally, the LAA registers a distinct pattern of contractions compared to the rest of the LA. These two anomalies could explain LAA arrhythmogenic potential in triggering AF (74) and its association with an increased thromboembolic risk. The LAA presents an irregular shape classified by Wang et al. (268) into 4 groups, a classification later improved by Kimura et al. (146) who assimilated its shape with a "*cactus*" when it presents a main lobe less than 4 cm long with more than 2 additional lobes; a "*cauliflower*" in case of a single main lobe of less than 4 cm long; a "*chicken wing*" when a main lobe of more than 4 cm long folds at an angle of less than 100^0; or a "*windsock*" in case of a main lobe of more than 4 cm long folded under an a folded angle of more than 100^0 over 1 cm (Fig. 13).

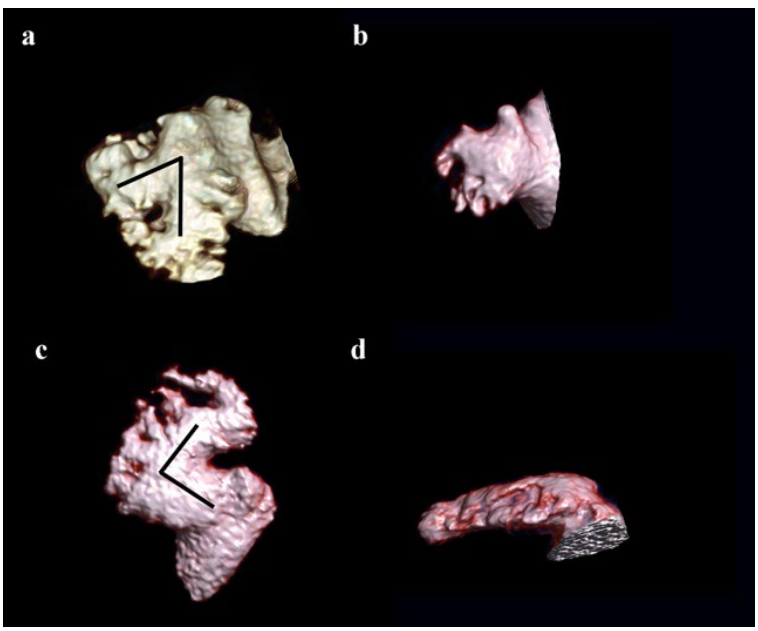


Fig. 13. LAA shapes: (a) "cactus", (b) "cauliflower", (c) "chicken wing", (d) "windsock" identified in patients from the study group (IBCV Iasi)

A saccular structure of regular shape, with smooth walls and a broad ostium, protruding

from the LA wall was considered a diverticulum (Fig. 14a). Alternately, if the protruding shape presented a narrow ostium and unregulated contour suggestive for pectinate muscles, it was considered an accessory appendage (Fig. 14b). These saccular structures occurring anywhere on the surface of the LA were classified according to the involved wall (anterior, posterior, right or left) and their position onto this wall (superior or inferior).

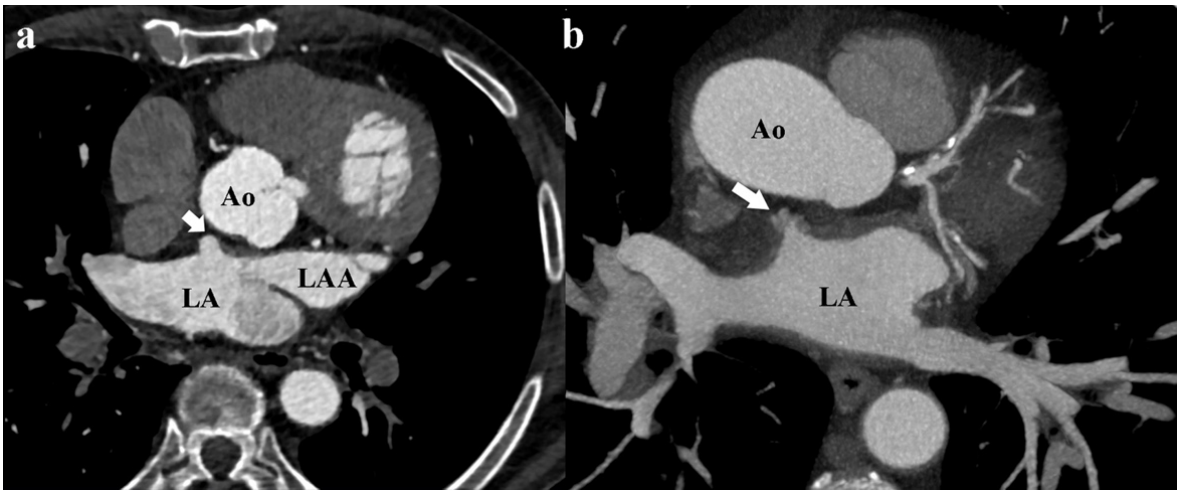


Fig. 14. Imaging aspect of left atrial diverticula (a) and accessory appendage (b) in two patients from the study group (IBCV Iasi)

Concerning the pulmonary veins (PVs), anatomy textbooks describe the presence of 4 PVs, two superior (right and left) and two inferior (right and left) with a distinct course from that of arteries or bronchi. Generally, the right superior PV drains the right upper and the middle lobes, the left superior PV the left upper lobe (culmen and lingula), and the inferior PVs, the corresponding inferior lobes. Variations in number (supernumerary veins), drainage (common trunk) size and orientation are not uncommon. Kato et al. (140) attempted a systemization of potential variants and described 6 branching patterns: 1) standard branching pattern with two superior and two inferior PVs, 2) short common left trunk, 3) long common left trunk (Fig. 15c), 4) supernumerary single right middle PV, 5) supernumerary two right middle PVs, 6) supernumerary right middle PV and right "upper" PV (Fig. 15b).

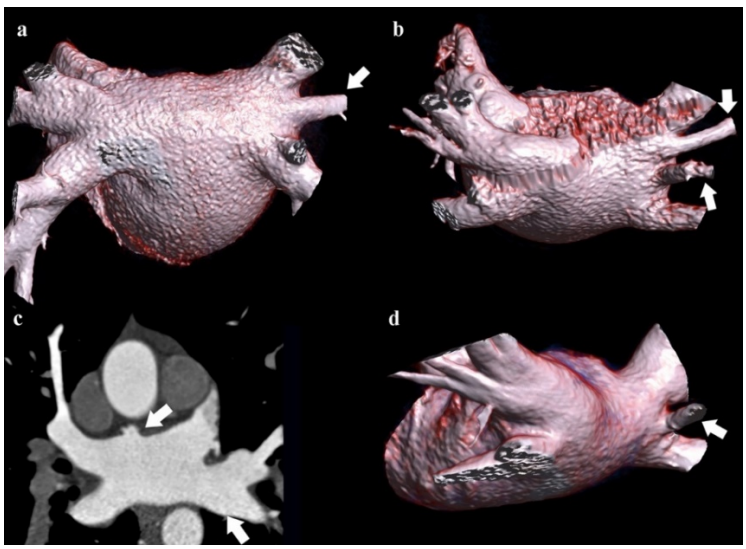


Fig. 15. (a) Separate right middle PV and short common left trunk, (b) Accessory intersegmental PV associated with a right middle PV, (c) long common left trunk and accessory appendage, (d) accessory right intersegmental PV (IBCV Iasi)

Based on the findings of the current study, we added 2 additional combinations: a short or long common left trunk associated with a right middle PV (Fig. 15a), and the presence of accessory intersegmental PVs directed towards the apical or a basal segment of the right lower lobe (Fig. 15d).

Ectopic foci with electrical activity potential culprit for AF have been identified in the myocardial expansions located in the distal part of PVs, at the junction with the LA, in up to 94% of patients with AF (161). These foci of conduction tissue with pacemaker activity remain in this location after the heart tube looping process during development (191). Multidetector computed tomography (MDCT), a non-invasive sectional medical imaging method with high spatial and temporal resolution, is the technique of choice for evaluating PVs and LA morphology prior to radiofrequency catheter ablation (RFCA) in patients with AF. Anatomical variants of the LA, LAA and PVs same as LA accessory appendages with unknown functional impact are frequently found when performing cardiac MDCT.

My interest in this field is reflected by the following published papers and books:

Articles:

1. Tinica G, **Furnica C**, Anghel D, Chistol RO. Left atrial, left atrial appendage and pulmonary veins anatomical variants in patients with atrial fibrillation versus patients in sinus rhythm. Rev Med Chir Soc Med Nat Iasi. 2016; 120(2): 344-354.

Books:

1. Tinica G, **Furnica C**. The Heart. Clinical and Surgical Anatomy. 'Alexandru Ioan Cuza" University Publishing House, Iasi, 2015.
2. Tinica G, **Furnica C**. Surgical Anatomy of the Cardiovascular System. 'Gr.T.Popa" U.M.F. Iasi Publishing House, Iasi, 2017.

2.2.2. Aims

The current research is part of a series of studies in cardiac morphology aiming to identify and assess potential relations between the genesis of AF and LAA morphology; prevalence, location, and size of LA diverticula and accessory appendages; and PVs anatomical variants. Matched groups of normal individuals in sinus rhythm and patients of AF were used for this evaluation.

2.2.3. Material and methods

Study design

We retrospectively reviewed the cardiac CT (computed tomography) images of a group of 100 patients (63 men and 37 women aged between 23-78 years with a mean age of 56.75 years) with paroxysmal or persistent AF diagnosed less than 1 year prior to investigation and no underlying structural heart anomalies and compared findings with those observed on a control group of 100 patients in sinus rhythm (SR) (52 men and 48 women aged between 25-79 years with a mean age of 58.74 years) referred for CT evaluation of suspected coronary arteries disease (CAD) but with no or mild (less than 50% diameter stenosis) coronary lesions and no structural heart disease. Patients with AF underwent cardiac CT for LA morphology assessment prior to radiofrequency catheter ablation (RFCA).

All examinations were performed at the "Prof. Dr. George I.M. Georgescu'' Cardiovascular Diseases Institute from Iasi, Romania between September 2012-January 2014. Informed consent for the usage of images in research purposes was obtained prior to examination in all cases.

Demographic and clinical characteristics

Patients' clinical characteristics are summarized in Table XIV. Patients with structural

cardiac diseases (eq. valve heart diseases), prior cardiac surgery or RFCA were excluded from the study.

Table XIV. Clinical characteristics of patients from the two groups

	AF	Control	p
Age (mean ± SD)	56.75±11.39	58.74±11.23	<0.05
Sex ratio (M/F)	63/37	52/48	<0.05
Body mass index (kg/m^2)	25.6±4	26.1±3.5	n.s.
Diabetes mellitus	4 (4%)	8 (8%)	<0.05
AF type	65 paroxysmal, 35 persistent	-	-
AF duration (years)	5.2±3.5	-	-

Image acquisition technique

All the patients included in the studied groups (AF and control) were examined on the same 2x128-slices dual source multidetector computed tomography (MDCT) scanner model Siemens Somatom Definition Flash (Siemens Medical Solutions, Germany) using cardiac gating and the following scan parameters: 100 / 120 kV tube voltage, automatically modulated tube current by CareDose 4D algorithm, 0.75 mm slice thickness.

Depending on the heart rhythm, two scanning protocols were used:

a) High pitch retrospective scanning in patients with more than 71 beats per minute or irregular heart rates in order to perform additional reconstruction for optimal image quality;

b) High pitch prospective scanning in patients with stable heart rate of less than 70 beats per minute.

A tablet of 50 mg metroprolol tartrate (Metroprolol LPH, LaborMed Pharma S.A., Romania) was administered orally to all patients the morning of the examination if no contraindication was present for decreasing and stabilizing the heart rate. Prior to examination, after placing the patient on the exam table, 2 puffs of nitro-glycerine (0.8 mg) were administered sublingually for coronary artery dilation

Bolus tracking injection protocol was used for optimal contrast timing. A volume of 75-100 ml of contrast agent (Iomeron 400, Bracco, Milan, Italy) followed by 50 ml of saline chaser were injected via a cannula placed in the right mediobasilic or mediocephalic vein at a flow rate of 5 ml/sec. The premonitoring trigger was placed in the descending aorta with a triggering sensitivity of 150 Hounsfield Units (HU). Premonitoring started at 10 seconds after initiation of contrast agent injection, and effective scanning at 5 seconds after reaching peak aortic enhancement. All patients were scanned in a single breath hold and an average volume of 85 ml of contrast media was used. Automatic best-diastolic reconstructions were realised, and in cases where image quality proved poor with automatic settings, additional reconstructions at different R-R interval percentages (30-80% in 5% increments) were performed. All post-processing was carried out on a Syngo.via workstation (Siemens Medical Solutions, Germany). Images were evaluated by two independent radiologists in order to obtain more objective results.

Statistical analysis

The statistical analysis was performed on a Macintosh computer (Mac OS X platform) with IBM SPSS Statistics 22.0 suite and Microsoft Excel 15.20. Quantitative data was tested for normality and presented as mean value ± standard deviation (SD). Mean values between AF and control group were compared using Student's t test. Qualitative data was presented as percentages and compared using Pearson chi-square test. Independent predictors of AF were analysed with multivariate logistic regression analysis after adjusting for potential confounders with univariate analysis. A significance level of 5% was used for all tests.

2.2.4. Results

Atrial fibrillation group

The majority of patients included in the AF group presented a "*chicken wing*" shaped (43%) or a "*cauliflower*" shaped (25%) LAA. Left atrium accessory appendages were identified in 7 cases, as single structures in 6 cases and as double structures in a case. Six appendages were located on the right anterosuperior wall of the LA and one on the right anteroinferior wall. Left atrium diverticula were identified in 24 patients, as single structures in 22 cases and double in 2 cases (Table XV).

Table XV. Features of patients with AF and individuals from the control group

Parameter	AF	Control	p
LAA shape:			n.s.
-"cauliflower"	25/100	21/100	
-"cactus"	16/100	14/100	
-"windsock"	16/100	10/100	
-"chicken wing"	43/100	55/100	
LA accessory appendage:			n.s.
-prevalence	6/100	5/100	
-number	7	5	
-width	7.42±3.15 mm	7.34±2.97 mm	
-length	9.38±4.28 mm	9.94±3.97 mm	
-single	5/6	5/5	
-multiple	1/6	-	
LA accessory appendage location:			n.s.
-right anterosuperior	6/7	4/5	
-right anteroinferior	1/7	-	
-left anterosuperior	-	1/5	
LA diverticula:			n.s.
-prevalence	22/100	19/100	
-number	24	14	
-width	8.8±3.1 mm	8.1±3.62 mm	
-length	7.1±2.5 mm	6.5±1.7 mm	
-single	20/22	12/13	
-multiple	2/22	1/13	
LA diverticula location:			n.s.
-right anterosuperior	18/24	13/14	
-right anteroinferior	4/24	-	
-left anteroinferior	2/24	1/14	
PVs variants:			0.047
-common left trunk	30/100	18/100	n.s.
• short common left trunk	21/100	14/100	
• long common left trunk	9/100	4/100	
-right middle PV(s)	11/100	12/100	n.s.
• 1 right middle PV	9/100	9/100	
• 2 right middle PVs	2/100	3/100	
-accessory right intersegmental PV	6/100	5/100	n.s.
-association of variants	5/100	3/100	
AF – atrial fibrillation; LA – left atrium; LAA – left atrial appendage; PV – pulmonary vein; SR – sinus rhythm			

Similarly, to LA accessory appendages, 18 diverticula (75%) were located on the right anterosuperior wall, 4 (16.67%) on the right anteroinferior wall and 2 on the left anteroinferior wall (8.33%). When comparing LA accessory appendage and diverticula morphology, we noted

that appendages had a narrower base (7.42 mm) and increased length (9.38 mm) compared to diverticula (8.8 and 7.1 mm respectively). As for PVs variants, a common left venous trunk was the most frequently encountered variant (30%) followed by an independent right middle lobe PV(s) (single or double in 11% of cases). Accessory intersegmental PVs were noted in 6% of cases, while an association of variants was identified in 5% of cases.

Control group

Similarly, to AF patients, most control individuals presented a "*chicken wing*" shaped LAA (55%). Accessory appendages were identified in 5 cases (unique structures) and diverticula in 18 cases (17 single, one case with 2 diverticula). Both accessory appendages and diverticula were commonly located on the right anterosuperior wall.

Atypical locations were registered for one accessory appendage, on the left anterosuperior wall, and one diverticulum, on the left anteroinferior wall. A common left PVs trunk was observed in 18 cases and an independent right middle lobe PV(s) in 12 cases. Accessory intersegmental PVs were noted in 5 cases and an association of variants in 3 cases. Except the presence of a left common venous trunk, none of the variants proved to be associated with AF at univariate analysis

Multivariate logistic regression analysis confirmed the results of univariate tests and proved that the only potential independent predictor for AF was the presence of a left common trunk (odds ratio (OR) 1.32; 95% confidence interval (CI) 0.93–1.51; p=0.002).

2.2.5. Discussions

Morphological variants such as LA accessory appendages and diverticula are frequently encountered as incidental findings in patients addressed for cardiac CT examinations for various reasons and are not associated with congenital heart diseases. In particular cases, differentiating LA accessory appendages from diverticula is not easy as appendages might have a wide base or too subtle inner wall irregularities. Histologically, diverticula present all cardiac wall layers, but the myocardial one might be thinner than normal, slightly translucent. According to Wan et al. (267), LA diverticula are acquired conditions caused by parietal atrophy followed by LA thinning due to various cardiovascular diseases (atherosclerosis, arrhythmias, occlusion of the arteries supplying the atrium, mitral valve disease). Except Wang et al., we could not identify another study to certify these findings. In case of LA accessory appendages, Killen et al. (143) identified pectinate muscles with contractile properties contrary to diverticula's simple structures. Lee et al. stated a common embryonic origin of LA accessory appendages and LAA (162).

LA accessory appendages and diverticula were frequently encountered structures in the two analysed groups, with a cumulated incidence of 28% in the AF group and 24% in the control group. We noted a 3.7 times higher incidence of diverticula compared to accessory appendages in the AF group and 4.2 times higher in the control group.

There was no statistically significant difference in the prevalence of diverticula between the AF group (22%) and the control group (19%) The quantified incidence was similar to other studies from the literature (4,82,128,161,203,206,229,251,268) that stated a prevalence of 23.5 - 36% in AF patients and 16.7 – 41% in general population or patients in SR.

Both diverticula and accessory appendages were most frequently located in a right lateral position on the anterosuperior wall.

The size of accessory appendages and diverticula did not differ between the two groups and was within the size range reported by other researchers (Table XVI) (4,82,128,161,203,206,229,251,268).

Given the absence of any difference in location, size or incidence of LA diverticula and accessory appendages between the AF group and control group, we plead against a direct relation between these structures and AF aetiology.

Table XVI. Comparative analysis of literature findings

Study	**Prevalence of diverticula**	**Width of diverticula**	**Height of diverticula**	**Frequent location**
Peng et al. 2012	36% in AF 32.7% in SR	5.3±2.9 mm in AF	5.6±3.3 mm in AF	Right anterosuperior
Abbara et al. 2009	19.4% in GP	6.2 ± 3.9 mm in GP	6.4 ± 2.5 mm in GP	Superior anterior
Lazoura et al. 2012	23.5% in AF 20.5% in SR	8.1 mm in AF 7.2 mm in SR	8.1 mm in AF 7.8 mm in SR	Right anterosuperior
Troupis et al. 2012	40% in AF 36% in SR	3.6 mm in AF 5 mm in SR	4.7 mm in AF 6.2 mm in SR	Right anterosuperior
Shin et al. 2011	18.3% in GP	4.7 ± 2 mm in GP	4.7 ± 2.1 mm in GP	Right side of the upper left atrial wall
Incedayi et al. 2012	41% in GP	5.2 mm in GP	-	Anterosuperior
Poh et al. 2008	28% in GP	-	-	Anterosuperior
Wan et al. 2009	16.7% in GP	4.9 ± 3.2 mm GP	5.4 ± 2 mm GP	Anterior
Study	**Prevalence of accessory appendages**	**Width of accessory appendages**	**Height of accessory appendages**	**Frequent location**
Duerinckx et al. 2007	10% in GP	9 mm in GP	6 mm in GP	Right upper atrial wall
Abbara et al. 2009	8.5% in GP	3.9 ± 2.4 mm in GP	4.9 ± 2.1 mm in GP	Left lateral inferior posterior
Lazoura et al. 2012	6.5% in SR 6.5% in AF	6.3 mm in AF 5.7 mm in SR	8 mm in AF 9.4 mm in SR	Right anterosuperior
Troupis et al. 2012	8.5% in AF 10% in SR	4.7 mm in AF 4.6 mm in SR	6.9 mm in AF 12 mm in SR	Right anterosuperior
Incedayi et al. 2012	3.08% in GP	-	-	Inferolateral
Poh et al. 2008	14% in GP	-	-	
Study	**"Cauliflower"**	**"Cactus"**	**"Chicken wing"**	**"Windsock"**
Di Biase et al. 2012	2% in AF	28% in AF	50% in AF	19% in AF
Kimura et al. 2013	17.5% in AF	2.5% in AF	13.8% in AF	28.8% in AF
Wang et al. 2010	29.1% in AF+SR	5.9% in AF+SR	18.3% in AF+SR	46.7% in AF+SR
Study	**Prevalence PVs variants**	**1st most frequent variant**	**2nd most frequent variant**	**Study**
Kato et al. 2003	38% in AF	Common left trunk	Middle PV(s)	Kato et al. 2003
Anselmino et al. 2010	60% in AF	Common left trunk	Middle PV(s)	Anselmino et al. 2010
Bittner et al. 2011	44.6% in AF 29.5% in SR	Common left trunk	Middle PV(s)	Bittner et al. 2011
Kaseno et al. 2008	24% in AF	Middle PV(s)	Common left trunk	Kaseno et al. 2008
AF – atrial fibrillation; GP – general population; SR – sinus rhythm				

Even if LA accessory appendages and diverticula lack any functional significance, their presence must be signalled to electrophysiologists performing RFCA as their ostia might be confused to those of PVs during the ablation procedure with potential devastating consequences

such as perforation of the atrial wall with subsequent hemopericardium. During the current analysis no thrombus was visualized inside these structures.

A particular drainage of PVs is a frequently encountered anomaly both in patients with AF (52%) and in control group (38%), the quantified incidence being similar to other results reported in the reviewed literature (Table XVI) (18,40,138,140,155,172,201,252).

The most prevalent variants were common left trunk (30% in AF group and 18% in control group) and 1 or 2 accessory right middle PVs (11% in AF group and 12% in control group).

Precise knowledge of the anatomy of PVs is mandatory prior to RFCA as failure to isolate a PV could result in AF persistence, recurrence or PVs stenosis. According to Cronin et al. (64), the right middle PV generally has a small diameter thus making it difficult to identify and isolate during procedure, so it might be overlooked.

Similarly to our study, Bittner et al. (40) signalled a higher prevalence of a common left trunk in patients with AF compared to controls and proposed two hypotheses to explain the finding:

1) congenital variant that constitutes a risk factor for developing AF;

2) acquired condition secondary to LA remodelling associated with AF, the geometrical changes occurring during dilation pushing the carina between the two left PVs and creating a common left trunk.

In either case, the presence of a common left trunk is associated with the occurrence of AF. The prevalence of other PVs variants was not significantly different between the two studied groups.

The morphology of the LAA is complex and heterogeneous in patients with AF with or without a history of stroke (Table XVI) (74,146,268).

Di Biase et al. and Kimura et al. (74,146) identified a connection between the morphology of LAA and the risk of thrombotic stroke in patients with FA, the “chicken wing” shape being associated with a lower risk of stroke compared to “cauliflower” shape considered an independent predictor of stroke.

In our research, we identified no significant difference between the prevalence of different LAA morphologies between the control group and AF patients with no history of stroke. The shape of the LAA might be significant only in patients with AF at risk for stroke according the above-mentioned authors.

2.2.6. Conclusions

Left atrial accessory appendages and diverticula represents frequent anatomical variants encountered in patients addressed for cardiac CT examinations for various reasons. No difference in prevalence, size and location of LA accessory appendages and diverticula was identified when comparing patients with recurrent AF referred for RFCA with the control group in SR, an argument against a relation between these structures and the genesis of AF. The prevalence of LA shapes was similar in both groups, AF and control. A left common venous trunk was most frequently identified in patients with AF and proved to be an independent predictor for AF.

2.3. The impact of aortic root morphology on the therapeutic approach

2.3.1. Introduction

Surgery in aortic valve follows a continuous development due of the increasing use of conservative surgical techniques for repairing or replacing cardiac valves. Given the conical shape of the left ventricle (LV), the main role of the mitral and aortic valves consists in preventing the regurgitation of blood flow during the cardiac cycle. Intact morphology and functioning of aortic and mitral valves (AV and MV), intimately associated, are essential in maintaining the overall cardiac function. The complex interrelation of these structures become fully apparent when the valves fails through stenosis, regurgitation, or the combination of both. The anatomy of the aortic valve represents the basis of the challenging and complicate problems related to surgical correction, and sustains better prostheses design, more adequate to the morphological configuration.

The aortic valve represents the heart's anatomical core that connects the left ventricle to the ascending aorta. Structurally, the complex associated to the aortic valve consists of the outflow tract, aortic annulus, interleaflet triangles and the valvular leaflets themselves, aortic sinuses, commissures and the sinotubular junction.

The ascending aorta is composed of 2 parts: the aortic root, between the aortic annulus and the sinotubular junction, including aortic valve leaflets, leaflet attachments, sinuses of Valsalva, interleaflet triangles and the sinotubular junction, and the supra-coronary aorta, extending from the sinotubular junction to the origin of the brachiocephalic arterial trunk. The opening of the aortic valve is almost stress-free thanks to the systolic expandability of the root via the sub-commissural triangles. Similarly, valve closure is facilitated by vortices generated by Valsalva sinuses.

The aortic cusps are inserted on the aortic root in a semilunar manner, delimiting the sigmoidal perimeter of the aortic annulus. They are designated according to the coronary arteries: right coronary cusp, left coronary and non-coronary. Two diameters are essential for good valve function: the diameter of the base of the aortic annulus and that of the sinotubular junction. In the normal subject, the diameter of the sinotubular junction (27.4 ± 2.2 mm) is wider than that of the base of the aortic annulus (22.6 ± 1.4 mm), with a ratio of 1.2 (15).

The dystrophy of the ascending aorta is characterized by a dilation of the functional diameters of the aortic root (sinotubular junction greater than 35 mm and / or base of the aortic annulus greater than 25 mm) associated or not with a valvular lesion. There are 3 phenotypes, according to the diameter of the Valsalva sinuses: the aneurysms of the aortic root (diameter greater than 45 mm), the supra-coronary aneurisms and isolated aortic insufficiencies (diameter lower than 40 mm) (218).

The aortic root acts as a whole ensuring intermittent, unidirectional channelling of large volumes of fluid, while maintaining laminar flow, minimal resistance and least possible tissue stress and damage during varying hemodynamic conditions and demands.

In case of aortic valve regurgitation, aortic valve replacement has been the „*gold standard*" procedure for years irrespective to the cause. Recent studies (248) suggest that in case of aortic regurgitation due to aortic root dilatation with normal valve leaflets, aortic valve replacement is not necessary and valve sparing aortic root geometry correction is sufficient to correct regurgitation.

Aortic regurgitation is considered functional in such cases and determined by sinotubular junction dilatation +/- sinuses dilatation or by annular dilatation.

The 90's brought and endless discussions between two different schools concerning the valve sparing correction of aortic root diseases. David (67) proposed in 1992 the inclusion of the aortic valve in a prosthetic Dacron tube used to replace the abnormal ascending aorta with reimplantation of the coronary arteries in the graft. Yacoub (224), in 1993, suggested a different

approach consisting in remodelling a prosthetic tube to obtain 3 tongues used to replace the resected Valsalva sinuses with reimplantation of the coronary arteries similar to the modified Bentall procedure.

Both the David and Yacoub techniques involve resection of the aortic root and reimplantation of coronary arteries, a highly laborious intervention.

Hetzer (121,122,119,120), in 2007, postulated that, in many cases, aortic regurgitation associated to ascending aorta pathology can be reverted with correction of the aortic root geometry, and proposed the relocation of the aortic valve plane as a potential cure.

My interest in this field is reflected by the following papers and books:

Published article:

1. Butcovan D, Chistol RO, Antoniu F, **Furnica C,** Tinica G. Comparison of morphoclinical characteristics of giant cell aortitis and Takayasu aortitis in patients with ascending aortic aneurysm. Romanian Journal of Functional and Clinical, Macro- and Microscopical Anatomy and of Anthropology 2015; XIV(1): 35-38.

Books:

1. Varlam H, **Furnica C**, Leon MM. The Heart. Clinical Anatomy. Pim Publishing House, Iasi, 2011.
2. G. Tinica, **Cristina C.** The heart. Clinical and Surgical Anatomy. "Alexandru Ioan Cuza" University Publishing House, 2015.

2.3.2. Aims

The morphology of the aortic root is strictly related to its function and treating the aortic root pathology involves thorough knowledge of the anatomy and physiology of the aortic root, adequate lesion identification and appropriate selection of the surgical technique. Our study aimed to assess the feasibility, short- and long-term results of relocation of the aortic valve plane to its original anatomic position and orientation in patients with aortic regurgitation due to ascending aorta dilatation.

2.3.3. Material and methods

We performed a prospective follow-up study on 71 patients aged 51.04±12.07 years with aneurysm of the ascending aorta (22 cases – 30.98%) or type A aortic dissection (49 cases – 69.01%) treated with ascending aorta replacement with Dacron graft and aortic valve relocation at the Cardiovascular Institute from Iasi between 2002-2015.

Transthoracic and transoesophageal echocardiography together with computed tomography were used to diagnose the disease in all cases.

On the CT images a set of preoperative measurements were performed to assess the feasibility of the intervention: the distance between the deepest point of noncoronary sinus and the proximal rim of the brachiocephalic trunk ostium, the distance between the left coronary ostium and the distal rim of the left subclavian artery ostium, the diameter of the sinotubular junction, the diameter of aortic root at level of the Valsalva sinuses and the angle between coronary ostial plane and the sagittal plane.

The surgical intervention involved replacing the ascending aorta with a graft shorter than the initial length thus restoring the diameter of the sinotubular junction and the normal orientation of the aortic valve plane. The intervention was feasible only in cases with dilated sinotubular junction (effacement) and subsequent verticalization of the aortic valve plane.

2.3.4. Results

Demographic data of analysed patients is presented in table XVII.

Table XVII. Demographic data of operated patients

Aortic dissection	Aneurysm
Urgent surgery (49 cases) Mean age 47.4±11.01 yrs 30 males (61,22%)	Elective surgery (22 cases) Mean age 57.1±11.8 yrs 17 males (77,27%)

Patients with ascending aorta aneurysms benefited of elective surgery compared to patients with type A aortic dissection who were operated in an emergency setting.

The ascending aorta exceeded 50 mm in all cases with a normally sized annulus (Table XVIII).

Table XVIII. Morphologic evaluation of the aortic valve and ascending aorta

	Aortic dissection	Aneurysm
LVEF	59.18±9.35	54.88±8.83
Aortic insufficiency	2.95±1.14	2.46±1.32
Aortic annulus size	27,5	24,5
Ascending aorta	52,07	57,8
Aortic arch	40,8	32,3

Concerning the comorbidities, most patient were hypertensive as expected. A congenital malformation or genetic disease could be incriminated in a limited number of cases (Fig. 16).

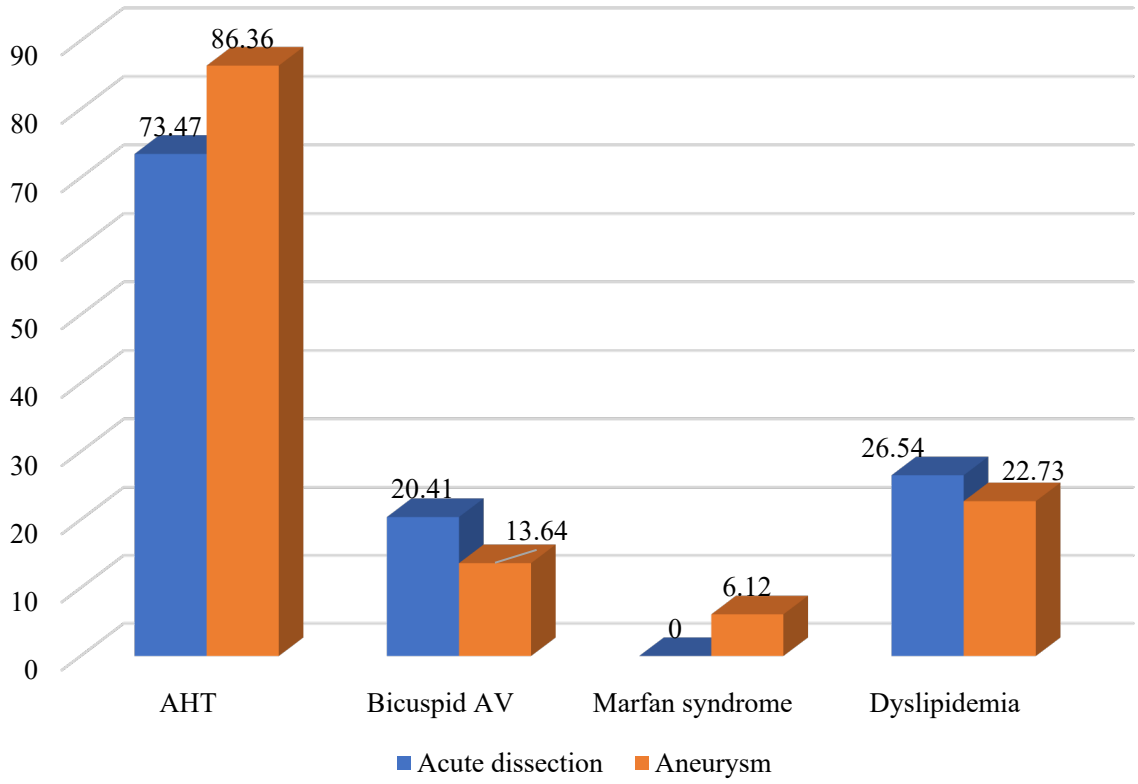


Fig. 16. Comorbid conditions in the study group

The ascending aorta was replaced with a shorter and a narrower graft aiming to restore the normal length of the vessel and of the sinotubular junction. A leaflet plication was necessary in most cases. Other cardiac procedures were also performed at the same time for patients with associated diseases (coronary heart disease, mitral or tricuspid valve disease) (Table XIX).

Table XIX. Operative parameters of analysed patients

	Aortic dissection	Aneurysm
Isolated ascending aorta replacement	49 cases	22 cases
Leaflet plication of the aortic valve	27cases (55%)	18 cases (81,82%)
Other procedures (CABG, MV/TV surgery)	8 cases (16,33%)	6 cases (27,27%)
Aortic cross-clamp time	65 ± 21 min	55± 19 min
Extracorporeal circulation time	125 ± 32 min	90 ± 28 min

Postoperative complications occurred more frequently in the aortic dissection group given the severity of the diseases and the emergency surgery (Fig. 17)

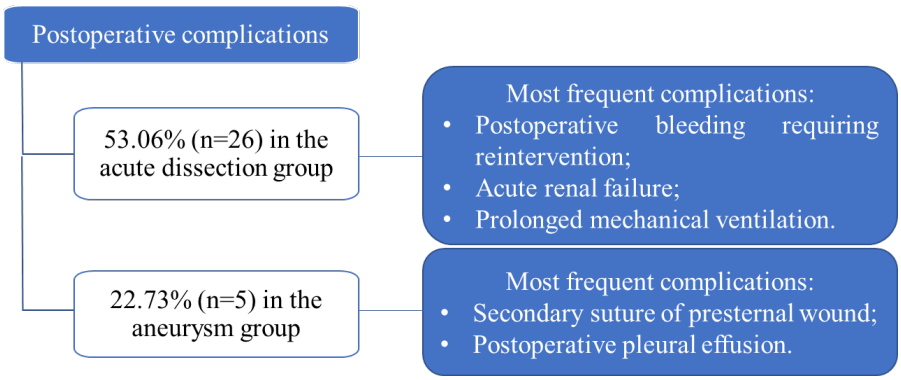


Fig. 17. Postoperative complications in the study group

Mortality rate was of 14.28% (7 cases) in the acute dissection group and 0% in the aortic aneurysm group.

The surgical intervention resulted in a significant reduction of aortic root diameters as illustrated in table XX.

Table XX. Preoperative versus postoperative aortic root diameters

CT evaluation	Preoperative	Postoperative
Diameter of the aortic root at coronary ostia (mm) (D)	43.1 ± 5.4	34.1 ± 3.2
Diameter of sinotubular junction (mm) (C)	44.9 ± 6.3	27.1 ± 2.8
Angle between coronary ostial plane and sagittal spine plane (degrees)	45.9 ± 9.3	63.5 ± 11.2
Left coronary ostium - left subclavian artery distance (mm) (B)	105.4 ± 16.1	89.1 ± 12.4
Noncoronary sinus - brachiocephalic trunk distance (mm) (A)	119.4 ± 11.7	96.1 ± 9.6

The medical imaging aspect revealed an aortic valve in the normal anatomic position with restoration of the aortic root geometry. The regurgitation completely disappeared in 56 cases (78.87%). A mild regurgitation without any clinical significance persisted in the rest of 15 cases (21.13%).

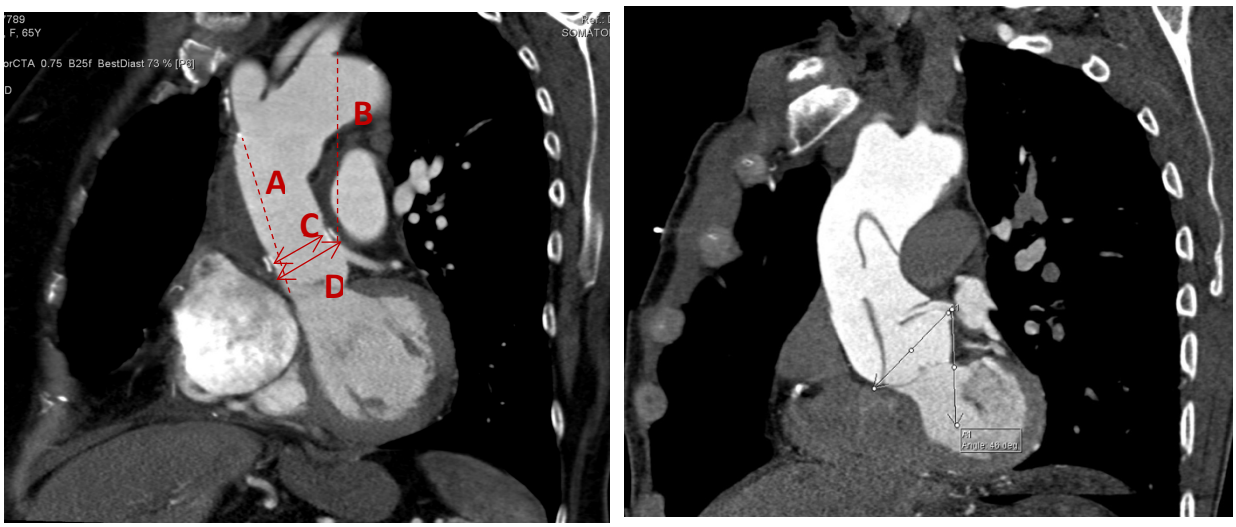


Fig. 18. Preoperative versus postoperative aspect of the ascending aorta (IBCV Iasi)

The distance between the noncoronary sinus and the arterial brachiocephalic trunk regressed by 19.51% and the distance between the left coronary sinus and the left subclavian artery by 15.46%. The aortic root was shifted upward to a more "normal" oblique position relative to the long axis of the spine. The angle between the transsectional plane of the aortic root and the spine widened by 17.6º. Usage of a narrower graft created a new sinotubular junction. Finally, the diameter of the aortic root at the level of the coronary ostia diminished from 43.1 mm to 341 mm and that of the sinotubular junction from 44.9 mm to 27.1 mm.

The results proved stable at an average of 5.73 years follow-up (Fig. 19).

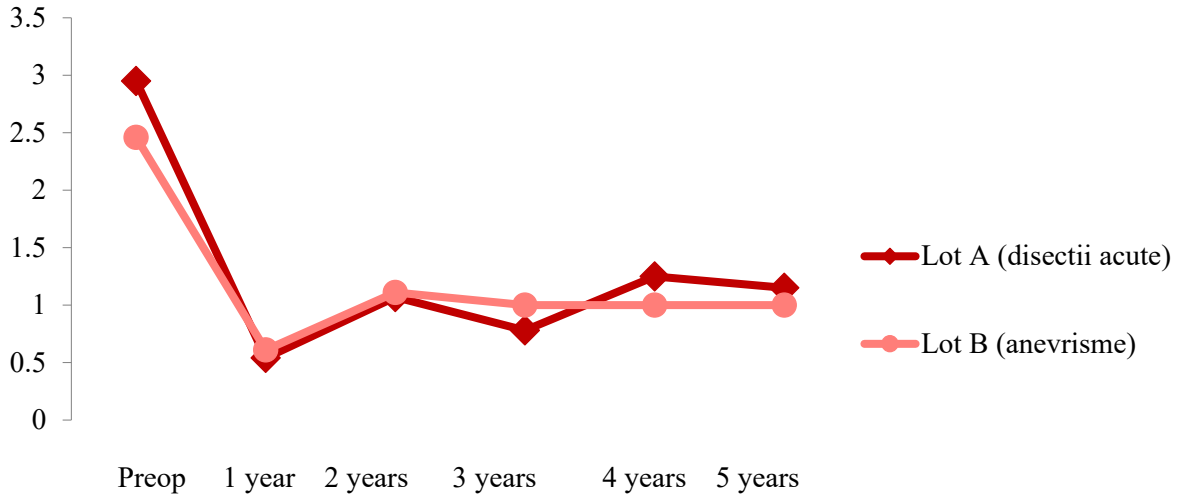


Fig. 19. Follow-up results in the studied population

The relocation of the aortic valve is associated with effective and long-lasting functional valve competence that obviates the need for complicated valve repair procedures or valve replacement.

2.3.5. Discussions

In aortic root aneurysm or type A aortic dissection with dilated ascending aorta, isolated dilation of the aortic sinuses interferes with the coaptation of aortic valve leaflet. It alters the anatomic relationships of the various components of the aortic root, but patients with aortic root aneurysms may present entirely competent aortic valves. Dilatation of the sinotubular junction or aortic annulus increases the mechanical stress on the aortic cusps, and on the long term they

might thin and stretch with potential structural damage. In the initial stages of the disease, the aortic leaflets can be spared, but in advanced stages, the aortic cusps may be beyond salvage (248).

An adequate preoperative evaluation through medical imaging is necessary and CT in particular is mandatory for therapeutic planning. Relocation of the aortic valve plane proves effective only in patients with regurgitation due to altered geometry and normal leaflets (121,122). Based on provided measurements, the surgeon can tailor the Dacron graft in order to resuspend the root.

The procedure finally accomplishes 4 target points:

- Restores the orientation of the aortic valve plane relative to the sagittal plane;
- Restores the ascending aorta narrowing at the site of the sino-tubular junction;
- Restores the width of the aortic root at its widest point (sinuses of Valsalva) by a shorter graft;
- Relocates the root to its normal anatomic position by using a shorter graft.

The previously proposed techniques (David and Yacoub) do not meet the complexity of the aortic root and valve function rendering the durability of the repair questionable (68,67,224) (Table XXI).

Table XXI. Comparison of David and Yacoub procedures

REMODELING	REIMPLANTATION
Very anatomic and physiologic (sinuses, cusp motion)	Support of the aortic wall
Increased risk of bleeding (long external sutures)	Less risk of suture bleeding
Increased risk of valve distortion (long tongue, short valve remnants)	Annulus stabilization
Lack of annular stabilization and long-term stability of results	Early and late failure (thickening and retraction of leaflet edges)

The relocation technique has the advantage of being a completely anatomical procedure that tries to restore the normal, complex, anatomy of the aortic root thus rendering durable and stable long-term results. All other procedures are non-anatomical. Despite trying to mimic the normal anatomy by constructing new sinuses for example, they fain to render a similar functionality and this explains limited stability of the results. The approach proposed by Hetzer is the only one that considers the fact that the morphologic characteristics and function of the aortic valve are interrelated to the aortic root and are usually reunited in a single functional unit.

Aortic valve relocation is basically a simple procedure and completely reproducible. Technical changes to optimize the geometry of the resuspended aortic valve can virtually eliminate late valve failure. The mainly mid-term results reported in our study are satisfactory but further studies with a larger number of patients are necessary to strengthen our findings. To our knowledge, this study is the second (after the initial promoter, Hetzer) to report the results of this surgical technique (121,122,119,120).

Aortic valve replacement is to be avoided whenever possible especially in young patients. Biological valves degenerate on the long term and mechanical valves need continuous anticoagulant treatment.

2.3.6. Conclusions

Aortic valve relocation is a simple, reproducible and durable procedure restoring the normal anatomy of the aortic root with disappearance of aortic regurgitation while sparing the native valve. The technique is particularly useful in young patients as it is associated with a normal life quality and expectancy.

2.4. The clinical significance of the morphological aspects of coronary arteries, coronary lesions and coronary artery *bypass* grafts

2.4.1. Morphology of coronary lesions in diabetic patients

2.4.1.1. Introduction

Cardiovascular diseases (CVD) are a major cause of morbidity and mortality exceeding cancer in various parts of the globe. Under these circumstances, identification of groups at high risk of myocardial ischemic events developed as a necessary preventive strategy intended to reduce subjacent complications and deaths.

Diabetes Mellitus (DM) is a severe proatherogenic condition at the crossroad of multiple pathogenic mechanisms yielding patients at high risk of major adverse cardiovascular events (MACE). Neuropathy, a microvascular complication of DM, is frequently associated with asymptomatic macrovascular complications, such as coronary and peripheral artery disease. Nowadays, DM is a public health problem, with more than 347 million persons diagnosed with this condition worldwide at the end of 2012, and a prediction of 552 million cases in 2030 (1,2). In Romania, the prevalence of DM increased from 7.6% in 2007 to 8.4% in 2010, and the incidence reported by the Health Ministry in 2010 was of 319.1 new cases for 100.000 inhabitants (1). World Health Organization (WHO) stated that direct costs of DM and related pathologies account for up to 15% of the Health Ministries' expenses (264). People suffering from type 1 and type 2 DM are at high risk for CVD, especially coronary artery disease (CAD), the leading cause of diabetes related morbidity and mortality, the 10-year mortality rate in diabetic patients with CAD exceeding 70% (45).

Cardiac computed tomography angiography (CCTA) allows the non-invasive study of coronary arteries in patients with chest pain, various atherosclerotic symptoms or multiple risk factors for CAD, through the quantification of coronary stenosis and calcium deposits in the coronary tree (***Agatston Calcium Score***). The calcium burden of coronary plaques is used worldwide to assess the risk of severe CAD. In the United States of America, it was approved by the Food and Drug Administration as a method of screening for CAD.

My interest in this field is reflected by the following published papers, books and research projects:

Articles:

1. Tinica G, Chistol RO, **Furnica C**, Luca C, Anghel D, Grecu M. Asymptomatic coronary artery disease in type 2 diabetes mellitus patients compared to a non-diabetic control group. Acta Endo (Buc) 2014; 10(2): 238-248.

Project:

1. **Furnica C** (director). Morphoanatomical and Pathophysiological Aspects of Coronary Artery Bypass Grafting in Terms of Long-Term Outcome (CABOT). Internal Grant 29031/18.12.2016, "Grigore T. Popa" University of Medicine and Pharmacy.

Books:

1. Varlam H, **Furnica C**, Leon MM. The Heart. Clinical Anatomy. Pim Publishing House, Iasi, 2011.
2. Tinica G, **Furnica C**. The Heart. Clinical and Surgical Anatomy. "Alexandru Ioan Cuza" University Publishing House, 2015.

2.4.1.2. Aims

The morphology (bifurcations, three dimensional curvatures) and structure of coronary arteries explain their vulnerability to atherosclerosis. Compared to the superficial femoral artery, atherosclerotic plaques in coronary arteries have less fibrotic elements and more lipids

thus making them unstable and prone to rupture. One of my research topics consisted in analysing the anatomo-clinical profile of coronary atherosclerosis in asymptomatic type 2 diabetic patients compared to asymptomatic non-diabetic patients to determine if there are any statistically significant differences concerning the prevalence of occult CAD.

2.4.1.3. Material and methods

Study design

The current research was designed as a retrospective case-control evaluation performed at the Cardiovascular Diseases Institute from Iasi, Romania, on a group of 120 non-diabetic and a group of 120 diabetic asymptomatic patients that underwent CCTA for various reasons, such as preoperative evaluation of coronary arteries in patients suffering from valvular or aortic diseases, screening for CAD in patients with risk factors, or atrial fibrillation prior to radiofrequency ablation therapy. All patients underwent CCTA between January 2013 and January 2014 and consented both for the examination and the usage of obtained results for research studies.

Patients presenting an acute coronary syndrome or ECG alterations compatible with myocardial ischemia, with prior evidence or under treatment for CAD were excluded from the study.

The diagnosis of DM was established when plasma glucose level exceeded 126 mg/dL (6.99 mmol/l) or 2–h plasma glucose exceeded 200mg/dl (11.1mmol/l) and patients were treated with dietary intervention, oral glucose-lowering agents, or insulin.

Image acquisition protocol

All 240 patients were examined using a 2nd generation 256-slices dual source multi-detector CT (MDCT) scanner (Siemens Somatom Definition Flash) with the following scan parameters: 100 or 120 kV tube voltage, tube current modulated by CareDose 4D algorithm, 128 x 0.6 mm collimation, gantry rotation time 280 ms. Two imaging protocols were used depending on heart rhythm and cardiac pathology: high pitch retrospective scanning in patients with high (≥71 beats per minute) or irregular heart rates and high pitch prospective scanning in patients with stable heart rate ≤70 beats per minute. After the patient was installed on the examination table, two puffs of nitro-glycerine spray (0.8 mg) were administered sublingually for coronary artery dilation. The examination started with a non-contrast examination for calcium score quantification followed by a coronary computed tomography angiography (CCTA) for evaluation of coronary stenoses. Bolus tracking injection protocol was used in all cases for optimal contrast opacification. An average volume of 100 ml of contrast media and 50 ml of saline chaser was injected intravenously, and the patient was scanned in a single breath-hold when the descending aorta opacification reaches 150 Hounsfield units (HU). Optimal reconstructions at different R-R interval percentages were performed (thickness 0.75 mm) and submitted to the Syngo.via workstation (Siemens Medical Solutions, Germany) for image analysis.

Renal function was assessed the day of the examination and was within the normal values in all cases. In patients treated with metformin-based oral antidiabetic drugs, the medication was suspended 48 hours after the examination and reinitiated after confirming the normality of the renal function in order to avoid lactic acidosis. No special precautions were taken in case of patients treated with insulin.

The calcium burden of coronary plaques was evaluated on the non-contrast examination using Agatston score algorithm implemented in Syngo.via software. The Agatston calcium score classifies the severity of CAD, based on the cut-off points widely used in the literature:

- ≤ 10 - minimal or insignificant CAD;
- 11-100 – mild CAD;
- 101-400 – moderate CAD;

- 401-1000 – severe CAD;
- >1000 - very extensive, diffuse, CAD.

Images obtained after contrast examination (0.75 mm thick) were analysed using the Syngo.via Coronary Analysis software application. Coronary arteries were evaluated by two radiologists on curve plane reconstructions (CPR), to identify, classify and quantify coronary lesions. Atherosclerotic plaques were defined as structures that cause an intima-media thickening (IMT) of more than 1 mm within or adjacent to the vessel lumen. The following parameters were assessed: atherosclerotic plaque type (calcified, noncalcified, mixed, ulcerated or thrombotic), presence and degree of coronary stenosis (less than 50%, 50-75%, 76-90%, equal or more than 91%), number of affected vessels (single or multi-vessel disease), location and number of stenoses. After conducting independent assessments, an interpretation consensus was reached in order to ascertain a final diagnosis.

Statistical analysis

Statistical tests were performed using SPSS 22.0 for Mac OS X. Quantitative data was tested for normality and presented as mean value ± standard deviation (SD). Student's t test and analysis of variance (ANOVA) were used for between group comparisons of mean values. Qualitative data was presented as percentages and compared using Chi-square of Fisher's exact test. A p value of less than 0.05 was considered significant.

2.4.1.4. Results

Clinical characteristics of study groups

The clinical features of diabetic versus non-diabetic patients are summarized in table XXII. In diabetic patients, mean time from diagnosis of this condition was 90±51 months (range 6 – 204 months). Twenty-eight patients (23.33%) were diagnosed with diabetic nephropathy, 22 (18.33%) with diabetic retinopathy, 30 (25%) with diabetic neuropathy, 8 (6.67%) with cerebrovascular disease, and 26 (21.67%) with peripheral artery disease (Table XXII).

Table XXII. Clinical features of analysed patients

	Diabetic patients	**Non-diabetic patients**	**p**
Age (mean ± SD)	58±11.4 years	61±10.2 years	n.s.
Sex ratio (M/F)	81/39	77/43	n.s.
Body mass index (kg/m^2)	27.8±4.2	28.5±3.5	n.s.
Cardiovascular risk factors			
Arterial hypertension	86 (71.67%)	72 (60%)	0.02
Dyslipidaemia	82 (68.33%)	71 (59.17%)	0.08
Current smoker	51 (42.5%)	55 (45.83%)	n.s.
Familial history	63 (52.5%)	58 (48.33%)	n.s.
Obesity	48 (40%)	29 (24.17%)	0.003

No significant differences were found between the two groups concerning lipid profile and plasma creatinine. Microalbuminuria registered higher values in diabetic group since 23.33% of patients already had nephropathy (Table XXIII).

Table XXIII. Blood and urine test results comparison between the two groups

	Diabetic patients	**Non-diabetic patients**	**p**
Total cholesterol (mg/dl)	210.1±50.2	205.3±43.2	n.s.
LDL cholesterol (mg/dl)	125.4±45.1	124.7±35.8	n.s.
HDL cholesterol (mg/dl)	46.3±12.2	50.6±19.7	n.s.
Triglycerides	158.2±75.4	163±94.8	n.s.
Plasma creatinine (mg/dl)	1.0±0.7	1.1±0.4	n.s.
Microalbuminuria (mg/dl)	105.3±95.2	43.7±37.8	0.002

Coronary atherosclerotic lesions were identified in 105 diabetics (87.5%) and in 75 non-diabetic patients (62.5%) the prevalence being significantly higher in the first group (p=0.023), but with no difference in the number of affected vessels (Table XXIV).

Table XXIV. Number of affected vessels in diabetic versus non-diabetic patients

Number of affected vessels	Diabetic patients	Non-diabetic patients	p
1 affected vessel	33 (32.67%)	27 (36%)	0.12
2 affected vessels	23 (21.90%)	14 (18.67%)	
≥3 affected vessels	49 (46.67%)	33 (44%)	

Most of coronary lesions involved the left anterior descending artery (LAD) in both groups, 87.62 of diabetic and 92% of non-diabetic patients, followed by the circumflex artery (CX) (50% of diabetic and 56% of non-diabetic patients) and the right coronary artery (RCA) (52.38% of diabetic and 42.67% of non-diabetic patients) with no differences between the groups.

Agatston calcium score registered significantly higher values in diabetic (350.3) compared to non-diabetic patients (158.7) (p=0.005) (Table XXV) (Fig. 20).

Table XXV. Agatston calcium score in type 2 diabetic patients compared to non-diabetic patients

Agatston score	Diabetic patients	Non-diabetic patients	p
Total	350.3±215.7	158.7±237.2	0.005
<10	11 cases (10.47%)	15 cases (20%)	0.004
11-100	23 cases (21.90%)	32 cases (42.67%)	
101-400	35 cases (33.33%)	11 cases (14.67%)	
401-1000	32 cases (30.48%)	15 cases (20%)	
>1000	4 cases (3.81%)	2 cases (2.67%)	

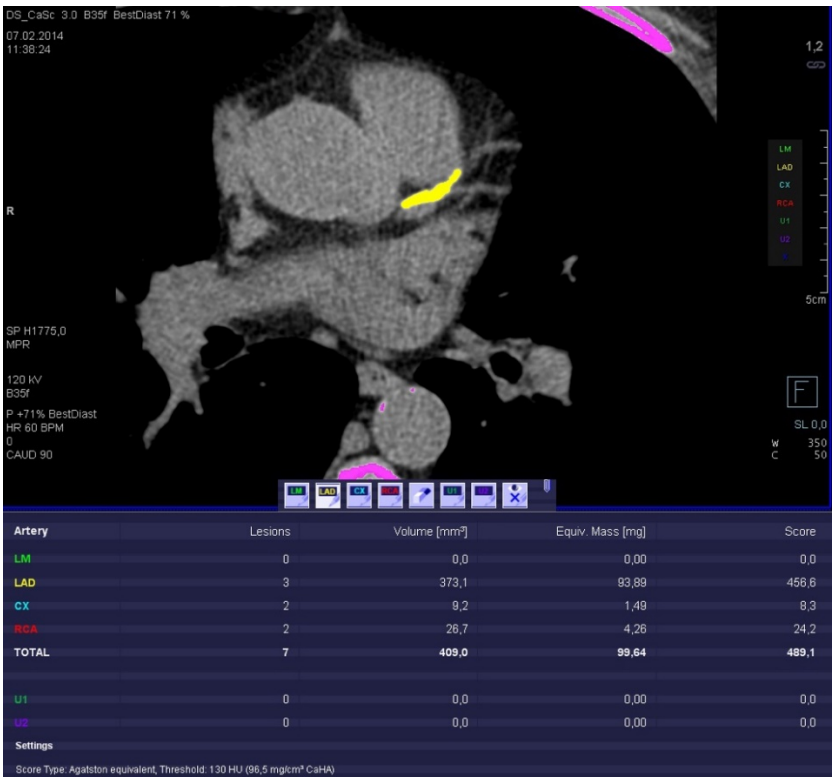


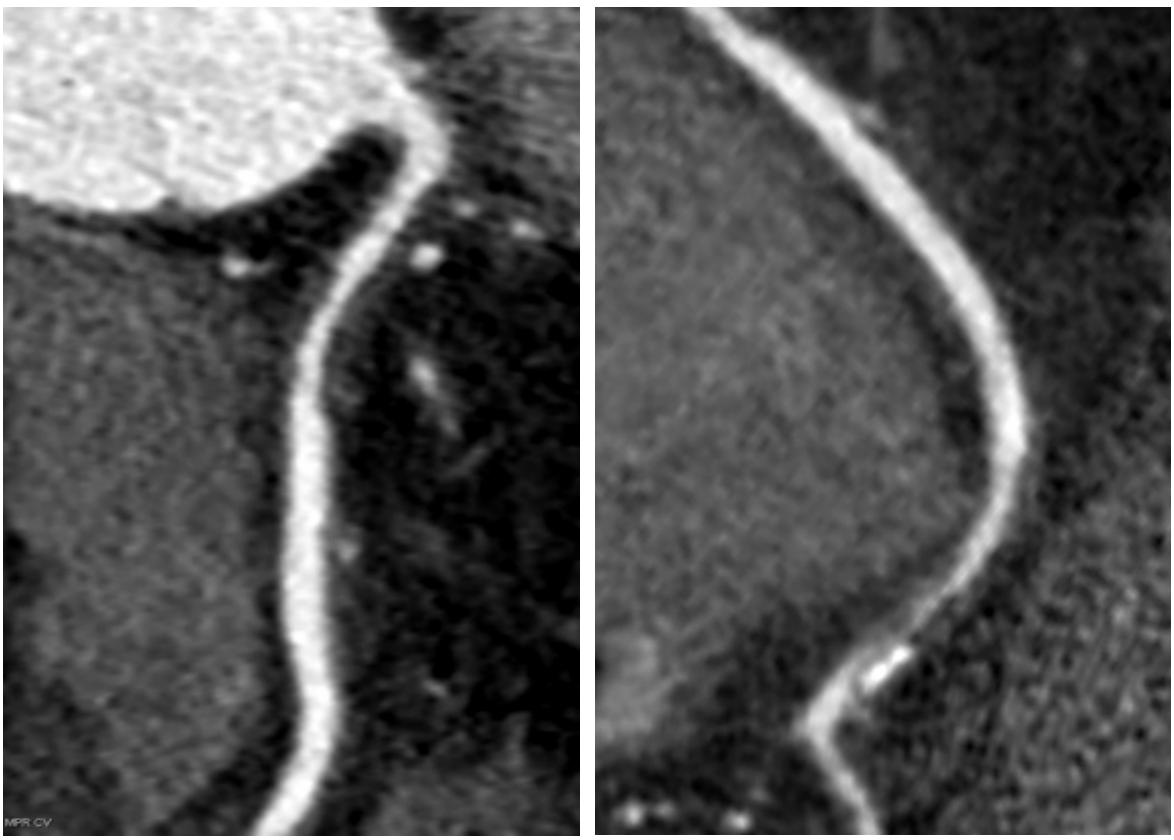
Fig. 20. Calcium score evaluation in a diabetic patient (IBCV Iasi)

Calcified atherosclerotic plaques were more frequent in diabetic patients (p=0.016), a situation anticipated by the higher values of the Agatston score. On the contrary, non-diabetic patients presented mostly mixed and non-calcified plaques (Table XXVI).

Table XXVI. Atherosclerotic plaques composition in type 2 diabetic patients compared to non-diabetic patients

Plaque type	Diabetic patients	Non-diabetic patients	p
Calcified	91 patients (86.67%)	51 cases (68%)	0.016
Mixed	74 cases (70.47%)	63 cases (84%)	
Non-calcified	41 cases (39.05%)	34 cases (45.33%)	
Ulcerated	2 cases (1.9%)	1 case (1.33%)	
Thrombotic	1 case (0.95%)	0 cases	

Vulnerable plaques (non-calcified, ulcerated, thrombotic) were found in 45 diabetics (42.86%) and in 35 non-diabetic patients (46.67%) with no significant difference between the two groups. More diabetic patients presented significant coronary lesions (≥50% stenosis) (53 cases, 50.48%) compared to non-diabetic patients (29 cases, 38.67%) (p=0.008) (Fig. 21).



a. **b.**

Fig. 21. Coronary plaques in a diabetic patient: a. 50% coronary stenosis caused by a non-calcified plaque with positive remodelling located in the 1st segment of the right coronary artery; b. 90% coronary stenosis caused by a mixed plaque in the 3rd segment of the right coronary artery (IBCV Iasi)

2.4.1.5. Discussions

Coronary artery disease, often asymptomatic in diabetic patients, is a worldwide leading cause of morbidity and mortality. Diabetic patients without typical symptoms generally have an intermediate probability of CAD, and might present to the hospital directly with ACS, as

CAD can manifest clinically only in advanced stages because of diabetic neuropathy. Also, diabetic patients have a higher prevalence of significantly stenotic plaques.

Early detection of CAD in diabetic patients is of paramount importance and challenging. Currently, there is no consensus in the literature on the diagnostic method to be used for early detection of CAD as systematic screening in asymptomatic high-risk patients is still a subject of debate.

Multidetector CT is the only method that allows a non-invasive investigation of the coronary arteries in patients with chest pain and in those at risk of CAD through the quantification of the Agatson calcium score and the angiographic evaluation after contrast agent injection.

Several studies suggested that the risk of ACS in asymptomatic diabetic patients is similar to the one registered in symptomatic nondiabetic patients (5, 6).

Many clinical trials (29) addressed the issue of improving event-free survival rate in diabetic individuals with clinical CAD, but fewer studies dealt with the prevention and early diagnosis of CAD before occurrence of symptoms.

In general, diabetic patients register a different risk profile compared to non-diabetic individuals, as the prevalence of arterial hypertension, dyslipidaemia, and obesity is higher in these patients, results explained by the strong association of metabolic syndrome with DM.

When performing the study, we found no significant differences between the lipidic profile in the two study groups suggesting a good metabolic control of DM.

Anand et al. (13) found a higher incidence of scintigraphic abnormalities of myocardial perfusion in asymptomatic diabetic patients with higher calcium scores, nearly 1/3 of patients with a calcium score higher than 400 having large ischemic defects.

In our series, the Agatston calcium score was higher in diabetic patients (350.3±215.7) compared to non-diabetic ones (158.7±237.2). More than half of the diabetic patients (63.81%) presented moderate or severe coronary calcifications in contrast to only 34.67% of the non-diabetic patients, results consistent with those previously published by Raggi et al. and Qu et al. (213,214).

The Agatston score is strongly associated with mortality, as it was affirmed in a review published by Thompson et al. (247), but based on the results of the current research, we may add that a 0 calcium score cannot exclude the presence of coronary plaques as there can be patients with noncalcified plaques only.

We identified significantly more coronary plaques in diabetic patients (87.5%) compared to non-diabetic ones (62.5%).

Similar findings in case of diabetic patients were reported by Kamimura et al. (81.19%), Hadamitzky et al. (86%) and Patel et al. (80.2%) (114,135,200,199,211). The prevalence of significant coronary stenoses was also higher in diabetic patients (50.48%) compared to non-diabetic patients (38.67%).

In the reviewed literature (114,199) we found a variable rate of 30-56.3% significant coronary stenoses (≥50%) in asymptomatic diabetic patients.

Hadamitzky et al. (114) found that only 30% of coronary plaques determined a ≥50% stenosis in his group of 140 diabetic patients without known CAD.

Both diabetic and non-diabetic patients included in the two study groups had two or more affected vessels. We noted a higher rate of diffuse involvement extending to the distal part of the vessels in diabetic patients. LAD was the most affected artery in the two groups.

Diabetic patients also had a higher prevalence of calcified plaques (86.67%), an extrapolation of the high Agatston score. Surprisingly, we accounted more mixed plaques in non-diabetic patients (45.33%) as opposed to diabetic patients (39.05%).

Pundziute et al. (211) suggested a faster evolution of atherosclerotic lesions in diabetic patients together with an increased rate of transition from noncalcified to calcified plaques.

However, we found no differences when comparing the prevalence of vulnerable and non-vulnerable plaques between the two groups.

Debates exist concerning the origin of the risk of ACS in diabetic patients, due to their insensitivity to CAD or to the prevalence of nonobstructive high risk plaques.

Goraya et al. (108) suggested that a higher burden in calcified plaques in diabetic patients could be explained by the accumulation of advanced glycation end products inducing the expression of genes and enzymes involved in the active calcification processes associated to atherosclerotic plaque formation.

Hyperglycaemia also induces osteopontin (a calcium-binding, phosphorylated glycoprotein that acts like a bridge between cells and minerals) expression in smooth muscle cells of the vascular wall.

Besides being implied in plaque calcification, osteopontin is also involved in plaque progression by promoting further platelet functional abnormalities.

Therefore, prolonged hyperglycaemia acts as a proatherogenic and prothrombotic factor that ultimately results in plaque calcification (226).

Given the fact that myocardial perfusion imaging studies are of limited access in our country, CCTA could be used as a screening method for identifying asymptomatic diabetic patients at risk for major cardiac events as it can rule out with high accuracy obstructive CAD.

Study limitation

The current study was performed in a single centre, was not designed as a cross-sectional one and was limited to a specific geographical area.

The patients enrolled in the study group presented plurifactorial coronary microvascular risk factors, such as diabetes mellitus, cigarette, smoking, dyslipidaemia and hypertension, facts that might suggest the possibility of false-positive results.

The number of patients enrolled in the study was limited and could contribute to bias.

The current approach based on image information representing anatomical rather than functional aspects can under or overestimates the impact of CAD, thus probably explaining the lack of correlation between detected lesions and asymptomatic CAD observed in our study.

The study will be extended with a functional evaluation through magnetic resonance imaging.

2.4.1.6. Conclusions

Asymptomatic diabetic patients display an increased prevalence of CAD compared to non-diabetic patients, more than half of asymptomatic diabetic patients having significant coronary stenosis.

Given the high prevalence of CAD among asymptomatic diabetic patients, CCTA could represent a possible screening method able to accurately detect silent atherosclerotic plaques, thus contributing to prevention of ACS by establishment of an early and adequate treatment.

2.4.2. The impact of morphological, pathophysiological and surgical factors on long-term graft patency in coronary artery bypass grafting

2.4.2.1. Introduction

Cardiovascular diseases (CVD) are the main cause of worldwide mortality (31%), responsible for more than 17.5 million deaths/year, estimated of 7.4 million due to coronary artery disease (CAD) alone (89). CVD mortality in Romania is higher than in Western Europe, 62% of deaths/year respectively (90). Medical treatment alone or associated with interventional procedures is insufficient in case of multiple coronary lesions or mechanical complications. In such cases, coronary artery bypass grafting (CABG), one of the most frequent surgical interventions in Europe (between 18 and 91 per 100.000 inhabitants), remains the only option (90). According to both European (88) and American (198) societies' guidelines, CABG is associated with a significant increase in life expectancy and quality of life in patients with unprotected left main or multi-vessel (≥3) disease. Despite proven advantages of CABG, the optimal grafting technique has not yet been established, debates still existing in the literature.

In 1964, Michael DeBakey performed the first successful CABG in humans by using a saphenous vein graft interposed between the ascending aorta and left descending coronary artery distal to a critical stenosis (3). The surgical technique evolved continuously for more than 60 years, and nowadays the intervention can even be performed minimally invasive and off-pump. *Despite all registered progress, clinical studies (no matter their type) did not manage to identify the ideal grafting technique in terms of grafting configuration, graft type, graft harvesting, graft preparation, anastomoses and optimal long-term patency.*

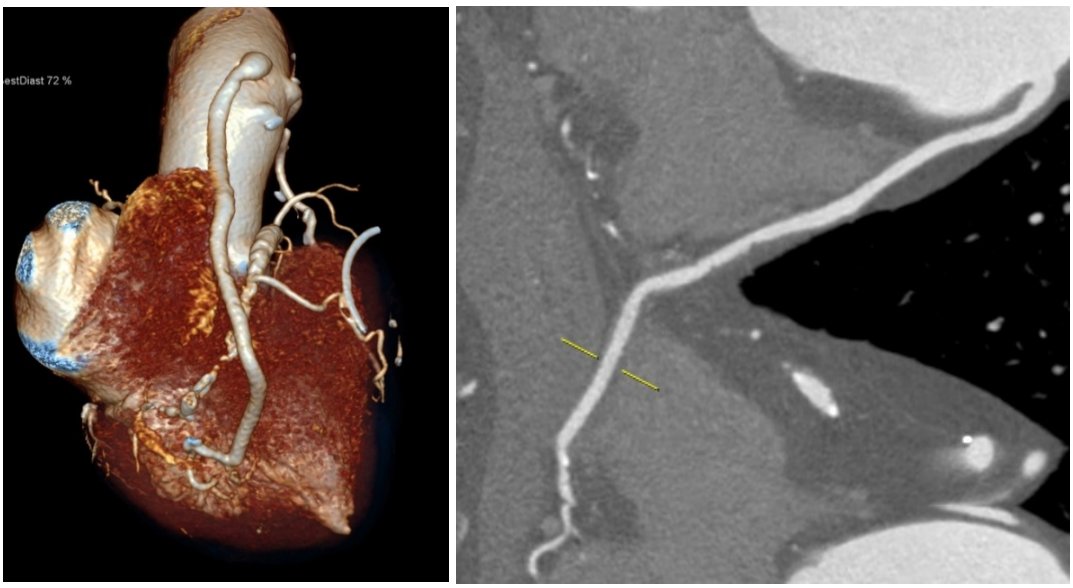
In the early days of the CABG, interventions were performed almost entirely using saphenous vein grafts (SVG) anastomosed to the ascending aorta. Venous wall has a different structure compared to the arterial wall, long-term venous graft patency being influenced by the calibre of the target coronary artery, degree of stenosis, surgical technique and grafted territory. Angiographic follow-up studies revealed a late attrition rate of venous grafts of 2 - 5% per year after surgery due to their intrinsic changes when placed in arterial circulation (105). Despite their anatomically imperfection, venous grafts are easy to harvest and to use, even for the unexperienced surgeon. Arterial grafts such as the internal thoracic (ITA) register extremely low attrition rate with very good long-term patency rates (96.4% over 15 years) compared to venous grafts (243). The left internal thoracic artery (LITA) has always been considered the "*gold standard*" graft for the left anterior descending artery. In 1995, Cameron et al. (49) published the results of a 20-year follow-up study and proved that the usage of an ITA graft increased the mean survival period with 4.4 years compared to venous grafts alone. David Taggard (241) extended the results of the previous study and affirmed that bilateral ITA usage offers even better survival rates than single ITA grafts.

Up to date, the only certitudes are that ITA is associated with better long-term patency and survival rates compared to SVG and that bilateral ITA usage increases survival more than single ITA. Most CAD patients have a multi-vessel disease and need revascularization of more than 2 coronary arteries, the completeness of revascularization being a factor conditioning intermediate and late survival.

The completeness of revascularisation (up to 5-6 distal anastomoses) is an important prognostic factor, but the pursuit of additional grafts and anastomosis techniques in order to achieve it has not proven to be an easy task. One potential additional graft is the radial artery (RA), a peripheral muscular vessel with enough length and superior calibre compared to ITA. It's muscular walls make it prone to spasm and intimal hyperplasia in case of inadequate harvesting and preparation, a fact that led to its abandonment in the dawn of CABG (21). In the years 2000, the RA was rediscovered, improved harvesting and preparation with papaverine and calcium channel blockers making it a viable option and a superior graft compared to SVG

in terms of long-term patency (91.8% versus 86.4%) (46,80). In spite of its major advantages, RA is sensitive to competitive flow through the native vessel, special attention must be paid to the degree of stenosis of the coronary artery (210). Various arteries have been proposed by several teams as alternatives to consecrated grafting (a. *gastroepiploica dextra, a. epigastrica inferior, a. splenica, a. ulnaris, a. subscapularis, a. gastrica sinistra*, and *a. circumflexa femoris lateralis*) but their usage is limited, and long-term reliability not confirmed yet. Conventional CABG with LITA and one or more SVGs is still widely used in the USA as insurance companies consider it the option of choice. Surgeons could be held liable if performing otherwise (103,164).

At the Cardiovascular Institute from Iasi, the policy is not to use all possible grafts for a single CABG intervention as survival rates generally exceed 10 years and patients may need redo-CABG as native vessel disease progresses and graft dysfunctions occurs (48,77) (Fig. 22).



a **b**

Fig. 22. Patent SVG to PDA graft: VR (a) and CPR (b) reconstructions (IBCV Iasi)

Complete revascularization must usually be accomplished with 2 to 3 grafts with best-proven patency rates (ITA, RA and exceptionally SVG) used to perform 5-6 distal anastomoses. In these circumstances, sequential and composite grafting, Y-grafts, T-grafts and combinations are required to increase the number of distal anastomoses and bypass all significant lesions with a limited number of grafts. In a pictorial review, Buxton illustrated several graft configurations usable in total arterial revascularization but their safety, efficacy and long-term patency has not been entirely clearly assessed (100,185,241). With complete revascularization, patients may receive 1-3 grafts/coronary territory (e.g. left anterior descending artery and one diagonal artery, two left marginal and one left posterolateral artery) so there are multiple cases with 5-6 distal anastomoses.

Long-term graft patency is a crucial prognostic factor for life expectancy and quality of life that relies on several parameters:

- Anatomical and histological – graft features (graft type, length and calibre) (103);
- Pathophysiological (competitive flow through the native coronary artery in non-critical stenosis, degenerative graft changes with an increased graft susceptibility to atherosclerosis) (80,134);
- Surgical – graft harvesting and preparation, grafting design and anastomosis technique (e.g. single, sequential, composite, Y/T, angle of anastomosis) (99,235,143).

In the performed studies we analysed patency generally assessed for individual grafts alone and not for CABG as a whole. In the meantime, the dilemma of designing an ideal grafting technique with increased long-term patency and significant hemodynamic improvement remained unsolved despite the increase in worldwide research. Three studies (28,29,30) *proposed two scores, the number of unprotected coronary territories (UCT) and the coronary artery protection score (CAPS), as being the most relevant for long-term prognosis than individual graft's patency as they reflect the (in)completeness of revascularization.*

Since 2000, more than 3000 patients underwent CABG interventions performed by a single team led by professor Grigore Tinica at the Cardiovascular Institute (Iasi, Romania). The revascularization technique varied in time according to scientific evidence from all venous grafts to total arterial revascularization and from "*one graft-one coronary artery*" to composite/Y grafts with 2-3 sequences per graft.

My interest in this field is reflected by the following published papers, books and research projects:

Articles:

2. Tinica, G, Chistol, RO, Bulgaru Iliescu D, **Furnica C**. Long-term graft patency after coronary artery bypass grafting: Effects of surgical technique. Exp Ther Med 2019; 17(1):359-367.

3. Tinica G, Chistol RO, Enache M, Leon Constantin MM, Ciocoiu M, **Furnica C**. Long-term graft patency after coronary artery bypass grafting: Effects of morphological and pathophysiological factors. Anatol J Cardiol 2018; 20(5): 275-82.

4. Chistol RO, **Furnica C**, Rusu AC, Tinica G. Computed tomography evaluation of coronary artery bypass grafts strengths and pitfalls: a tertiary center experience and pictorial review. Romanian Journal of Functional and Clinical, Macro- and Microscopical Anatomy and of Anthropology 2016; XV(2): 179-187.

Books:

1. Tinica G, **Furnica C**. Morphological Predictors of Graft Patency in Coronary Artery Bypass Grafting. "Gr.T.Popa" U.M.F. Iasi Publishing House, 2018.

Book chapters:

2. Tinica G, **Furnica C**, Chistol RO. Cardiac Surgery Risks in Liver Dysfunction in Radu-Ionita F, Pyrsopoulos NT, Jinga M, Tintoiu IC, Sun Z, Bontas E eds. Liver Diseases. A Multidisciplinary Textbook. Springer, 2020, pp. 799-810.

2.4.2.2. Aims

Together with a team of anatomists, radiologists and cardiac surgeons we aimed to perform a multidisciplinary research to assess long-term graft dysfunction, to identify morphological, pathophysiological and surgical factors associated with long-term graft patency and to analyse the translation of graft patency in terms of long-term survival, major adverse cardiac events (MACE) and redo-revascularization of grafts or native coronary arteries.

The novelty of the research consisted in its integrative approach, the herein being the first study to analyse the combined effect of several factors upon graft patency and to integrate graft patency evaluated through medical imaging into CABG prognosis as a whole, by taking into account the protection of coronary territories.

The final endpoint of the research was to identify the profile of the grafting technique (vessel type, graft harvesting and preparation, anastomosis, grafting configuration and design) offering the best long-term results. Improvement of the surgical technique according to obtained results may lead to decreased long-term morbidity and mortality and inherent diminishment of health-care costs associated with hospitalization and additional interventions.

2.4.2.3. Materials and methods

Patient population and surgical technique

Demographic, clinical, echocardiographic, and angiographic data on patients undergoing CABG at the Cardiovascular Institute from Iasi have been prospectively collected and introduced into a database since 2000, together with intraoperative (extracorporeal circulation type and time, aortic cross-clamp time, CABG technique, number and type of grafts, and associated procedures) and postoperative data (intensive care unit parameters, complications, and mortality within 30 days).

The CABG technique varied according to the practice at the time of surgery from total venous to total arterial revascularization and from one graft–one anastomosis to composite and sequential grafting.

In order to be included in the study group, the patient had to fulfil the following *inclusion criteria's*:

- Signed agreement for data analysis as part of medical research;
- Adulthood (above 18 years old);
- CABG for multivessel coronary atherosclerotic disease;
- Complete medical record including identification data, contact data, baseline characteristics, preoperative data (cardiovascular risk factors, previous cardiovascular interventions, echocardiography, coronarography), intraoperative data (type of graft, harvesting technique, grafts' configuration, number and type of anastomoses, target vessel), postoperative data (complications);
- Follow-up data at a minimum of 10 years after CABG - MACE, check-up coronarography or coronary CTA;
- Known status (alive, deceased) when research is performed.

Exclusion criteria:

- patients < 18 years;
- incomplete medical record;
- no follow-up data;
- unknown status (uninsured);
- deceased patients with unknown graft patency.

Patient re-evaluation. The status of all 394 patients who received CABG between 2000 and 2006 and discharged from the hospital was verified in 2016, at a minimum of 10 years after the intervention, using the National Health Insurance House database. Two hundred sixty-nine (68.27%) were recalled by invitation letter or phone call to a graft patency evaluation by coronary computed tomography angiography (CCTA). A total of 127 patients who agreed to the CCTA evaluation and presented no contraindications to iodinated contrast administration were evaluated after a mean postoperative period of 139.78 ± 36.64 months. None of these patients presented signs of early graft failure such as within 30 days' myocardial infarction or acute left heart failure.

Postoperative long-term medical treatment consisted of beta blockers, statins, and enteric-coated aspirin in all cases. Patients who were treated with an RA graft additionally received a calcium channel blocker (amlodipine) for the first 3 months to prevent graft spasm.

Methods

All 394 patients' data was encoded into a single Excel database. After data collection, patient status was checked on the National Health Insurance House's webpage based on personal identification number and patients with unknown status were excluded.

Follow-up data was obtained from the Institute's electronic medical platform (InfoWorld).

Examination reports for patients who benefited from CCTA or conventional

coronarography evaluation of graft patency between 2014-2016 was encoded in the database together with the time period elapsed from CABG to the respective examination, no matter if the patient was deceased or alive when the research was performed.

Patients who did not benefit from CCTA or conventional coronarography evaluation of graft patency between 2014-2016 were invited through invitation letters or phone call (upon valid contact data) to a CCTA.

Patients who responded to the invitation, agreed to undergo a CCTA and had no contraindications to iodinated contrast media administration benefited from a one-day hospitalization and the following investigations: clinical evaluation, blood sampling with routine laboratory tests, electrocardiogram, echocardiography, CCTA.

All CCTA examinations were performed following the protocol detailed in the previous study. Image analysis results were encoded in the previously created database.

The study was approved by the Ethics Committee of the "Grigore T. Popa" University of Medicine and Pharmacy and by the Ethics Committee of the "Prof. Dr. George I.M. Georgescu" Cardiovascular Diseases Institute.

Statistical analysis

Information encoded in the database was analysed using SPSS Statistics Desktop 22.0 for Mac. Quantitative data was tested for normality and presented as mean value ± standard deviation (SD), minimum, maximum, quartiles. Qualitative data was presented as ranks, scores and percentages.

Parametric and nonparametric tests were used for data comparison with a p value of less than 0.05 considered as significant.

Univariate analysis was used to identify potential predictors and hazard ratios (HR) with 95% confidence interval (CI) for estimation of the risk associated to a certain variable. Multivariate analysis (ROC curve) was used for independent predictors. Survival rates as function over time were obtained by the Kaplan-Meier method.

2.4.2.4. Results

The preoperative, operative and postoperative data of the 127 patients are illustrated in Tables XXVII-XXIX.

Table XXVII. Preoperative data

Parameter	Value	Percentage
Mean age (y) ± SD	67.54 ± 8.84	-
Female sex	19	14.96%
Family history	41	32.28%
Smoking	49	38.58%
Diabetes mellitus	28	22.05%
Dyslipidaemia	97	76.38%
MVD	19	14.96%
AHT	77	60.63%
COPD	8	6.30%
NYHA III – IV heart failure	24	18.90%
Prior AMI	65	51.18%
Arrhythmias	23	18.11%
Mean LVEF (%)	53.81±10.77	-
Number of affected coronary arteries **Diffuse disease** **Three vessel disease**	2.86±1.24 29 71	- 22.83% 55.91%

MVD: multivascular disease; AHT: arterial hypertension; COPD: chronic obstructive pulmonary disease; AMI: acute myocardial infarction; LVEF: left ventricular ejection fraction.

Table XXVIII. Operative data

Parameter	Value	Percentage
Emergency surgery	3	2.36%
Associated interventions	13	10.24%
ACC time (min) ± SD **ECC time (min) ± SD**	90.01±61.35 136.82±64.13	
Mean number of grafts/patient **Mean number of arterial grafts/patient** **Mean number of venous grafts / patient** **Mean number of distal anastomoses/patient**	2.68±0.94 1.64±1.20 1.52±0.79 3.14±1	
Conventional CABG (at least 1 SVG) **TAR** **Single graft** **Total venous**	79 38 5 5	62.20% 29.92% 3.94% 3.94%
IABP usage	1	0.79%
Complete revascularisation	102	80.31%

ACC: aortic cross clamp; ECC: extracorporeal circulation; TAR: total arterial revascularisation; IABP: intra-aortic balloon pump.
Associated interventions: valve surgery, atrial fibrillation ablation, ascending aorta replacement, left ventricular aneurysm repair.

Table XXIX. Postoperative data (within 30 days)

Parameter	Value	Percentage
Reintervention for haemorrhage or sternal dehiscence	10	7.87%
Acute renal failure	2	1.57%
Arrhythmia	31	24.41%
Neurological complications	2	1.57%
Deep sternal wound infection	2	1.57%
Other infections (urinary tract, pneumonia)	3	2.36%
Digestive complications (ileus, *Clostridium difficile* infection)	4	3.15%

Risk factors for early postoperative morbidity

In the initial part of the study, we tested the prognostic effect of pre, intra and postoperative parameters on the short-term outcome, namely within 30 days' complications, and identified of the following independent predictors:

- For re-intervention: CKD, diffuse CAD, prolonged ICU hospitalisation and 24 h pericardial drainage;
- For AKI: diabetes mellitus, CKD, COPD, IABP usage, logistic EuroSCORE, prolonged intubation and ICU hospitalisation;
- For neurological complications: pre-operative arrhythmias, COPD, CAD severity (number of diseased coronary arteries), prolonged intubation and ICU hospitalisation;
- For infectious complications: age, MVD, LVEF, IABP usage, logistic EuroSCORE, prolonged intubation and ICU hospitalisation (table XXX).

Risk factors for within 30 days' mortality

After identifying the prognostic factors for early morbidity, we evaluated within 30 days' mortality. Early postoperative death occurred in 3 cases (0.76%). Two patients presented

with low preoperative LVEF and needed emergency CABG and left ventricular repair/mitral valve prosthesis for acute mechanical complications in the first 24 hours after AMI. The 3rd patient also underwent emergency CABG for acute LAD stent thrombosis. The limited number of cases did not allow a statistical analysis.

Risk factors for late postoperative morbidity – major adverse cardiac events (MACE)

Late postoperative morbidity was evaluated considering 219 patients presenting at least one follow-up consultation between 2013-2016 at the Cardiovascular Diseases Institute.

Table XXX. Independent predictors for within 30 days' complications

	P	Odds Ratio	95% confidence interval
REINTERVENTION			
CKD	0,001	**4,314**	1,851-10,057
Diffuse CAD	0,044	**2,409**	1,023-5,673
ICU hospitalisation	0,0001	**1,508**	0,704-2,912
24h drainage	0,0001	**1,002**	1,001-1,003
ACUTE KIDNEY INJURY			
Diabetes mellitus	0,003	**4,467**	1,649-12,103
CKD	0,001	**5,293**	1,968-14,230
COPD	0,007	**4,472**	1,507-13,272
IABP	0,039	**4,580**	1,076-19,490
Logistic EuroSCORE	0,036	**1,088**	1,005-1,177
Prolonged intubation	0,015	**2,522**	1,199-5,304
ICU hospitalisation	0,0001	**4,502**	1,995-10,157
NEUROLOGICAL COMPLICATIONS			
Arrhythmias	0,027	**6.145**	1.232
COPD	0,0001	**13,189**	3,114-55,863
Number of diseased arteries	0,005	**3,027**	1,407-6,512
Prolonged intubation	0,001	**4,685**	1,919-11,440
ICU hospitalisation	0,001	**10,231**	2,711-38,609
INFECTIOUS COMPLICATIONS			
Age	0,098	**1,956**	0,882-4,376
MVD	0,098	**2,109**	0,878-4,640
LVEF	0,041	**1,956**	1,041-3,675
IABP	0,028	**4,206**	1,16—15,173
Logistic EuroSCORE	0,027	**1,081**	1,009-1,158
Prolonged intubation	0,078	**1,902**	0,931-3,885
ICU hospitalisation	0,0001	**6,206**	3,046-12,647

The results of multivariate logistic regression plead for a decreasing risk of saphenous vein graft dysfunction with 42.3% for every postoperative year. Three-vessel disease in the moment of surgery was associated with 11.3 times increased chance of MACE (table XXXI).

In case of *de novo* lesions, the odds of MACE decreased with 26.1% for every postoperative year. Moreover, the presence of a multivessel CAD (≥3) decreased the odds of developing new lesions with 82.9%, specifically 21.1% attributed to each additional graft.

Table XXXI. Multivariate logistic model for evaluation of MACE risk factors associated to venous grafts malfunction

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. EXP(B)	
							Lower	Upper
Interval	-.550	.121	20.530	1	.000	**.577**	.455	.732
Afectare tri	2.425	.816	8.823	1	.003	**11.305**	2.282	56.010
Constant	.901	.888	1.029	1	.310	2.462		

In case of multivessel CAD with complete revascularisation, the degree of coronary protection is higher than in case of single or two vessel disease with unprotected native vessels still able of developing new lesions. Coronary artery disease occurs later and more severe in women than in men, female sex being also associated to 1.89 times increased odds of *de novo* lesions (table XXXII).

Risk factors for late postoperative mortality

When analysing patient data, we identified the following independent predictors of long-term mortality (table XXXIII):

- age (2.6% increased odds for every additional year in the moment of surgery);
- three vessel CAD (OR 2.060);

Table XXXII. Multivariate logistic model for evaluation of MACE risk factors associated to *de novo* lesions

	B	S.E.	Wald	df	Sig.	Exp(B)	95	EXP(B)
							Lower	Upper
Interval	-.302	.086	12.258	1	.000	**.739**	.624	.875
Afectare tri	-1.764	.625	7.962	1	.005	**.171**	.050	.583
Sex	.635	.520	1.487	1	.223	1.886	.680	5.232
Nr. Graft	-.237	.338	.493	1	0.082	**.789**	.407	1.530
Constant	1.582	1.08	2.147	1	.143	4.867		

- reduced LVEF (<30% LVEF was associated to a 1.956 increased chance compared to LVEF 31-50%);
- number of grafts (odds reduction with 48.4% for every additional graft);
- completeness of revascularisation (16.3% odds reduction);
- number of distal venous anastomoses (each anastomosis increases the odds with 26%);
- neurological complications (OR 4.639).

Long-term graft patency assessment

For the 127 patients who presented for CCTA evaluation, a total number of 340 grafts (2.68 grafts/patient) were used to perform 399 distal anastomoses (3.14 anastomoses/patient). Most anastomoses (220 - 55.14%) were realised using arterial grafts, especially ITAs (122 LITA, 53 RA, 45 RITA) and fewer (179 - 44.86%) using SVGs.

The overall graft patency at 10 to 16 postoperative years was higher for arterial grafts, especially ITAs - 90.16% LITA (12 occluded grafts), 75.55% RITA (11 occluded grafts), 79.25% RA (11 occluded grafts), and lower for SVGs - 74.3% (46 occluded grafts).

Table XXXIII. Multivariate logistic model for evaluation of long-term mortality risk factors

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. EXP(B)	
							Lower	Upper
Paliere EF	.672	.208	10.482	1	.001	**1.959**	1.304	2.943
Afectare tri	.723	.296	5.970	1	.015	**2.060**	1.154	3.680
Nr. Graft	-.662	.181	13.376	1	.000	**.516**	.362	.735
Revascularizare completă	0.646	.157	6.138	1	.000	**.837**	.412	1.153
№ ADV	.231	.137	2.854	1	.091	**1.260**	.964	1.648
Compl neuro	1.535	.849	3.269	1	.071	**4.639**	.879	24.484
Varsta	.026	.014	3.434	1	.064	**1.026**	.999	1.055
Constant	-2.124	.921	5.320	1	.021	.120		

- *The influence of morphological factors*

The influence of the *graft length* on patency rates was analysed after indexing its value to the height of the patient (151–190 cm).

The analysis was performed separately for each graft-target vessel pair, but the limited number of cases for certain configurations did not allow a statistical analysis.

In the case of grafts with enough cases (LITA–LAD, RA–PDA, SVG–diagonal, SVG–MO, SVG–PDA, and SVG–RCA), no statistically significant difference was found when comparing mean graft length according to graft status (Table XXXIV).

Table XXXIV. Graft patency according to length

Graft	Patent	Occluded	p
LITA-LAD	0,117	0,119	0,818
RA-PDA	0,844	0,824	0,541
RA-Diagonal	0,066	-	
RA-MO	0,089	-	
RA-MO (Y)	0,071	0,064	-
RA-RCA	0,0867	0,072	-
RA-IB (Y)	0,024	0,028	-
RITA-Diagonal (Y)	0,040	0,031	-
RITA-MO (Y)	0,065	0,074	-
RITA-PL (Y)	0,095	0,074	-
RITA-RCA	0,113	0,106	-
RITA-IB (Y)	0,046	0,024	-
SVG-Diagonal	0,62	0,74	0,680
SVG-LAD	0,082	-	-
SVG-MO	0,83	0,75	0,933
SVG-PDA	0,09	0,079	0,533
SVG-PL	0,095	0,064	-
SVG-RCA	0,0736	0,0732	0,637
SVG-IB	0,067	0,052	-

LITA: left internal thoracic artery; LAD: left anterior descending artery; RA: radial artery; MO: marginal obtuse artery; RCA: right coronary artery; IB: intermediate branch; RITA: right internal thoracic artery; SVG: saphenous vein graft; PDA: posterior descending artery; PL: posterolateral artery.

Graft patency varied according to *coronary territory* (Table XXXV). The maximum patency rate was obtained with the RA for the RCA territory, RITA for the anterolateral territory, and SVG for the CX territory (Fig. 23).

Table XXXV. Graft patency according to coronary territory

	Right coronary territory occlusion rate	Circumflex artery territory occlusion rate	Anterolateral territory occlusion rate
RITA graft	3/8 (37.5%)	7/23 (30.43%)	1/14 (7.14%)
RA graft	6/31 (19.35%)	4/16 (25%)	1/6 (16.67%)
SVG	24/68 (35.29%)	11/63 (17.46%)	11/48 (22.92%)

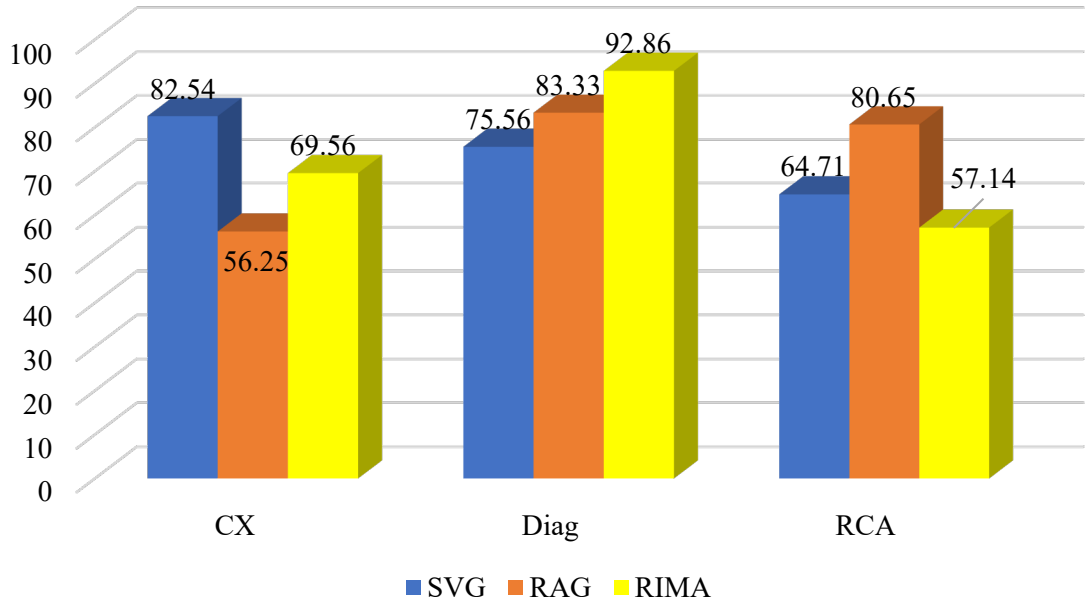


Fig. 23. Graft patency according to coronary territory

The most important coronary artery, LAD, was analysed separately from other target vessels. In 118 of 122 cases (96.72%), the "gold standard" LITA graft was used for revascularization, followed by SVGs in 3 cases (2.46%) and *in situ* RITAs in one case (0.82%). No SVG–LAD or RITA–LAD occlusion was identified but the effectiveness of these grafts cannot be generalized given the small number of cases.

The LITA–LAD graft occluded in only 12 patients (9.83%), in 7 cases potential causes of competitive flow being identified at CCTA examination (concomitant grafting of diagonal arteries with no interposed segment of over 75% stenosis—2 cases, grafting to an LAD with less than 75% stenosis—4 cases, and subsequent percutaneous left main stenting—1 case) (Fig. 24).

After analysing graft patency according to target territory, we evaluated the influence of *stenosis severity* and *vessel calibre*. In the case of venous grafts, we recorded no significant difference in target vessel degree of stenosis between patent (mean stenosis 90.5%) and occluded grafts (mean stenosis 90.62%) (p=0.607).

For arterial grafts, the difference was statistically significant (p=0.005), with a mean target vessel degree of stenosis of 91.22% for patent grafts and 78.52% for occluded grafts.

Using the area under the curve of ROC, we identified a stenosis severity of 90% as a threshold value with an 80% sensitivity and specificity in stating graft occlusion. Logistic regression computed an occlusion OR of 3.02 for arterial grafts anastomosed to target vessels with <90% stenosis (95% CI 1.321–6.902, p<0.001).

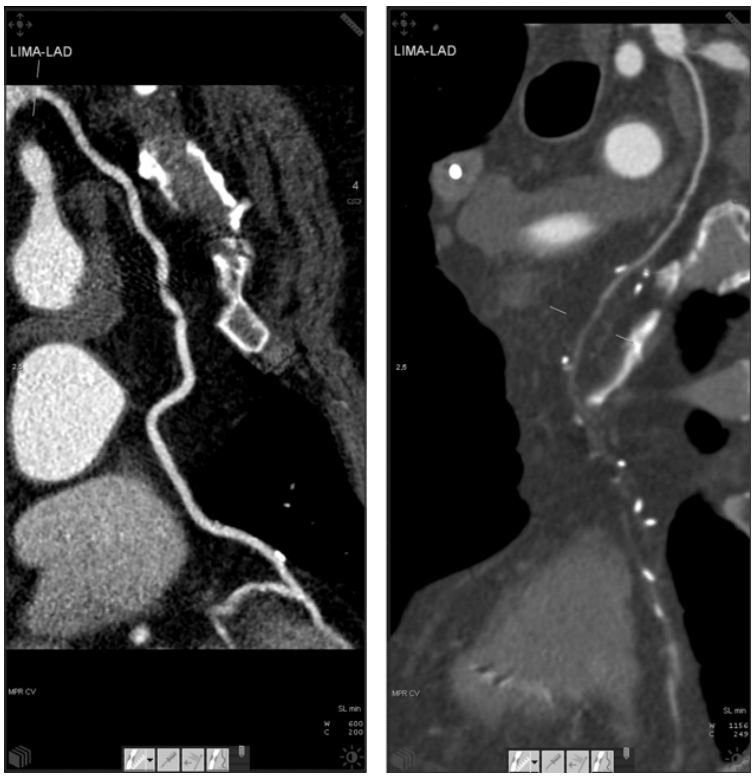


Fig. 24. CCTA aspect of patent and occluded LAD (IBCV Iasi)

For analysing graft patency according to target *vessel calibre*, coronary arteries were divided into two groups upon the calibre immediately downstream from anastomosis: ≤1.5 mm and >1.5 mm. For the SVG, 43.33% of grafts anastomosed to ≤1.5 mm target vessels occluded on the long-term compared to 22.15% of those anastomosed to >1.5 mm target vessels (p=0.001) (Fig. 25).

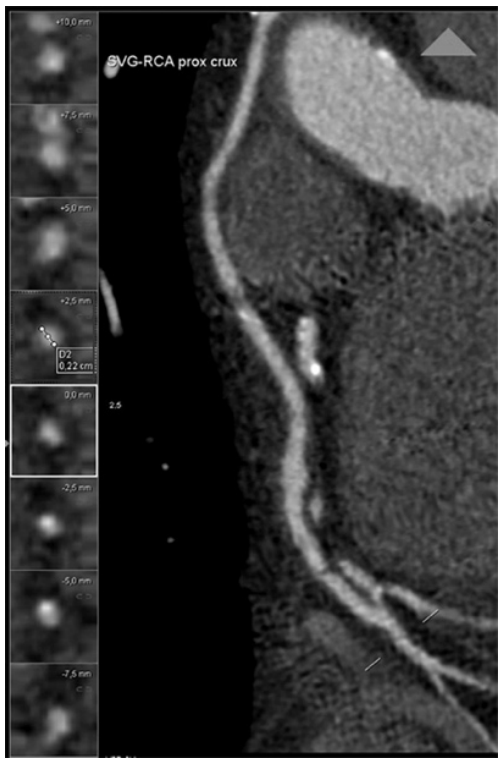


Fig. 25. SVG patency according to RCA calibre (IBCV Iasi)

In case of arterial grafts, we obtained similar results with a 30.77% occlusion rate for grafts anastomosed to ≤1.5 mm target vessels versus 15.03% in the case of >1.5 mm target vessels (p=0.008). Logistic regression quantified a 2.63 occlusion OR for SVGs (95% CI 1.32–2.98, p=0.0041) and 2.31 occlusion OR for arterial grafts (95% CI 1.53–3.19, p=0.0001) anastomosed to ≤1.5 mm target vessels.

- *The effect of proximal anastomosis type*

For grafts with different types of proximal anastomosis, such as RITA and RA, we analysed graft patency according to *proximal anastomosis type* (*in situ* graft, composite graft with Y/T anastomosis, and graft anastomosed to the ascending aorta). Saphenous vein grafts and LITA were excluded from this analysis, as the first were anastomosed proximally to the ascending aorta, and the latter used *in situ* in all cases but one.

The RITA graft was used *in situ* in 8 cases (17.78%), as a composite graft with proximal anastomosis to LITA in a Y/T manner in 36 cases (80%), and as a free graft anastomosed to the ascending aorta in 1 case (2.22%). The occlusion rate was of 3/8 (37.5%) for *in situ* RITA and 8/3936 (22.22%) for composite grafts. The free graft was patent. Chi square test showed no association of RITA patency with proximal anastomosis type (p=0.501).

The RA was used as a free graft anastomosed to the ascending aorta in 40 cases (75.47%) and as a composite graft anastomosed Y/T to LITA in 13 cases (25.43%). The occlusion rate was of 6/40 (15%) for the free graft and 5/13 (38.46%) for the composite graft. The Chi-square test identified a significant association of graft patency with proximal anastomosis type ($\chi^2 = 10.932$, p = 0.001)(Table XXXVI).

Table XXXVI. Association of RA graft patency with proximal anastomosis type

Variable	Occluded	Patent	Pearson Chi-Square	p
RA-Aorta	6 (15%)	34 (85%)	10.932	0.001
RA-LITA	5 (38.46%)	8 (61.54%)		

RA – radial artery graft, LITA – left internal thoracic artery

Logistic regression quantified a 0.110 occlusion OR (p = 0.002) for the RA graft anastomosed to the ascending aorta, thus certifying a protective effect against long-term failure (Table XXXVII).

Table XXXVII. Prognostic value of the proximal anastomosis type (RA-aorta)

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Proximal anastomosis	-2.205	.722	9.327	1	.002	.110	.027	.454
Constant	.470	.570	.680	1	.410	1.600		

RA – radial artery graft, B - unstandardized regression weight, S.E. – standard error, Wald - Wald chi-square test, df – degrees of freedom, Sig. – significance level, Exp(B) - exponentiation of the B coefficient, C.I. – confidence interval

- *The effect of Y/T anastomosis angle*

The *mean angle* for Y/T anastomoses with both grafts patent was 47.21º compared to 56º for anastomoses with occlusion of the free arterial graft (RA or RITA). In the absence of normal distribution, we used the Wilcoxon-Mann-Whitney U test to analyse the effect of the anastomosis angle and identified a significant difference between the anastomosis angle of patent versus occluded grafts (p = 0.015), a smaller angle being registered in case of patent anastomosis (Table XXXVIII) (Fig. 26). At the ROC curves analysis, we did not identify a high sensitivity and specificity threshold angle with prognostic value in affirming the risk of occlusion for Y-anastomoses.

Table XXXVIII. Proximal and distal anastomosis angle comparison between occluded and patent grafts

	Occluded	Patent	p
Y/T anastomosis angle	56±27.22º	47.21±25.05º	0.015
Side-to-side anastomosis (sequential grafting)	53.97±23.54º	48.60±21.14º	0.005
End-to-side anastomosis (sequential grafting)	90.80±11.27º	65.12±26.04º	0.002
End-to-side (single distal anastomosis)	44.94±29.52º	39.46±21.97º	0.034

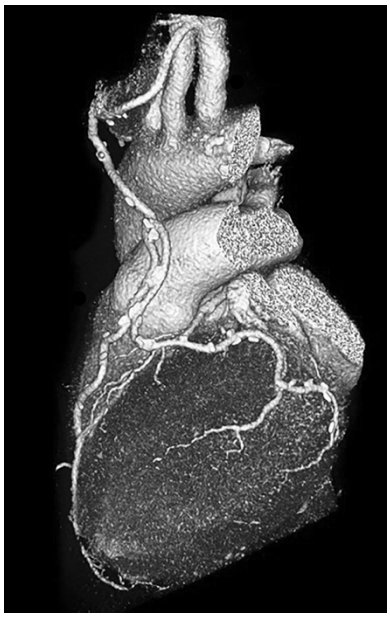


Fig. 26. Small Y anastomosis angle with patent graft (IBCV Iasi)

- *The effect of distal anastomosis type and angle*

Most *distal anastomoses* were end to side (368 cases), only 31 being side-to-side and performed with 27 grafts (sequential anastomoses) (Fig. 27).

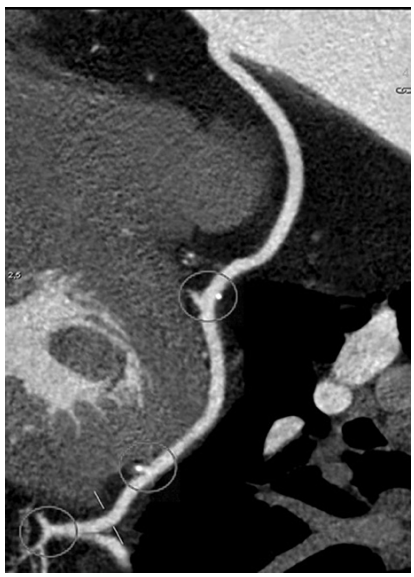


Fig. 27. Patent sequential anastomoses (IBCV Iasi)

Arterial grafts were preferred for sequential grafting - 18 arteries (occlusion of 7 end-to-side anastomoses and 9/20 side-to-side anastomoses), the rest of 9 grafts being venous

(occlusion of 2 end-to-side anastomoses and 0/11 side-to-side anastomoses). The small number of cases did not allow statistical testing, but one can observe a higher patency rate of venous grafts with sequential anastomoses.

The angle of anastomosis was important in sequential grafting, the mean value being of 48.60º for patent and 53.97º for occluded side-to-side anastomoses. In case of end-to-side anastomoses, the angle was 65.12º for patent and 90.80º for occluded ones (p = 0.002) irrespective to graft type.

For single distal end-to-side anastomosis, arterial grafts proved to be sensitive to the anastomosis angle with a mean value of 39.46º ± 21.97º for patent and 44.94º ± 29.52º for occluded grafts (p = 0.034).

Compared to arterial grafts, venous grafts were not sensitive to distal anastomosis angle. Using the area under the curve (AUC) of ROC, an angle of 60º was determined as a threshold value with an 80% sensitivity and specificity in affirming arterial graft occlusion (Fig. 28).

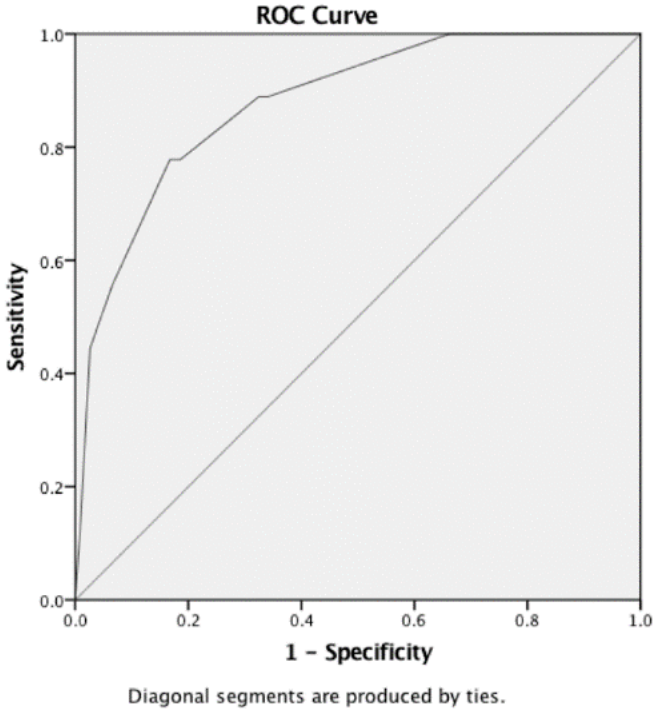


Fig. 28. ROC curve for an anastomosis angle of 60º

Logistic regression identified an occlusion OR of 5.149 for arterial grafts in case of a distal anastomosis angle ≥60º (p<0.001) (Table XXXIX).

Table XXXIX. Prognostic value of a distal anastomosis angle ≥60º

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)		Occluded anastomoses
							Lower	Upper	
Angle	1.639	.444	13.630	1	<0.01	5.149	2.157	12.292	14 (8.38%) for <60º
Constant	-2.367	.302	61.476	1	<0.01	.094			6 (17.14%) for ≥60º

B - unstandardized regression weight, S.E. – standard error, Wald - Wald chi-square test, df – degrees of freedom, Sig. – significance level, Exp(B) - exponentiation of the B coefficient, C.I. – confidence interval

2.4.2.5. Discussions

Numerous studies debating CABG have been published over the years, but graft patency has been assessed for individual grafts alone and not for CABG as a whole. Despite the increase in worldwide research, the optimal grafting technique offering considerable haemodynamic improvement and long-term graft patency remains an unsolved dilemma. We divided the factors influencing graft patency into morphological (vessel type, graft length, and calibre) (21,210), pathophysiological (competitive flow through the native coronary artery, graft degenerative changes) (210), and surgical (technical expertise, graft harvesting and preparation, grafting design, and anastomosis technique) (103,164) and evaluated long-term CABG results according to these parameters.

Graft type. The largest meta-analysis comparing long-term ITAs and SVGs patency was performed in 2001 by Taggard et al. on 15,962 patients (240). They identified a 10-years patency rate of 90%–95% for ITAs while 75% of SVGs presented stenotic or occlusive lesions. Benedetto et al. (35) extended the study and analysed 9 randomized trials including 1620 angiographic controls at 1–7.7 years after CABG and quantified a 4 times higher occlusion risk for SVGs and 3 times for RA grafts compared to RITA grafts. On a group of 2120 elderly patients (>70 years old), Habib et al. (113) proved an increased survival rate of 5 to 10 years for the ITA–RA association compared to the ITA–SVG association. In our study, the highest patency rate was obtained with LITAs (90.16%), followed by RAs (79.25%), RITAs (75.55%), and SVGs (74.3%). Saphenous vein grafts are prone to a particular type of dysfunction when placed in the arterial circulation given their different wall structure, namely thrombosis in the first month (due to focal destruction of the venous endothelium while harvesting), intimal hyperplasia between 1 month and 1 year, and atherosclerosis after 1 year. Autopsy studies identified atherosclerotic lesions in dissected SVGs starting from the first postoperative year (118). These lesions rarely generate significant stenosis in the first 3 postoperative years and are responsible for clinical symptoms after 5 years. Arterial grafts are resistant to atherosclerotic lesions, but the RA is a muscular artery vulnerable to spasm in the case of inadequate harvesting and competitive flow. Fibro-intimal hyperplasia as an isolated process occurs particularly in ITA grafts. Internal thoracic artery grafts rarely occlude as they share similarities with native coronary vessels – same wall structure and calibre.

Graft length. Opposite to graft type, the influence of graft length upon long-term patency was not investigated by extensive studies. According to small series (265) and case presentations (184), a short, tensed arterial graft is prone to spasm and a short venous graft can flatten with the hypo perfusion of the grafted territory. A graft with excessive length is also undesirable as it is predisposed to transection and kinking. Graft length could prove to be insufficient in case of inaccurate estimation of the cardiac volume (during extracorporeal circulation the heart is arrested and depleted of blood, its volume being smaller), peripheral localization of the target vessel (PDA, MO), anatomical features of the graft (high ITA bifurcation), harvesting or manipulation errors (destruction of a graft segment), and pulmonary hyperinflation in emphysema (during extracorporeal circulation the lungs are collapsed, their inflation tensioning the graft). Several techniques could be applied if a length deficit is diagnosed in time during the surgical intervention: composite anastomosis, elongation with a venous segment, using a skeletonized instead of a pedicled graft, right atrial plication (265), and grafting the CX territory via the transverse sinus (Fig. 29). In our study, the limited number of grafts for each configuration allowed statistical analysis only for LITA–LAD, RA–PDA, SVG–diagonal, SVG–MO, SVG–PDA, and SVG–RCA configurations with no significant difference between the mean length of patent and occluded grafts. Patent grafts presented minimal curvatures, allowing graft accommodation to respiratory movements and cardiac distension.

Coronary territory. In our study, the patency of both arterial and venous grafts was

influenced by the coronary territory. The maximum patency rate for the RCA territory was obtained with RAs, for the anterolateral territory with RITAs, and for the CX territory with SVGs. Opposite to our results, two studies (134,170) reported lower patency rates for the RA graft anastomosed to vessels from the RCA territory compared to the anterolateral territory. Parissis et al. (197) performed a meta-analysis in 2015 on 44 studies analysing the patency of grafts used to re vascularize the RCA territory and concluded that both the RA and the RITA patency rates are superior to the SVG patency, results confirmed by our study that proved the supremacy of the RA (80.65% patency rate) in front of the SVG (64.71%) but not of the *in situ* RITA (62.5%).

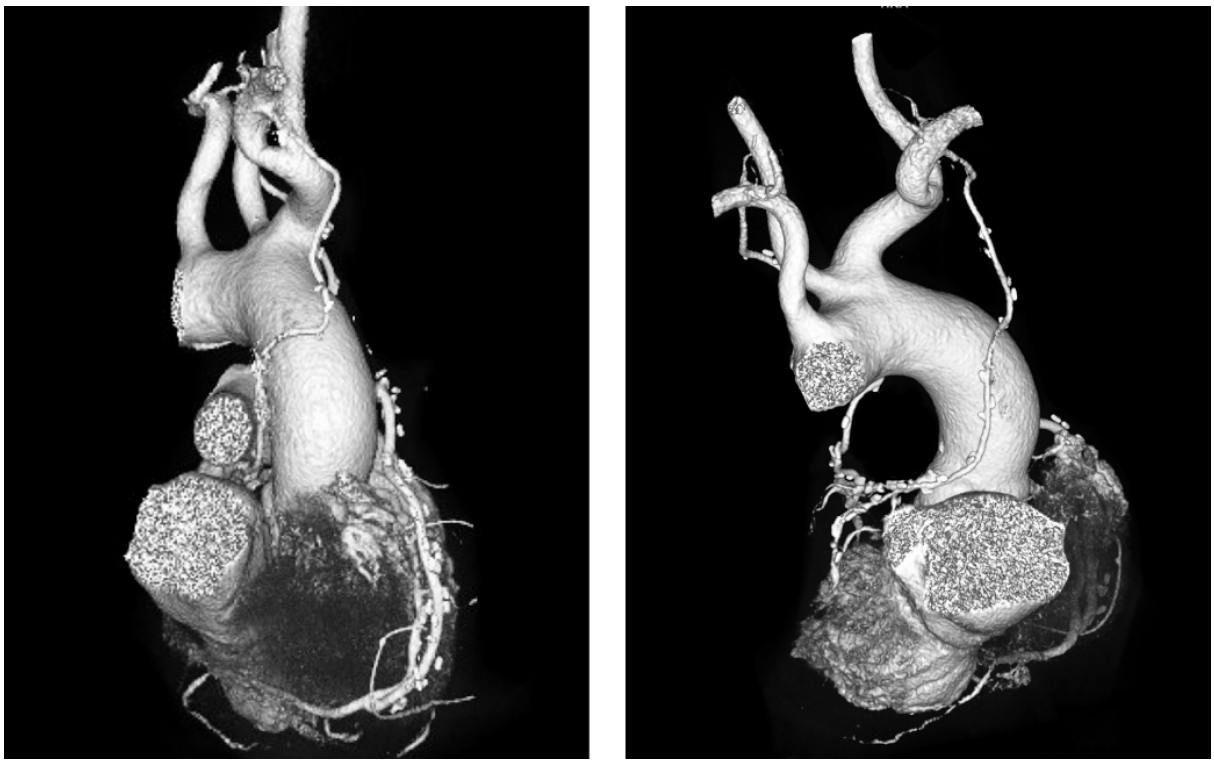


Fig. 29. Graft to the CX territory via the transverse sinus (IBCV Iasi)

Target vessel status. According to Poiseuille's law, vessel resistance is proportional to the length and inversely related to the fourth power of the inner diameter. Competitive flow between a graft and the target coronary artery occurs when they have similar conductance. In such cases, both the graft and the target vessel contribute to the perfusion of the distal vascular bed in variable proportions and in competition depending on the hemodynamic conditions.

The impact of competitive flow on wall shear stress was analysed by Qiang et al. (212) who confirmed theoretical data, namely that blood flow through the graft is conditioned by native vessel flow. The amplitude of competitive flow is influenced not only by the severity of target vessel stenosis but also by the volume of myocardial tissue perfused by the grafted artery. Our study proves the vulnerability of arterial grafts to competitive flow with a mean target vessel stenosis of 91.22% for patent graft compared to 78.52% for occluded grafts and an occlusion OR of 3.02 for arterial grafts anastomosed to target vessels with <90% stenosis. The SVGs were not sensitive to target vessel degree of stenosis.

The SVGs were anastomosed in all cases directly to the aorta and, therefore, perfused at higher pressures compared with free arterial grafts with proximal Y/T anastomosis to the LITA. Venous grafts also have a thinner media that does not allow lumen diameter adjustment to metabolic needs. These two aspects could explain why SVGs are not sensitive to the degree of stenosis of the target vessel.

Competitive flow was computer simulated by Ding et al. (76) who used an ITA graft model (4.6 mm diameter) anastomosed to the LAD (4.5 mm diameter) under an anastomosis angle of 45°. Flow simulations for stenosis severities of 30%, 50%, 75% and 100% were performed and showed that the higher the degree of LAD stenosis was, the lower the mean velocity was in the proximal LAD before the anastomosis and higher in the ITA. In the initial and terminal part of the cardiac cycle, a reverse flow was detected in the grafts anastomosed to LAD with 30% and 50% stenosis. This phenomenon generated by competitive flow decreased in case of 75% stenosis and completely disappeared in 100% stenosis. Competitive flow may occur secondary to residual flow through a non-critical stenosis or due to retrograde flow through coro-coronary auto-anastomoses (collateral circulation) as proven by Maniar et al. (170).

Opposite to the persistent competitive flow through a non-critical stenosis, the one generated by collateral branches diminishes gradually in the postoperative period until complete extinction as collateral branches close if the graft efficiently perfuses the target vessel. According to Kawamura et al. (141), a LITA–LAD graft dysfunction can also occur secondary to competitive flow induced by a grafted diagonal artery if no significant (≥75%) stenosis is interposed between the origin of the grafted diagonal artery and the LITA–LAD anastomosis. On the contrary, a well-perfused CX by a grafted MO is unable to generate competitive flow in the LITA–LAD graft as the increased length of the interposed segment in the latter case allows flow attenuation. Kute et al. (154) performed a series of simulations and demonstrated that the flow in the proximal segment of the target vessel is an important determinant of the hemodynamic at the distal end-to-side anastomosis. Since hemodynamic forces interfere with the response of endothelial cells, flow status in the proximal artery may trigger intimal hyperplasia and, therefore, diminish long-term graft patency.

Another parameter interfering with long-term graft patency is the calibre of the target vessel. A value ≤1.5 mm is associated with both arterial and venous graft occlusions. In 1979, Roth (219) performed the first research analysing the relationship between graft patency and target vessel calibre and identified a 90% patency rate at 1 year for SVGs anastomosed to coronary arteries with a >1.5 mm diameter and a 65% patency rate in the case of anastomosis to ≤1.5 mm coronary arteries. In 2004, Goldman et al. (107) resumed and extended the study and identified a 10-year patency rate of 88% for SVGs and 100% for ITAs anastomosed to coronary arteries with a diameter >2 mm compared with 55% for SVGs and 82% for ITAs anastomosed to ≤2 mm target vessels. Increased patency rates in larger vessels are explained by the superior runoff and graft flow.

Proximal anastomosis. In our study, we found a higher patency rate when the RITA was used as a composite graft for the anterolateral or CX territory (78.38%) compared with *in situ* usage for the RCA territory (62.5%). Radial artery graft also registered higher patency when anastomosed to the ascending aorta (85%) compared to composite grafting with LITA (61.54%).

Several studies (48,77,100,241,243) compared the patency of *in situ* and free pedicled ITAs. Dion et al. (185) stated they prefer an *in situ* pedicled ITA to the free graft each time the local anatomy, the topography and number of lesions allow it, the physiological response being predictable in terms of flow and graft calibre. They evaluated the patency of ITA grafts at 7.5 years after the intervention irrespective of proximal anastomosis and target territory and found a patency rate of 96.3% for *in situ* ITAs and 86.5% for free grafts anastomosed to the ascending aorta or used for Y/T anastomosis.

Fukui, Calafiore, and Tatoulis (48,100,243) consider, based on angiographic results obtained at 12 months, 17.5 months, and 41.5 months postoperatively, that there are no differences in patency rates and long-term outcome between free ITAs used for composite grafting and *in situ* ITAs and neither between pedicled and skeletonised grafts. In our research,

in situ RITA was used only for re-vascularizing the RCA territory and free ITAs as composite grafts for the anterolateral or CX territory, thus introducing another variable in the equation, the coronary territory. In 2012, Mukherjee et al. (185) analysed the outcome of RITA grafts and SVGs used to re-vascularize the RCA territory by performing a meta-analysis on 226 recent articles and concluded that SVGs registers superior patency rates compared with RITA grafts in this particular scenario. The poor outcome of RITA grafted to the right coronary territory could be explained by graft stretching in case of right heart dilation and poor runoff with different haemodynamic conditions.

In our study we registered higher patency rates for RA grafts anastomosed proximally to the ascending aorta versus composite grafting in a Y/T configuration with *in situ* LITA grafts. Similar results were reported by Jung et al. (134) who analysed 893 patients, 451 with RA grafts anastomosed to the ascending aorta (group I) and 422 with RA used as for composite grafting with LITA (group II). They reported significantly higher patency rate in group I than in group II in the early postoperative period (98.3% vs. 94.5%), at 1 year (93.8% vs. 90.5%), 2 years (90.5% vs. 85.3%), and 5 years (74.3% vs 65.2%) after the intervention. Jung et al. attribute the difference to a higher perfusion pressure and accelerated flow in case of direct aortic connection, thus preventing graft dysfunction.

In composite grafting, the long-term patency was conditioned by the anastomosis angle, with smaller values registered with patent free grafts (47.21^o) compared to occluded free ones (56^o). No *in vivo* study analysing Y anastomosis angle was identified in the literature. Song et al. (235) performed an experimental research and simulated flow through a 3D model of a Y anastomosis by computational fluid dynamics. Their findings support our results by demonstrating that the more acute the angle of anastomosis, the smaller are the energy loss and the reverse flow into the graft.

Distal anastomosis. Opposite to venous grafts, arterial grafts also proved vulnerable to distal anastomosis angle, with a mean value of 39.46^o for patent grafts and 44.94^o for occluded ones. In our study we found an occlusion OR of 5.149 in cases of a distal end-to-side anastomosis angle ≥60^o. The first efforts to optimise anastomosing technique aimed to improve local haemodynamic by modifying the anastomosis geometry as several experimental researches proved that tissue remodelling around the distal anastomosis is conditioned by the end-to-side angle, a factor influencing flow fields and wall shear stress (WSS) (143). Staalsen et al. (143) used polyurethane grafts do demonstrate that no flow disturbances occur at the toe and one diameter downstream from an anastomosis under an angle of 15^o, and a zone of recirculation extending from the toe to one diameter downstream appears in 45^o and 90^o anastomoses. An anastomosis angle of 30^o is generally associated with a uniform flow and a smooth transition between graft flow and target vessel flow.

Similar results were also obtained for sequential anastomoses, with an angle of 48.60^o for patent side-to-side anastomoses compared with 53.97^o for occluded and 65.12^o for patent end-to-side anastomoses versus 90.80^o for occluded irrespective of graft type. The distal end-to-side anastomoses of sequential grafts were performed at wider angles compared to their equivalent in case of single terminal anastomosis because they were mostly used to re-vascularize posterolateral arteries on the diaphragmatic surface of the heart or the posterior descending artery.

Frauenfelder et al. and Fei et al. (93,99) evaluated sequential anastomoses in experimental setting and demonstrated that wider angles generate higher WSS values and flow oscillation around the toe and along the bed of the target vessel. The main disadvantage of this simulation is related to the assumption that the graft and target vessel are in the same plane which is far from reality.

However, the results were not completely inaccurate as Sherwin et al. (228), who investigated the influence of out-of-plane geometry, found that the anastomosis bed was most

affected by flow oscillation generated by wider anastomoses angles yielding to intimal hyperplasia and long-term occlusion.

Bonert et al. (42) compared the patency of side-to-side with end-to-side anastomoses and concluded that the parallel disposition of the two vessels, the graft and target coronary artery, in a side-to-side anastomosis contributes to maintaining graft patency by diminishing the haemodynamic stress and spatial gradients. In end-to-side anastomosis, the haemodynamic forces act perpendicular to the coronary artery wall and generate important variations of WSS (1.5 Pa) with stagnation and flow separation zones (42).

In our study, the limited number of sequential anastomoses did not allow a statistical comparison of side-to-side to end-to-side anastomoses, but venous grafts proved to have a higher patency rate in a side-to-side configuration.

Although limited by the sample size, our research is the first to attempt a quantification of factors conditioning graft patency using CCTA as evaluation method, as there is a lack of *in vivo* studies examining morphological, pathophysiological, and surgical factors that influence long-term graft outcome.

Most studies in the field are performed on *in vitro* or computerised models that cannot consider all possible graft configurations.

A single morphological study of coronary grafts on CCTA examinations was performed by Tremblay et al. (250) who attempted to identify morphological and morphometrically factors associated with a saphenous vein bridge (SVB) dysfunction on a group of 40 patients. They analysed SVB length, SVB segment lengths, SVB lumen sectional areas, anastomotic angulations and intrinsic SVB angulations and concluded that CCTA could be used to identify quantitative graft parameters associated with graft dysfunction.

Our study extends this idea and identifies morphological and morphometrically factors associated with long-term graft patency that could lead to improving the surgical technique to increase graft life span and reduce the risk of MACE.

When imagining a grafting configuration, one must not omit practical aspects such as feasibility and duration, as the intervention must be accomplished in a reasonable time. Bias was controlled as much as possible by analysing data according to the aforementioned factors, all cases being operated by the same surgical team.

To summarize, a series of independent predictors of graft dysfunction have been identified in the current study for each graft type, arterial or venous (table XL).

Table XL. Predictors of graft dysfunction

Venous grafts
• Grafting the RCA;
• Grafting coronary arteries with <1,5 mm diameter;
• Female sex;
• Family istory;
• Endarterectomy.
Arterial grafts
• Grafting CX branches using RAG;
• Target vessel stenosis <90% especially with RAG;
• Grafting coronary arteries with <1,5 mm diameter;
• Proximal Y anastomosis with RAG;
• Y anastomosis angle >56^{o};
• Sequential grafting;
• Distal anastomosis angle >60^{o};
• Multivascular disease.

We also identified a series of aspects to be considered when imagining a CABG design:

- Graft compatibility with arterial pressure and ability to sustain the blood flow necessary for target vessel adequate perfusion with minimal parietal stress and haemodynamic forces in order to minimise intimal hyperplasia (argument for TAR);
- Careful graft harvesting and manipulation to avoid intimal lesions;
- Graft-target vessel compliance to avoid mismatch;
- Distal anastomosis with optimal haemodynamic performance (reduced anastomosis angle, grafting far from a stenosis with persistent flow);
- Usage of sequential grafting to increase the number of side-to-side anastomoses with a minimal anastomosis angle;
- Grafting design adapted to the individual patient and topography of lesions.

As far as early prognostic factors are concerned, they may be divided into:

- *factors impacting the ability to tolerate surgery* (COPD, CKD),
- *factors associated with disease severity* (AMI, LVEF, heart failure NYHA class III-IV),
- *factors impacting intervention complexity* (prior cardiac surgery, emergency surgery, ischemic mitral regurgitation).

Venous grafts dysfunction and *de novo* lesions occurred mostly in the first 8 postoperative years; the risk being reduced afterwards according to logistic regression. Our conclusion is different from the one identified in most studies that report an increased incidence of the two instances between 5 and 10 years postoperatively but few studies are performed on patients operated more than 10 years ago after year 2000.

Native disease progression was responsible for most coronary events in patients with arterial grafts compared to patients that benefited from venous grafts.

Total arterial revascularisation exerts a protective effect on native coronary arteries thus diminishing the progression rate of atherosclerotic lesions in grafted territory from 43% at 10 years in case of veins, to 11% for RA grafts and 8% for internal mammary arteries with variations according to target coronary territory.

On the long term, SVGs usage is associated with an increased risk of recurrent major adverse cardiac events. A LVEF<30%, three-vessel disease, increased number of distal venous anastomoses, prolonged ICU stay, neurological complications and advanced age increase the risk of long-term mortality.

Complete revascularisation with multiple grafts decreases long-term mortality (positive prognostic factor for survival) while neurological complications, reduced LVEF postoperatively, increased number of distal venous anastomoses, prolonged ICU stay and advanced age increased long-term mortality rate (Fig. 30).

The current study completes available data with long-term mortality at 10-16 years postoperatively (31.73%) on a group relevant for the Romanian population.

Most studies analysing long-term mortality associated to CABG have been performed on patients operated and followed before introduction of novel therapeutic strategies targeting global cardiovascular risk (statins, antiplatelet drugs).

For these reasons, previous researches reporting results obtained on patients operated in decades ’70-’80 currently have a limited applicability.

Total arterial revascularisation (TAR) reduces the incidence of cardiovascular events compared to conventional CABG. Among the methods of improving the long-term survival the current literature recommends an aggressive reduction of risk factors (statins, low dose aspirin, AHT treatment, smoking cessation, glycaemic control).

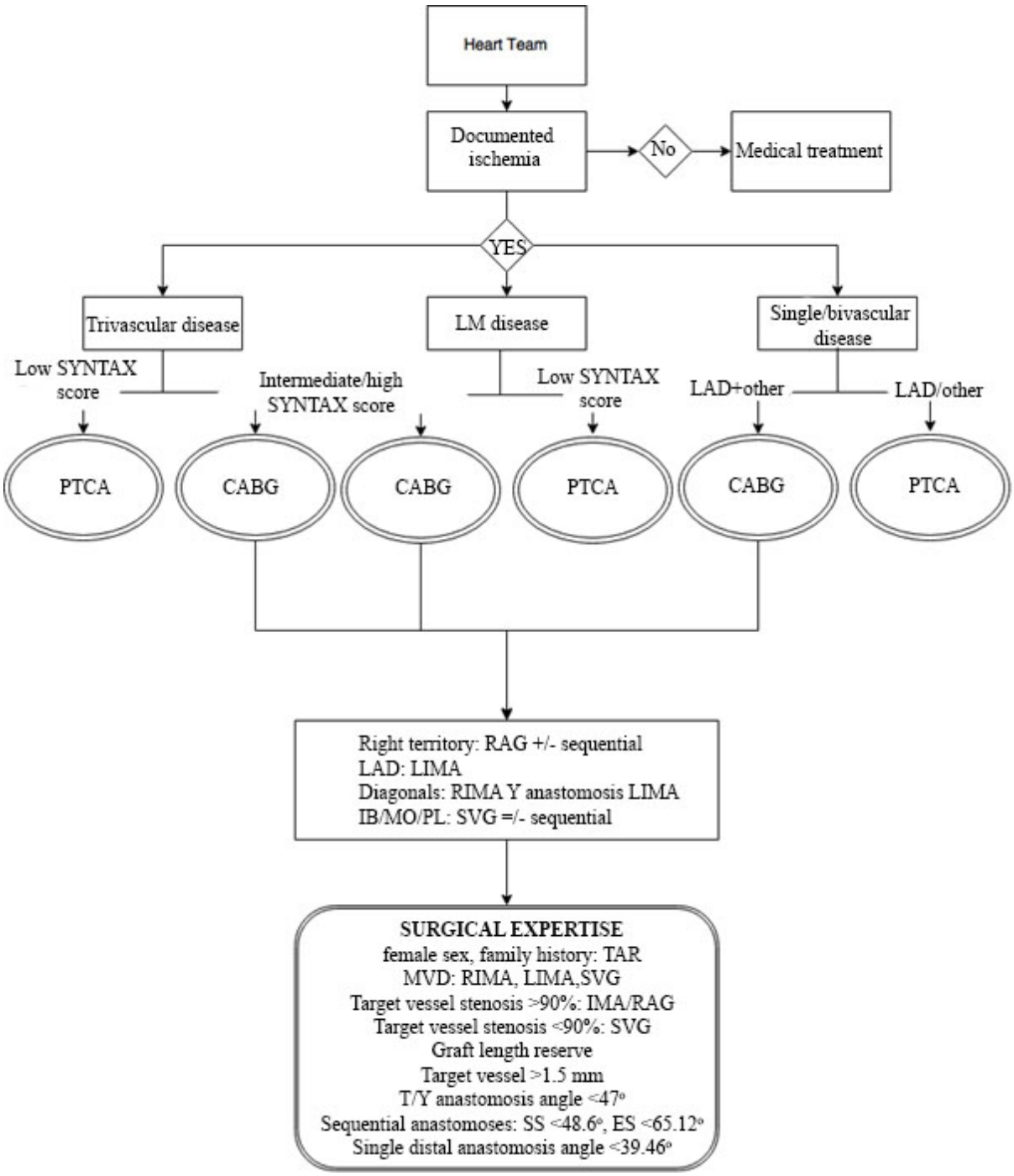


Fig. 30. Personal decision algorithm in coronary heart disease

Based on the obtained results, we imagined the following optimal graft and grafting technique profiles (table XLI).

The practical application of the findings of this study allow an optimization of the cost-benefit relationship by: facilitating graft selection and choice of surgical technique; reducing operative times secondary to sequential anastomoses; diminishing early morbidity and mortality risk through targeted interventions depending on risk factors; increasing long-term patency rate of the grafts with subsequent reduction of morbidity, need for redo revascularisation and long-term mortality; adjusting the postoperative therapeutic management according to MACE risk associated to graft status.

Tabel XLI. Ideal graft and optimal grafting technique profiles according to grafted territory

Coronary territory	Graft and grafting technique profiles
RCA	• Target vessel stenosis ≥90%; • RA graft with one or more distal anastomoses (sequences); • No graft tension; • Grafting coronary arteries with a diameter >1.5 mm (with/without prior endarterectomy); • Distal anastomosis angle <60º for end-to-side anastomosis and <48.60º for side-to-side anastomosis.
LAD	• Target vessel stenosis ≥90%; • LIMA graft; • Anastomosis angle <45º; • Anastomosis to the medium segment of the LAD (diameter >1.5 mm) with/without prior endarterectomy; • No graft tension; • Avoid grafting a diagonal artery upstream from the LIMA-LAD anastomosis if no stenosis >90% is interposed between the origin of the diagonal artery and LIMA-LAD anastomosis.
Diagonal arteries	• Target vessel stenosis ≥90%; • Y RIMA-LIMA anastomosis with *in situ* LIMA; • Distal anastomosis angle <39.46º; • Y angle <47º; • Grafting coronary arteries with a diameter >1.5 mm (with/without prior endarterectomy); • No graft tension.
CX	• Target vessel stenosis ≥90% for arterial grafts and ≥75% for SVG; • Venous graft in male patients or arterial graft in female patients with one/several distal anastomoses (sequences); • Distal anastomosis angle <60º for end-to-side anastomosis and <48.60º for side-to-side anastomosis; • Grafting coronary arteries with a diameter > 1.5 mm and no endarterectomy in case of venous grafts; • No graft tension.

2.4.2.6. Conclusions

Morphological parameters such as graft type, target territory, target vessel calibre, and degree of stenosis, are important factors conditioning long-term graft patency. A large coronary artery with a severe stenosis has a good runoff and is associated with higher long-term patency rates, especially if located in the left coronary territory. The right coronary territory has particular morphological features associated with lower patency rates, the radial artery being the graft of choice in such circumstances. The surgical technique is a key element for long-term graft outcome. A small anastomosis angle, both for proximal composite and distal anastomoses, is associated to a higher long-term patency of the free graft. Radial artery grafts registered higher patency rates when anastomosed to the ascending aorta compared with composite grafting with LITA, whereas *in situ* RITA anastomosed to the RCA territory is associated with a lower patency rate compared with free RITA used to re-vascularize the anterolateral or CX territory as part of composite grafting.

CHAPTER 3. ANATOMICAL BASIS IN DIFFERENT CLINICAL APPROACHES

Anatomy might be considered an obsolete science, but even if the human body may not seem to change structurally, the ways of viewing, conceptualising and intervening with it, certainly do.

The term "*anatomy*" originates from the Greek "*anatomē*," or dissection, and concerns the study of structural organization of organisms and their parts.

Anatomy, as a basic science, has to ensure morphofunctional knowledge of the human body, human-environmental interactions, and clinical and semiotic methodologies, theoretical and practical knowledge related to large systems in internal medicine, base of diagnostic and therapeutic approaches, drawing contextual limits in psychiatric, neurological, and sense organ-related sciences, maternal-child and reproductive medicine, internal medicine and oncology, diagnostic laboratory and radiology, general and emergency medicine and surgery, public health, forensic medicine and professional ethics.

Ironically, due to the expansion and integration of disciplines within the medical curriculum, in a time when knowledge of anatomy becomes increasingly important, we are facing now a crisis in anatomical education demonstrated by a reduced time for teaching and/or human dissection.

Equilibrium between this episteme of anatomy education could be achieved after considering the perceptions of anatomy stakeholders.

Knowledge of the anatomy undelying everyday clinical and radiological image examination still remain components of everyday clinical practice.

In my opinion, medical research and anatomy education are two sides of the one coin: for anatomy to reinvent itself, anatomists need to engage with medical research (from a clinical and/or a scientific perspective) as well as implement educational innovations (ideally while investigating the learning of their own students).

It goes without saying that anatomical knowledge is the bedrock of clinical surgery and indeed all of medicine.

At the other extreme, if advances in anatomy are not taught to students they will be condemned to live in a past era of the subject. Anatomy understanding and the ability to study in detail different human structures evolved, thus becoming goals of modern medical research.

This also applies to learning materials as these should provide the major link to recent research findings as well as refinements to fundamental anatomical principles.

Current initiatives in anatomy has to be focussed on development, evolution, physiology, pathology, and regenerative medicine.

In my opinion, anatomy is a necessity for general practitioners, surgeons and for all those, who are involved in invasive diagnostic and therapeutic procedures in order to decrease the medical errors.

This is the reason why we tried to integrate anatomy in different medical disciplnies, creating various research directions.

3.1. Clinical anatomy of the trigeminal nerve

3.1.1. Introduction

Trigeminal neuralgia (TN), a chronic neuropathic pain disorder, has a series of unique features like sporadic episodes of extreme, sudden burning or shock-like unilateral face pain lasting from a few seconds to 2 minutes and following the sensory distribution of the trigeminal nerve. The pain can be physically and mentally incapacitating (273).

In most cases no structural lesion is detected but in almost 15% of patients medical imaging methods like MRI, CT or angiography can identify a vein or artery that compresses the nerve which results in focal demyelination (242).

My interest in this field is reflected by the following published papers and books:

Articles:

2. Sava A, **Furnica C,** Petreus T, Chistol RO, Motoc AGM. Trigeminal nerve: MRI anatomy and case presentation of trigeminal neuralgia due to arterial compression. Rom J Morphol Embryol 2012; 53(4):1097–1102.

Books:

2. **Furnica C,** Chistol RO. Trigeminal Nerve. Anatomoclinical Study. PIM Publishing House, Iasi, 2009.

3.1.2. Material and methods

Starting from a clinical case of trigeminal neuralgia investigated by MRI, our team performed a medical imaging review of the clinical anatomy of the trigeminal nerve.

A 50-year-old female patient accusing right-side facial neuralgia was addressed to the neurology department and an MRI investigation was indicated to investigate the source of the pain.

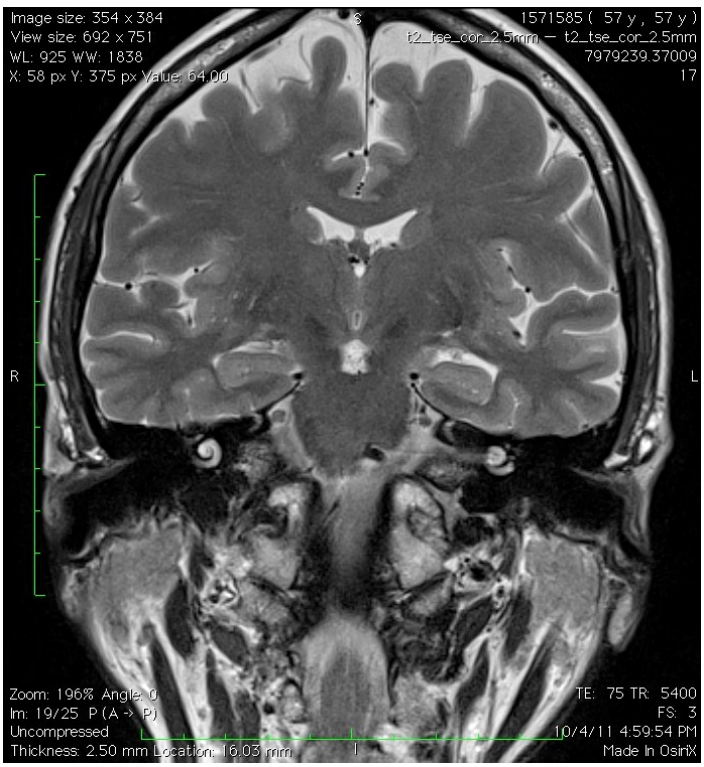


Fig. 31. T2 TSE sequence showing intersection of the left trigeminal nerve with the superior cerebellar artery and one of its branches (personal data)

3.1.3. Results

Axial sequences revealed that the superior cerebellar artery crossed the left trigeminal nerve at 9 mm after exiting the pons. MRI sequences better illustrate the narrow relation between the trigeminal nerve and 2 arteries (Fig. 31 and 32).

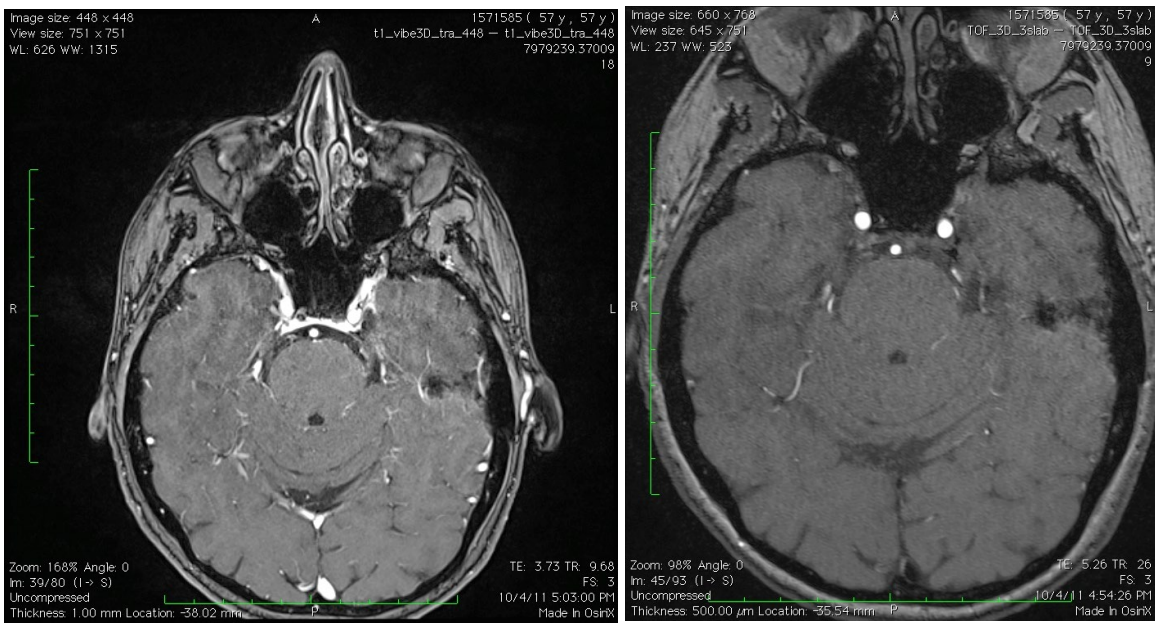


Fig. 32. Volumetric interpolated brain examination (VIBE) and Time of Flight (TOF) sequences displaying how the left trigeminal nerve passes beneath the superior cerebellar artery (personal data)

After demonstrating the vascular cross-compression of the trigeminal nerve a microvascular decompression through a small occipital craniotomy was attempted as the patient stated no amelioration of her condition after treatment with anticonvulsants for two years. An inert implant was placed in order to maintain the decompression.

Six months after the surgery the patient reported no recurrence of symptoms.

3.1.4. Discussions

The trigeminal nerve, the shortest and the largest of the cranial nerves with exclusive cephalic distribution, is mixed, with branchiometric organization, and supplies the sensitive and motor innervations of structures derived from the first pharyngeal arch.

The transdural segment of the trigeminal nerve is incomplete, limited to the cavum Meckeli. The nerve lasts from the superficial origin to the concave margin of the Gasser ganglion and presents a transcisternal segment, *pars compacta*, located beneath the *tentorium cerebelli*, and a transdural segment, *pars triangularis*, contained in cavum Meckeli (105).

Pars compacta, with a sagittal disposition, is a fascicular cord with ellipsoid shape on the cross section. It presents an anteromedial, pontine surface, a posterolateral, cerebellar surface, a superior margin, crossed by the superior cerebellar artery that separates it from the trochlear nerve, and an inferior margin related with the loop of the anteroinferior cerebellar artery.

From its origin, *pars compacta* have an ascendant course with a mediolateral direction, perforates the Liliequist membrane, crosses the pontocerebellar cistern, inflects laterally, enters the trigeminal pore and continues with *pars triangularis* to the concave border of the Gasser ganglion (270).

Pars triangularis has a horizontal disposition, a trapezoid shape and presents a superior surface related to the hypocampal uncus through the superficial lamina of the cavum, an inferior surface related through the deep lamina of the cavum Meckeli to the abducens nerve, greater

and lesser petrosal nerves and the intrapetrosal segment of the internal carotid artery, a medial border related to the abducens nerve, a lateral border participating to the formation of the posteromedial triangle (270). *Pars triangularis* has a particular, false plexial aspect because the thin fasciculi of the *pars compacta* dissociate, fan and intersect in various directions before entering the *hilus ganglii*.

The cavum Meckeli, the largest perineural cistern of the base of the skull, is a meningeal structure of the middle cerebral fossa presenting a the lesser base, oriented posteromedially and corresponding to the trigeminal pore, a greater base, oriented anterolaterally, corresponding to the sphenoidal margin of the *foramen lacerum* and sending towards the superior orbital fissure, *foramen rotundum* and *foramen ovale*, three dural tunnels that contain the terminal branches of the trigeminal nerve and their adjacent cisterns, a medial border that fuses with the lateral wall of the cavernous sinus, a lateral border along which the superficial and deep *cavum laminae* reunite and attach on the contour of the trigeminal fossa (255).

The trigeminal ganglion (semilunar, of Gasser) contains the primary afferent neurons whose central axons will form the sensory root of the trigeminal nerve. It is a flattened crescent shaped structure contained in the cavum Meckeli, elongated and thinner at extremities, with a narrowing, *isthmus ganglia*, between the origins of the maxillary and mandibular nerves (270).

Structurally, the trigeminal ganglion consists of pseudounipolar neurons grouped in columns separated by axon bundles and of satellite cells that encapsulate each neuronal soma. Each pseudounipolar neuron of the Gasser ganglion emits a short prolongation which bifurcates in a peripheral branch that takes the way of a terminal trigeminal branch and a central branch that forms the sensitive root (radix sensoria) (270).

The most frequent disorder of the trigeminal system is trigeminal neuralgia with a reported incidence of 5.9/100,000 in women and 3.4/100,000 in men in the USA (105). The disease is characterized by episodes of intense facial pain in the territory of one of the trigeminal branches, especially of the maxillary nerve. The pain is triggered by simple touch of a skin area and varies with remission times and intensifications.

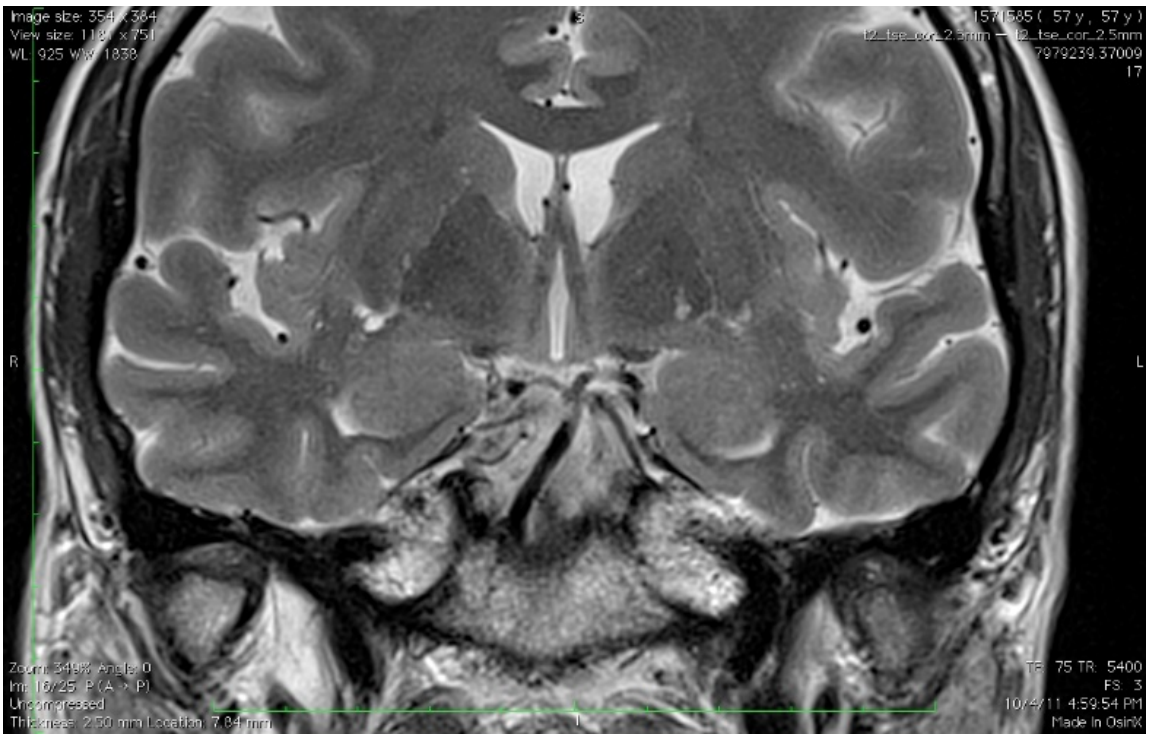
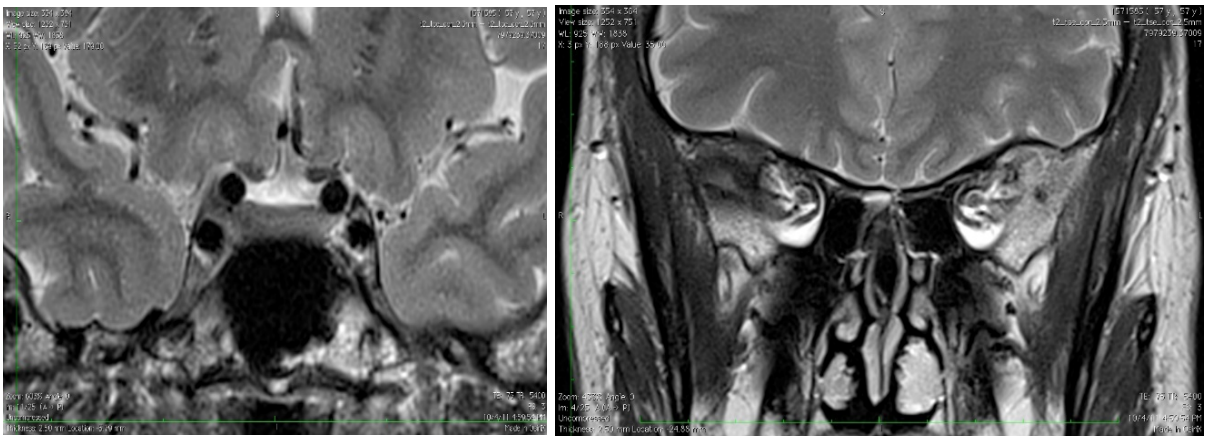


Fig. 33. Gasser ganglion (T2 TSE sequence) (personal data)

The trigeminal lesions localization could be: supranuclear, unilateral, of central motor neuron type - unilateral paralysis of masticator muscles with deviation of the mandible to the lesion side (pseudobulbar palsy - spastic masticator paralysis).

Lesions of the trigeminothalamic tract result in:

- anesthesia of the controlateral surface;
- in the brainstem, a lesion of the motor nucleus determines fasciculations, paresis or atrophy of masticator muscles;
- in the cerebellopontine angle, impairment of trigeminal roots determines paresis of masticator muscles, ipsilateral facial hemianesthesia and the loss of the corneal reflex;
- in the cavum Meckeli and the apex of the petrosal part of the temporal bone, the trigeminal nerve could be impaired in the apical petrositis, Gradenigo syndrome or the paratrigeminal syndrome Raeder when the trigeminal lesion is accompanied by Horner syndrome (105).



A. **B.**

Fig. 34. A. Maxillary branch of the trigeminal nerve in the cavernous sinus and B. Mandibular branch in the infratemporal fossa (T2 TSE sequence) (personal data)

The pathophysiologic mechanism is still unclear, but demyelination leading to abnormal discharge is probably the cause.

The most frequent causes include vascular compression in the posterior fossa, gasserian tumour and multiple sclerosis involving the brainstem.

The artery most commonly responsible for the compression is the superior cerebellar artery followed by an abnormal course of the basilar artery (169).

Patients with pain refractory to medication could be referred for surgical decompression if MRI examination reveals a vascular compression.

3.1.5. Conclusions

MRI is an excellent technique to evaluate the trigeminal nerve. Imaging of Meckel's cave, the cavernous sinus, the skull base foramina, the pterygopalatine fossa and the peripheral trigeminal nerve course should be included. In order to narrow the differential diagnosis, a segmental approach is indicated.

3.2. Clinical gynaecologic anatomy

3.2.1. The clinical anatomy of endometriosis

3.2.1.1. Introduction

Endometriosis represents a frequently encountered pathology of the women at reproductive age and corresponds to ectopic development of endometrial cells outside the uterine cavity (126).

The 3 most frequent localisations are: external intraperitoneal endometriosis (adnexial or peritoneal), external subperitoneal endometriosis (rectovaginal septum, sacrouterine ligaments, digestive tract, round ligaments, vesico-uterine pouch) or uterine adenomyosis, previously considered as internal endometriosis and now treated as a separate entity (25).

Chronic pelvic pain during menstruation is the main clinical symptom. Pain can occur in any moment, especially in the pre and post-menstrual period.

Endometriosis should also be suspected in all patients addressing for infertility and dyspareunia.

My interest in this field is reflected by the following published paper:

1. Chistol RO, **Furnica C**, Leon MM. MRI imaging in endometriosis: personal study and pictorial review. Gineco.ro 2012; 8(27): 24-29.

3.2.1.2. Material and methods

The study was performed during September 2011- January 2012 on a number of 38 female patients (19-51 years) underwent MRI examination for suspected endometriosis based on clinical or ultrasound examination. Informed consent prior to inclusion in the study was obtained in all cases.

Pelvic MRI was performed using a Siemens MAGNETOM Symphony 1.5T machine and drotaverine (NoSpa 40 mg/2ml) was administered by intravenous injection in all cases in order to reduce intestinal motility. The study protocol included T2 TSE (Turbo Spin Echo) weighted sequences in all the three planes, T2 TSE sequence with fat saturation in the transversal plane, T1 TSE and T1 TSE with fat saturation sequences in the transversal plane.

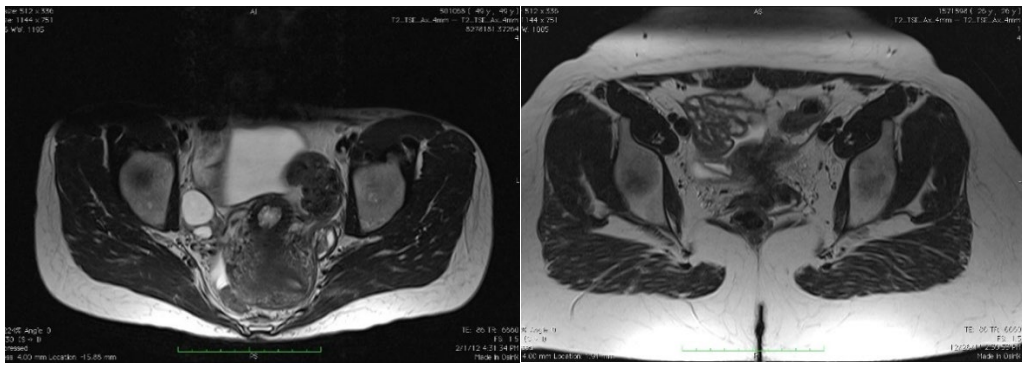
Slice thickness was of 4 mm in all cases. Injection of contrast agent was not necessary in any of the cases.

3.2.1.3. Results

MRI diagnosed deep endometriosis in 26 out of the 38 patients (68.42%), adenomyosis associated to endometriosis in 2 cases (5.26%), adenomyosis not associated to deep endometriosis in 1 case (2.63 %), abdominal wall endometriotic implant associated to deep endometriosis in 1 case (2.63%%) and no endometriotic lesions in 8 cases (21.05%).

Concerning the anatomical distribution of deep endometriotic lesions, most of them interested the rectovaginal septum (18 cases – 69.23%), the sacrouterine ligaments (15 cases – 57.69%), the uterine torus (12 cases – 46.16%), the adnexes (13 cases – 50%), the pouch of Douglas (9 cases – 34.61%), the posterior vaginal fornix (5 cases – 9.23%), the rectosigmoid serosal surface (5 cases – 9.23%), the small intestine serosal surface (2 cases – 7.69%), the surface of the bladder (2 cases – 7.69%) and anterior vaginal fornix (1 case – 3.84%) (Fig. 35).

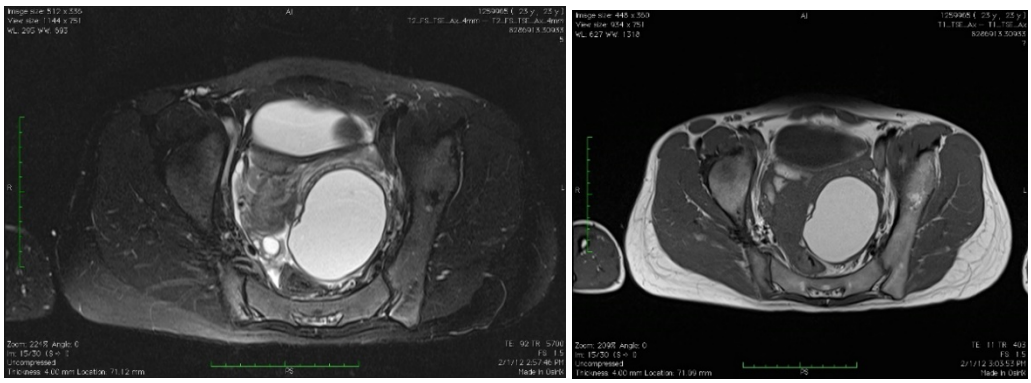
Many of the cases presented with pelvic fluid (17 cases – 65.38%) and 2 patients with intestinal involvement manifesting as peritoneal ascites. Adnexial involvement consisted in endometriomas in 2 cases, endometriomas associated to endometriosic implants in 5 cases and endometriosic implants only in the rest of 6 patients.



a **b**

Fig. 35. Thickening of the left ovarian fossa (a) and of the left round ligament (b) (T2 weighted sequence) (personal data)

Endometriomas appeared hyper intense in both T1 and T2 weighted sequences with and without fat saturation as they are characterized by a rich glandular component and the presence of haemoglobin degradation products (Fig. 36).



a **b**

Fig. 36. Voluminous endometrioma of the left ovary: high intensity signal in both T2 fat sat (a) and T1 (b) weighted sequences (personal data)

Endometriotic implants were mixed (fibrous masses with haemorrhagic spots) in 7 cases (26.92%) (Fig. 37).

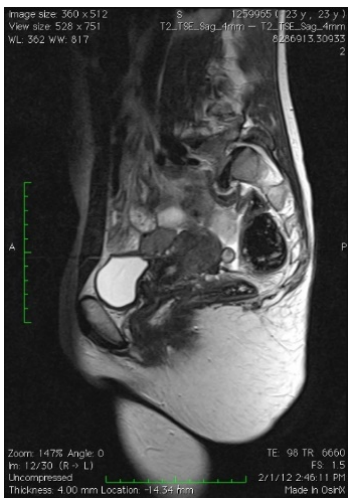


Fig. 37. Hemorragic endometriotic implant in contact with the fundus of the uterus (T2 weighted sequence) (personal data)

Endometriotic implants presented as spiculated, retractile fibrous masses hypo intense in both T1 and T2 weighted sequences with and without fat saturation and were encountered in

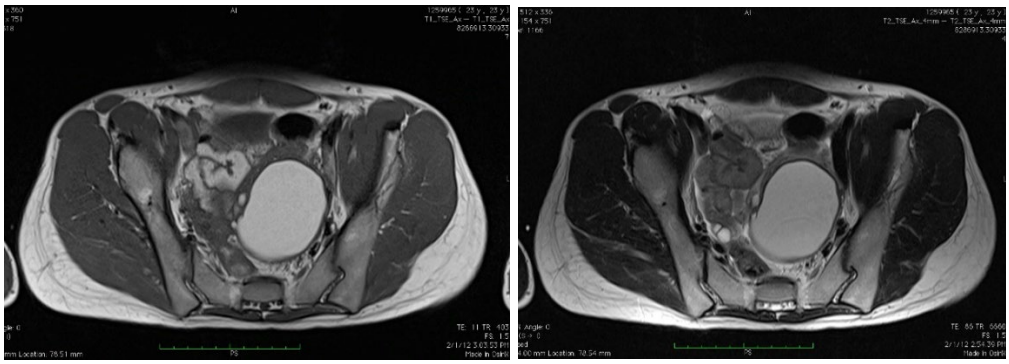
9 of the 26 cases (34.61%). These implants are responsible for filling of the Douglas pouch (traction of the uterus and rectum), and for the intestinal and ovarian adhesions.

Most patients (21 cases, 80.77%) presented thickening of sacrouterine ligaments, rectovaginal septum, peritoneum, round ligaments or ovarian fosses.

3.2.1.4. Discussions

Various authors have proposed several classifications of endometriosis in the last 10 years but we will be referring in our discussions to the classification proposed by Del Frate (73) in 2006 who divided deep endometriosis into posterior and anterior lesions. Anterior lesions are represented by endometriosis of the bladder and were encountered in 2 of 26 deep endometriosis cases (7.7%), comparable with the frequency reported by the international literature of 6.4% in all cases (57).

Posterior endometriosis is further subdivided into retroperitoneal and intraperitoneal lesions. Intraperitoneal lesions are in the recto-uterine pouch, on the rectosigmoid serosal surface and less frequently on the small intestine serosal surface (25), situation confirmed by our study as we identified small intestine lesions in only 2 cases (Fig. 38).



a **b**

Fig. 38. Same patient as in previous image presenting an endometriotic implant with low intensity signal in both T1 (a) and T2 (b) weighted sequences on the small bowel surface in the right iliac fossa (personal data)

Endometriotic implants on the rectosigmoid colon appear as low signal, nodular thickenings of the wall in both T1 and T2 weighted sequences. Three of the 5 patients with rectosigmoid endometriosis also had endometriotic implants in the recto-uterine pouch, an association that needs further investigation. The local inflammation induced by endometriotic lesions could lead to a total obstruction of the recto-uterine pouch making vaginal laparoscopy extremely difficult if not impossible (57). Adherences pull on the posterior surface of the uterus (retroflexion) and the anterior surface of the rectosigmoid colon. All the intestinal loops in the region are attracted towards the inflammation while the recto-uterine pouch and the posterior vaginal fornix ascend. This form of endometriosis was associated in our study with a severe clinical presentation involving dysmenorrhea and pain.

Retroperitoneal deep endometriosis is further divided into (25):

- type I lesions involving the rectovaginal septum;
- type II lesions involving the uterine torus and sacrouterine ligaments;
- type III hourglass-shaped lesions.

In a recent work, Kinkel (147) reported rectovaginal septum lesions in 14.5% of cases compared to 69.23% in our study. The higher incidence in the Romanian population could be explained by the limited availability of MRI examination and late presentation, patients being frequently examined in advanced stages, when endometriotic lesions are disseminated to the entire pelvis.

Endometriosis usually has a predilection for the uterine torus, the reported frequency being of 69.2% (147) versus 46.16% in our study. In most cases (8 out of 12 patients) it associates involvement of the sacrouterine ligaments (Fig. 39).

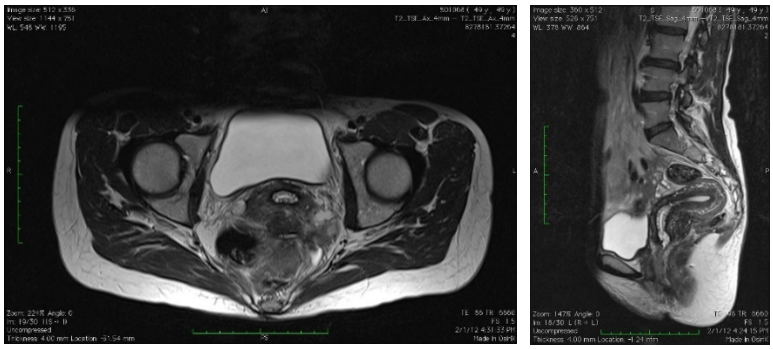
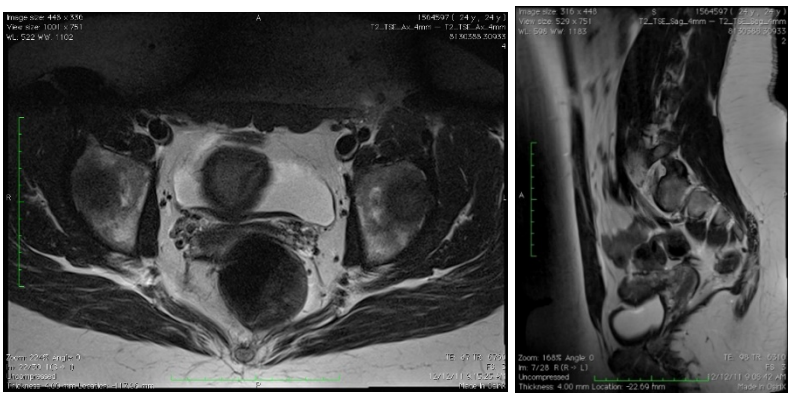


Fig. 39. Voluminous endometriotic nodule with hemorrhagic spots developed on the uterine torus (T2 weighted sequences) (personal data)

Sacrouterine ligaments thickening is frequently encountered in patients who already had pelvic surgery for a different pathology and are typical for a chronic inflammatory status. Their aspect should be judged in clinical context and a nodular aspect could be considered an endometriotic lesion (fig. 40).



a **b**

Fig. 40. Thickening of the left and nodular thickening of the right sacrouterine ligament (a). Thickening the uterine torus and retractile endometriotic implant attracting the sigmoid colon (b) – T2 weighted sequences (personal data)

Hourglass-shaped lesions occur when endometriotic implants extend from the uterine torus to the anterior wall of the rectosigmoid colon (173). These lesions situated under the recto-uterine pouch could penetrate the rectal wall and are hardly to pass undiagnosed.

Two conditions received special attention: the association between adenomyosis and endometriosis and endometriosis of the abdominal wall.

Adenomyosis and endometriosis could be causally related as Leyendecker suggested in his work (163). An abnormal function of the junctional zone determines disturbed uterine contractions that could disseminate endometrial glands and allow the endometrium to penetrate the myometrium (159). We considered a thickening of more than 13 mm of the junctional zone associated to hyperintense spots as highly specific for adenomyosis (Fig. 41). Larsen et al. (159) reported adenomyosis in 34.6% of patients with endometriosis, Kunz (153) in 79% of patients and Bazot (31) in 27% cases. These discrepancies are explained by the different diagnostic criteria used. As no consensus exists, it is difficult to compare different studies.

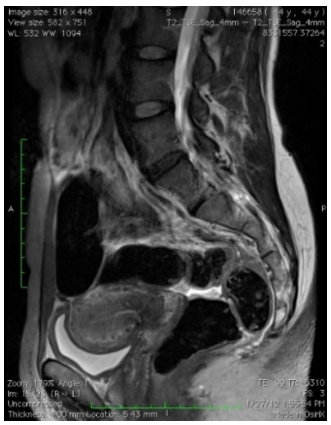
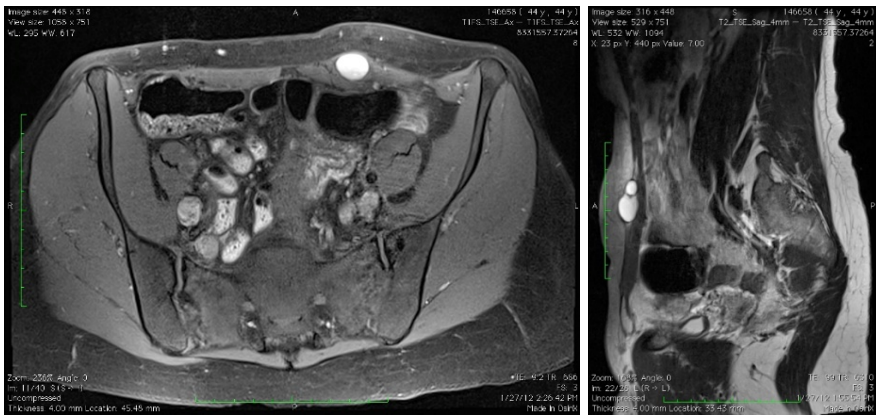


Fig. 41. Adenomyosis in a patient with endometriosis: thickening of the junctional zone with hyperintense spots similar to the normal endometrium (T2 weighted sequence)

Our team encountered a particular situation, an endometriotic implant of the left rectus abdominis in a patient that previously had laparoscopy for endometriosis. According to case reports as no extensive study exists, endometriosis of the abdominal wall could have different localizations: umbilical, the rectus abdominis muscle, laparoscopy trocar orifices or postoperative scars and could be the result of translocation of endometrial or decidual tissue during surgical procedures. This type of endometriosis is often mistaken for other abnormal conditions (84) such as a suture granuloma, parietal hernia, or metastatic lesions (Fig. 42).



a **b**

Fig. 42. Hemorrhagic endometriotic nodule in the left rectus abdominis muscle in the patient that previously had laparoscopy for endometriosis: T1 fat sat (a) and T2 (b) weighted sequences (personal data)

Concerning the technical aspect, we did not use vaginal or rectal opacification with sterile ultrasound gel as it increases the examination time and brings supplementary discomfort to the patient with no practical benefice as new MRI devices have a very good spatial resolution. The intestinal transit was slowed with drotaverine in all cases.

3.2.1.5. Conclusions

MRI imaging can accurately identify endometriotic lesions no matter their topography.

In order to make a clear differential diagnosis with other pelvic lesions T1 and T2 both TSE and fat sat sequences are necessary. For a precise anatomical localization, it is mandatory to obtain T2 images in all the three planes, most of the lesions (especially of the rectovaginal septum, uterine torus, sacrouterine ligaments) being identifiable on the sagittal sequence.

Intestinal and round ligaments lesions are easily seen on the axial sequence.

3.2.2. 3D morphological evaluation of gynaecologic pathology

3.2.2.1. Introduction

Cystadenofibromas of the fallopian tubes are rare benign tumours with few cases reported in the literature. Usually, the tumour is asymptomatic and incidentally discovered during surgery for other genital pathology.

We report the case of a 30-year-old woman with a serous cystadenofibroma of the fallopian tube, presenting with chronic abdominal pain and secondary infertility. The diagnosis of a tubal tumour was suspected at 2D and 3D ultrasound (US) examination and confirmed during laparoscopic surgery.

My interest in this field is reflected by the following published paper:

1. Grigore M, Popovici R, **Furnica C**, Pristavu A, Hamod A, Gafitanu D. Three-dimensional ultrasound and HDlive in tubal serous cystadenofibroma: a case report and literature review. J Med Ultrason 2017; 19(4) : 444-446.

3.2.2.2. Case report

A 30-year-old woman was addressed to the gynecologist for chronic pelvic pain and secondary infertility.

The endovaginal US examination revealed a septate uterus and a complex parauterine structure adjacent to the left ovary, 4 cm long, with regular wall and fine papillae on the internal surface (Fig 43a).

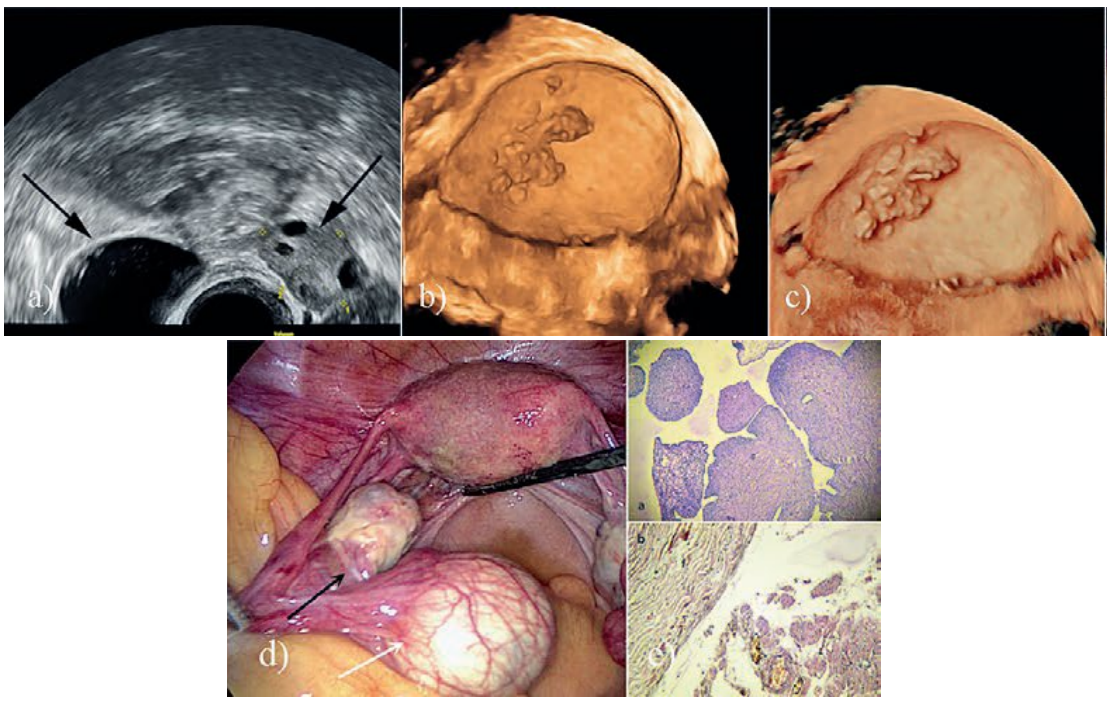


Fig. 43. a) Endovaginal 2Dultrasonography of the tumour (black arrow – ovary, white arrow – tumour with papillae inside);b) 3D ultrasound of the tumor – tumor pappilae are seen inside of the tumour; c) HDlive three-dimensional ultrasound of the tumor the pappilae are clearly seen; d) Laparoscopic image of the tumor (black arrow – left ovary, white arrow – fallopian tumour); d) histo-pathological examination – cystadenofibroma (up) and cyst wall and fallopian tube (down) (H&E staining) (personal data)

The 2D Doppler examination displayed no vascularisation of the papillae. The 3D sonography with HDlive software (Voluson E8, GE Healthcare) confirmed the fine, regular aspect of vegetations inside the tumour (Fig. 43b, 43c). CA 125 and CA19-9 tumoral markers were within the normal range.

Because of the complex structure and no objectivation of a connection with the ovary, a fallopian tube benign tumour was suspected. After discussing the therapeutic management with the patient, there was performed a laparoscopic cystectomy.

The tumour was attached to the serosal surface of the tube (Fig. 43d) and histological examination confirmed serous cystadenofibroma of the fallopian tube (Fig. 43e).

The patient recovered uneventfully and was discharged 3 days postoperatively. Two months after, she became spontaneously pregnant.

3.2.2.3. Discussions

Cystadenofibromas of the fallopian tube are rare benign tumours with low malignancy potential (70).

The first case was reported by Iwanov in 1909 (129) and its origins are unclear. It is considered to be an embryologic remnant rather than a neoplastic proliferation. Gurbuz et al. (112) affirmed that the topography, histology and immunohistology of the lesion suggest it to be an embryologic remnant of the müllerian duct.

The tumour is usually a round, solitary mass located inside or attached to the serosal surface or fimbriated part of the fallopian tube.

The internal and/or external surface can be fimbriated or papillary.

Two histological components are present, a connective stroma without nuclear pleomorphism or mitosis and papillary structures lined by epithelial cells on the surface of the tuba (112).

Most cases reported in the literature were asymptomatic, and most were incidental findings during surgery for another pathology.

In all cases, in which the tumour was discovered incidentally, a salpingectomy or adnexectomy was performed.

For only one case, in which the tumour was discovered during an in vitro fertilization evaluation, a cystectomy was performed (231).

The diagnosis of cystadenofibroma could be difficult because macroscopically and ultrasonographically these tumours seem malignant thus resulting in radical surgery (70).

In our case, the preoperative suspicion was helpful in deciding the type of surgery.

We believe that with a careful ultrasound examination, combining 2D Doppler and 3D US, the diagnosis could be at least suspected.

In the case we reported, patient's symptoms completely disappeared after surgery and she became pregnant one month after without any treatment.

Because of the good prognosis and low malignant potential, preoperative diagnosis is essential to avoid radical surgery and preserve fertility.

However, in patients over 50 years of age, presenting with any ovarian or fallopian tube tumour, there is no need for a conservative approach (70).

3.2.2.4. Conclusions

Cystadenofibromas of the fallopian tube can be diagnosed preoperatively with careful clinical and ultrasound examination.

A correct diagnosis is important especially in young patients who desire a pregnancy and ultrasound examination is particularly important before planning the surgery.

3.3. Clinical anatomy in forensic sciences

3.3.1. Introduction

Current specialized literature considers demonological possession as a *borderline* phenomenon balanced on the thin line between culturality and scientific knowledge. Certain cultures consider demonic possession an intrinsic part of social behaviour unlike European cultures which consider possession a form of mental disorder (151).

A psychiatric system operating based on criteria specific to the beginning of the 20th century is unable to follow and treat a mental patient outside the hospital. Once discharged, the patients, either returning home or vagabonds, tend to ignore or are otherwise unable to continue taking the prescribed medication; and their progress is often unrecorded. Additionally, the screening of mental diseases in our society leaves a lot to be desired especially in rural areas where a great number of mental diseases are tolerated by the community in their early stages, the persons presenting such conditions often being referred to as "village madmen". Therefore, these people live a somewhat peculiar life, while treading the limits of their natal community they are not excluded completely. Because of excessive tolerance or social indifference, the number of crimes committed by mental patients has reached alarming levels. Many of these tolerated individuals suffer a psychiatric decompensation at a point in their life, when they commit extremely serious antisocial acts.

The forensic onset of mental illnesses causes higher mortality rates in rural communities, especially in closed groups.

My interest in this field is reflected by the following published paper:

1. Scripcaru V, Iliescu DB, **Furnica C**, Scripcaru A, Nistor PP. Demonology and suicide - Forensic implications. Romanian Journal of Legal Medicine 2017; 25(2): 211-216.

3.3.2. Case report

A monk from a Moldavian monastery, aged 39, is found, during a random traffic check performed by the local police, driving a car on public roads without holding a driver's license. His behaviour and statement during the official inquiry raise suspicion and policemen request a forensic psychiatric assessment. The analysis of monk's psychiatric history reveals that, at the age of 32, he was hospitalized three times for acute psychotic disorder with schizophrenic symptoms. Since his condition was thought to be potentially life threatening both to himself and other traffic participants, after his first hospitalization he was forbidden from driving cars on public roads. More recent psychiatric examinations revealed a cooperating patient, in a calm psychomotor state, who reciprocates in dialogue, is slightly suspicious, exhibits poor hygiene skills and careless clothing, hypo-mobile and slightly disagreeing look and mimic, monotonous voice and normal motor activity. The patient denies the occurrence of any psycho-productive phenomena and shows no signs of altered mnesic functions. His thinking is coherent and has a normal rate, with interpretative tendencies. The patient also presents restricted affect, extreme sensitivity to unfriendly attitudes, tendency to bear grudges, diminished appetite, mixed sleep disorders, elective hypobulia, self and allopsychic temporal and spatial orientation, preserved self-conduction and self-care capacity, social integration and relation difficulties. The person above admits having driven the car many times after his license had been cancelled, in order to settle monastery problems. The other monks were reported to have encouraged and supported him on many occasions, by convincing him that he was sound of mind and that his license had been unfairly cancelled. Therefore, convinced that he was not suffering from any mental illnesses he threatens with requesting repeated forensic psychiatric assessments, until "*somebody admits that he is not sick*". He ultimately admits hearing, especially during night-

time, divine voices which advise him how to behave and what to do the following day. He also mentions episodes of isolation and refusal of dialogue, which he explains thusly: "*everybody around me says many meaningless unimportant and uninteresting things. That is why I prefer to shut up a day or two, or as long as necessary, and to speak only when God gives me an order*!" The forensic psychiatric assessment concludes that he lacks the mental capacity necessary for driving vehicles on public roads, but it is our personal belief that he will continue defying this decision, continuing to consider himself sane.

3.3.3. Discussions

Descriptions of demonic possession and exorcism can be found in the Old Testament and in the Book of Samuel, which illustrate the interrelations among sin, exorcism and possession. Saul is changed into an evil spirit as retribution for his sins. King David chases a malefic spirit by playing the harp in front of the local monarch. The New Testament describes numerous exorcist methods, predominantly before the crucifixion of Christ. Although diseases, possession and exorcism are considered to be the results of sins, the Bible describes each of them separately. Jesus Christ has the demiurgic capacity to distinguish between disease and demonic possession (179).

Despite the breakthroughs of modern psychiatry, the demonic possession doctrine has not completely disappeared nowadays. The beliefs in the demonic aetiology of mental illnesses are multicultural and occur in all stages of the history of medicine.

The scientific approach to demonic possession includes several different perspectives. *the ritualistic, voluntary and reversible type* approved by society and practiced during religious ceremonies, and *the non-ritualistic, peripheral, involuntary and pathological type*, in which the subject's spirit is inhabited by supernatural beings against his will (227).

Kroll (151) tries to distinguish between demonic possession and mental disorder referencing the criteria proposed by the Catholic Church, namely internal conflict, recovery after exorcism, presence of a phenomenon of spirit transfer from one person to another, or from human to animal.

Some patients, with or without religious faith, confess to feeling an external influence, sometimes even characterizing it as possession, by outer spirits/powers (180). In most cases, these beliefs follow religious models, and their attitudes are accounted for by the admitted existence of demonic and spiritual powers.

Due to the evolution of behavioural sciences, alternative explanations gradually replaced the demonic model.

The multi-factor etiological model includes (227):

- **a psychodynamic approach** according to which abnormal behaviours originate in a series of intrapsychic conflicts;
- **a humanistic approach** when the subjects are either too susceptible and vulnerable to others' opinions, or incapable of accepting and understanding themselves;
- **a behavioral pattern** according to which abnormal behaviour has the same origin as normal, classically conditioned or operated behaviour;
- **a cognitive approach** due to cognitive process alteration'
- **a biological approach** according to which abnormal behaviour derives from psychological processes involving cerebral determinism;
- **a mixed bio-psychological approach**, which admits interactions among biological, psychological and social factors;
- **a psycho-analytical approach.** The classical psychoanalysis school does not accept the idea of demonic possession. Jung does not tackle demonic possession directly, as he is rather interested in glossolalia (the ability to speak different languages due to possession by divine spirits.

Psychiatrists long time considered demonic possession as a component of demonic dissociation. Kroll and Bachracu summarize the correlations between mental conditions and demonic possession symptoms in table XLII (151).

Table XLII. Correlations between mental conditions and demonic possession symptoms (kroll)

Possession Symptoms	**Possible Mental Condition**
Personality alteration	Multiple personality
Use of obscene language, obscene behavior, blasphemy	Gilles de la Tourette's syndrome
Belief in demonic possession	Schizophrenia
Consciousness alteration	Somnambulism Trance

The classification of patients suffering from such conditions is made according to the International Classification of Diseases (ICD-10) and Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV-R).

The psychiatrist is generally thought of as nothing more than the scientific successor of the priest, who has solved the spiritual problems of humanity for centuries (132).

We think that a clear distinction should be made between religious behaviours, involving attitudes and cultural ideas specific to a practicing Christian, and behavioural deviations which contain a mystical component (table XLIII).

Table XLIII. Mental illnesses that may involve demonic semiology

Affective disorders	Major depressions (clinical or unipolar depression) Seasonal affective disorders Bipolar disorders (manias, depressions)
Anxiety disorders	General anxiety Panic and panic attack Obsessive compulsive disorders Posttraumatic stress syndrome
Dissociative disorders	Multiple personality (dissociative identity) Dissociative amnesia Dissociative fugue
Schizophrenia	Paranoia Disorganized Catatonic Undifferentiated
Development disorders	Autism ADHD Conduction disorders Different levels of mental retardation
Personality disorders	Antisocial personality Narcissistic personality Histrionic personality Paranoid personality Borderline personality
Somatoform disorders	Conversion disorders (hysteria) Hypochondria

The foundations of the Christian behavioural orientations are found in the Bible (both the Old and the New Testament), where peculiar or even dangerous compulsive behaviours are described, as well as the verbal passing of certain curses by demonic forces. The classical

attitude of the Church is exorcism, sometimes involving dramatic acts performed by the priest and/or possessed, until complete healing (151). According to the Catholic Church, the existence of evil spirits is inoculated, by defining exorcism as a doctrine and reporting numerous cases, as well as by the existence of special group of priests able to undertake such a ritual (180). Patients with demonic ideation are usually seen not only by a psychiatrist but also a priest and various individuals belonging to the sub-cultural area, namely magicians, wizards, clairvoyants, etc. concomitantly.

Among the factors increasing vulnerability to demonic possession we identified stress factors of various origins. The behaviour of these people takes on different forms depending on their primary organic disorder.

Patients suffering from depression present strong feelings of self-damnation, experience a loss of affinity to any group, give up their religious practices which they consider useless, and deny the existence of the Divine. They generally believe that their life is guided by demonic forces which transcend themselves surpassing even God.

Anxious-depressive patients attribute the cause of their condition to occult aetiologies. Their ego-dystonic obsessive-blasphemous thoughts are seen, in such cases, as demonic attacks, which have a destructive somato-psychic potential.

Occultism is frequent in patients with personality disorders and affects both their social life and the incidence of their sexual conflicts. A violent conflict with their personal religious beliefs and ideals or with those of the group the patients belong to is experienced.

The mystical-religious delirium proper to schizophrenia urges many patients, in the early or even in the advanced stages of the illness, to get closer to sanctuaries, especially monasteries and convents. Given their passion for religion and financial difficulties that often accompany their conditions, those subjects who enter monasteries are received with no reserves and especially without any investigation into their pathological history. There they find the isolation specific to their illness, meanwhile religion, inaccurately interpreted and approached from an extremist point of view, creates a favourable environment for the "blooming" of incipient delirious ideas. Religious beliefs are often shared so passionately that other individuals living in the same environment often adhere to them, which in turn permits the creation of delirious group-meetings.

The doctor's attitude towards such a patient should be empathic and unconditioned by any personal belief systems, thus opening the way to subsequent explorations. The doctor is usually consulted for an interpretation of what the patient him/herself cannot explain. As soon as the patients receives a consistent explanation for the attitude or occult faith to which they adhere, the signs and symptoms are remitted spontaneously, and they no longer see themselves as the victims of something unexplainable, uncontrollable and esoteric. The religious rituals practiced by the patients are usually landmarks on their way to self-healing, psychiatric medication being often perceived by such subjects as inefficient.

When the patient's response to medication is positive, this enables the patient to gain a broader view of the determinant psychosocial factors. Thus, to some patients, the idea of possession gradually becomes an illusion, which ultimately is given up.

3.3.4. Conclusions

The psychiatrist's competence supplemented by his/her own belief in religious values influence the formulation and therapy of demonic possession phenomena. We support, from both a medical and a scientific viewpoint, the implementation of legal regulations making it mandatory for the family doctors of various communities to conduct periodic medical examinations of such patients with the help of psychologist or psychiatrists. This would prevent and even avoid many antisocial behaviours and help keep religious faith intact in its harmony and sacredness.

SECTION II. SHAPING THE FUTURE

In my opinion, nowadays there is a strong need in our country to conduct research studies for devising medical curriculum that should be rationally balanced with basic sciences and clinical knowledge.

This is way currently we are preparing extensive research directions that will involve students, Ph.D. students and medical personnel, promote interdisciplinarity and state of the art medical care, generate knowledge to be disseminated through scientific papers in ISI journals, and raise the standard of care offered to our patients.

I. Neuroanatomical analysis of the aging brain

I.1. State of the art

Unfortunately, humans are born immature: infants cannot speak, walk, use tools, or put themselves in the place of others. Brain development continues well after birth and, it has the fastest rate in the first year of life with neurons increasing in size, forming trillions of connections.

The brain thus becomes a vast network of connections. These networks represent not only the substrate of cognitive functions, but also make possible the understanding of the clinical consequences of brain diseases.

The study of neural connections, whether anatomical or functional and a better understanding of the networks they form is a major issue in the study of the human brain. Most of the studies on the effects of aging on brain connections often only consider young persons, the elderly and Alzheimer patients. In order to better understand these changes, it should seem legit to follow individuals from an early age as it is recognized that neural aging begins around 20 years of age.

The XXIst century is the era of networking. The concept of network is therefore very generally defined as a set of objects or people connected or maintained in connection.

The graph theory allowed the study of networks and define them as a set of nodes or vertices linked together by edges or lines.

One of the recurring characteristics in brain connection networks is the existence of "hubs" (or routers).

A "hub" is a node with a high degree of connections and a high centrality which measures how many shortest paths between pairs of nodes in the network pass through it. A node with high centrality is therefore crucial for efficient data transportation. A hub is a characteristic of the connection network (193).

Another feature of the network of brain connections is the so-called "small world" which can be defined as the combination of a small average distance between nodes and a high "clustering" coefficient. The "clustering" coefficient quantifies the probability that two nodes connected to the same node are themselves directly connected to each other (30).

Brain anatomy has often played an ambiguous role in the countless studies aimed at revealing the functioning of the human mind. The ambition to associate each cognition process to the activity of a particular structure of the brain gave rise in the course of history to many hypotheses which culminated at the beginning of the 19th century with the phrenology of Gall that aimed to localize brain functions (233).

The observation of patients with focal brain lesions and the electrical stimulation of the cortex in animals and then in humans during certain neurosurgical operations allowed scientists

(150) to draw the first functional maps. Localization and globalist visions were then gradually unified into a "*connectivist*" vision (220) of brain functioning which associates each cognitive process with the global activity of a network of localized modules.

The study of the brain networks using the graph theory applied in neuroimaging research is increasingly used to test structure/function hypotheses and well as a methodological tool to examine brain networks, their organization, typology and dynamics.

It has been found that the brain shares the properties of networks like centrality, hubs, clustering, small-world or synchronization. A better understanding of brain networks on a large scale is of crucial importance.

These networks are not only responsible for cognitive processes, but they also make it possible to understand the clinical consequences of brain diseases (237).

Thanks to diffusion MRI, it is possible to reconstruct the fibre tracts within the WM. This technique called *tractography* allows the study of anatomical connectivity and gave rise to a new term, "connectome".

The *connectome* is defined as a complete map of neural connections in a brain (36). Functional connectivity refers to the concept of temporal correlation of the activity of distinct neuronal populations. Such temporal correlations are the result of distant neural interactions within a network through anatomical connections.

Thus, the notion of functional connectivity differs from that of anatomical connectivity in the sense that an anatomical connection can be used or not in the accomplishment of a task. In a similar manner, the functional connectivity between two brain areas does not imply the existence of a direct anatomical connection between the two since the correlation of the neuronal activity of these areas can be mediated by a third area.

Studies analysing functional connectivity using the graph theory model have shown that the network of brain connections has a high degree of "clustering". Several cerebral areas including the precuneus, the insula, the superior parietal lobule, and the superior frontal gyrus have this important feature (236).

I.2. Aims

A future research direction aims to study the perennial changes of cerebral connections that occur continuously during the aging process in order to differentiate the physiological from the pathological aging.

I.3. Expected results

Evaluating healthy subjects of all ages will allow us to assess cerebral aging, the correlation between morphological and neuropsychological changes and identify most affected areas.

At the end of the study we aim to obtain a global chart of the aging brain, both morphological and functional.

While much research has focused on the diseases of aging, there are few studies on the aging of the brain in the absence of any neurodegenerative disease.

There seems to be an unclear transition zone between physiological aging and pathological aging, so one can hypothesize that there could be a quantitative threshold in terms of neurons and connections for mental function and coping abilities.

II. Creation of a Multinational Congenital Cardiac Care Network (MCCCN)

II.1. State of the art

Currently, decision-making process in CHD still relies on consensus opinion of experts, small prospective and retrospective studies, or registries and does not reflect the individual patient. Despite technical advances, patients operated for CHD still experience increased long-term morbidity rates. Clinical course, surveillance and long-term outcome information is scarce due to the lack of large registries.

According to EUROCAT, only 22 European countries have CHD registries, most of them at a regional scale (253).

Only one European registry exists, the European Congenital Heart Surgeons Association (ECHSA) Database which is static and has limited functionality due to reduced number of data fields. Except the lack of surveillance data, developing countries face the lack of trained medical personnel as no university offers post-graduate of fellowship studies in the field of CHD.

II.2. Aims

The heart team aims to create a framework of governance in CHD based on partnership and links between health care professionals and organizations from primary, secondary and tertiary care, IT. The research directions rely on cooperation, service integration, coordination, provision of state-of-the-art effective care, early diagnosis and individualized approach in CHD, and inter-disciplinarily.

The main objective is to set up a Multinational Congenital Cardiac Care Network (MCCCN) that involves medical personnel and patient mobility in order to achieve best possible care.

By developing and delivering a novel concept for CHD patient care based on 3D-Printed CHD models, expert agreement, multinational cooperation we hope to integrate the new paradigm of "predictive personalized medicine" into the therapeutic approach of CHD using 3D printing tools, to understand and implement optimal health services in a systematic manner and to create a pool of knowledge in the field of CHD unique in the diversity and depth of expertise, by making available a full range of diagnostic capabilities.

By managing a highly tailored and comprehensive CHD database we aim to consolidate available services to an integrated pool and to train undergraduates, postgraduates and medical personnel by creating a reference centre for CHD at Iași.

The study of the morphological and functional changes of malformed hearts following various therapeutic procedures may enhance the long-time prognosis of CHD patients.

II.3. Expected results

To provide optimal patient-specific care to individuals suffering from CHD at a multinational scale. An EEAB would compensate the lack of experience in some cardiac surgery centres and assure best possible care for a patient. Integration of 3D modelling into surgical planning would provide a tool for outcome improvement as the surgeon could design preoperatively the intervention and adjust surgical details after visualising cardiovascular anomalies.

CONCLUSIONS

With the passing of the ages, anatomy has evolved with ups and downs its transmission from one generation of physicians to another, in an undulating pattern.

Based on Latin, the most logical linguistic system, anatomy is a formative discipline, modulating the logic, outlining learning and thinking patterns, defining the cognitive processes during different stages of medical approach.

Anatomy defines medical thinking, forming a medical culture, creating and shaping large medical schools using anatomical models.

As physicians, we have a responsibility to our profession and patients and to ourselves, consequently, an imperious need to both maintain a high standard for medical education.

I strongly plead for an open European academic labour market, receptive to sharing with regions in the world (internationalization of curricula, multicultural faculty, etc).

In my opinion structural anatomical issues are not aims in themselves, but basic values and needs compulsory in translating abstract science in medico-surgical practice.

Interdisciplinary as a new methodology is needed – in face of current medical problems, requiring creative, multidisciplinary academicals, scientific and educational approaches.

Better use of national and international cooperation between all medical disciplines is compulsory in a hybrid multicultural (traditional/informatically-based) system type approach based on intercultural competences, in order to model responsible citizenship and outstanding healthcare professionals.

REFERENCES

1. ****_Diabet zaharat - date statistice la nivel internaţional, naţional şi judeţean_, Institutul Național de Sănătate Publică, Ministerul Sănătății, România. http://www.insp.gov.ro/cnepss/wp-content/uploads/2011/11/Date-statistice.pdf
2. ****Diabetes mellitus: a major risk factor for cardiovascular disease. A joint editorial statement by the American Diabetes Association; The National Heart, Lung, and Blood Institute; The Juvenile Diabetes Foundation International; The National Institute of Diabetes and Digestive and Kidney Diseases; and The American Heart Association. *Circulation* 1999; 100(10): 1132-3.
3. ***_The Michael E. DeBakey Papers._ https://profiles.nlm.nih.gov/ps/retrieve/Narrative/FJ/p-nid/331 [accessed August 31st 2016]
4. Abbara S, Mundo-Sagardia JA, Hoffmann U, Cury RC. Cardiac CT assessment of left atrial accessory appendages and diverticula. *Am J Roentgenol* 2009; 193: 807-12.
5. Acar C, Jebara VA, Portoghese M et al. Comparative anatomy and histology of the radial artery and the internal thoracic artery: implications for coronary artery bypass. *Surg Radiol Anat* 1991; 13: 283–8.
6. Acar C, Jebara VA, Portoghese M et al. Revival of the radial artery for coronary artery bypass grafting. *Ann Thorac Surg* 1992; 54: 652–60.
7. Ahmed S, Johnson PT, Fishman EK, Zimmerman SL. Role of multidetector CT in assessment of repaired tetralogy of Fallot. *Radiographics* 2013; 33(4): 1023-36.
8. Ahn KH, Lyoo IK, Lee HK et al. White matter hyperintensities in subjects with bipolar disorder. Psychiatry *Clin Neurosci* 2004; 58: 516–21.
9. Alexopoulos GS, Meyers BS, Young RC et al. Vascular depression' hypothesis. *Arch Gen Psychiatry* 1997; 54: 915–22.
10. Allen HD, Driscoll DJ, Shaddy RE, Felter TF. *Moss & Adams' Heart Disease in Infants, Children, and Adolescents: Including the Fetus and Young Adult.* 8th ed. LWW, 2012.
11. Alvarez JC, Cremniter D, Lesieur P et al. Low blood cholesterol and low platelet serotonin levels in violent suicide attempters. *Biol Psychiatry* 1999; 45(8): 1066-9.
12. American Psychiatry Association. *Diagnostic and Statistical Manual of Mental Disorders* 4th ed. (DSM–IV). APA, 1994.
13. Anand DV, Lim E, Hopkins D et al. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. *Eur Heart J* 2006; 27: 713—21.
14. Anderson RH, Shirali G. Sequential segmental analysis. *Annals of Pediatric Cardiology* 2009; 2(1): 24-35.
15. Anderson RH. Clinical anatomy of the aortic root. *Heart* 2000; 84(6):670-3.
16. Andreini D, Pontone G, Mushtaq S et al. A long-term prognostic value of coronary CT angiography in suspected coronary artery disease. *JACC Cardiovasc Imaging* 2012; 5: 690-701.
17. Angelini P. Embryology and congenital heart disease. *Texas Heart Institute Journal* 1995; 22(1):1-12.
18. Anselmino M, Blandino A, Beninati S et al. Morphologic analysis of left atrial anatomy by magnetic resonance angiography in patients with atrial fibrillation: a large single center experience. *J Cardiovasc Electrophysiol* 2011; 22: 1-7.
19. Applegate KE, Goske MJ, Pierce G, Murphy D. Situs revisited: imaging of the heterotaxy syndrome. *Radiographics* 1999; 19(4):837-52.
20. Atis A, Demirayak G, Saglam B et al. Craniorachischisis with a variant of pentalogy of Cantrell with lung extrophy. *Fetal Pediatr Pathol* 2011;30:431–6.

21. Aydin S, Aydin S, Nesimi Eren M et al. The cardiovascular system and the biochemistry of grafts used in heart surgery. *SpringerPlus* 2013; 2: 612.
22. Bahnini J, Meyer Ch, Manzini N. Les traumatismes de la rate: traitement conservateur ou exerese? Chirurgie 1989; 115:45–50.
23. Baikoussis NG, Papakonstantinou NA, Apostolakis E. Radial artery as graft for coronary artery bypass surgery: Advantages and disadvantages for its usage focused on structural and biological characteristics. *J Cardiol* 2014; 63(5): 321-8.
24. Baldwin RC. Depressive disorders. In Jacoby R, Oppenheimer C. *Psychiatry in the elderly*. Oxford: Oxford University Press; 2002. pp. 627-76.
25. Balleyguier C, Chapron C, Eiss D. Imagerie de l'endométriose. *EMC-Radiologie* 2004; 1: 36–49.
26. Bara T, Gyorgy E. Partial splenectomy. *Medical Update* 1999; 4: 176-180.
27. BARI Investigators. The final 10-year follow-up results from the BARI randomized trial. *J Am Coll Cardiol* 2007; 49(15): 1600-6.
28. Barta PE, Pearlson GD, Powers RE et al. Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. *Am J Psychiatry* 1990; 147(11): 1457-1462.
29. Barthelemy O, Jacqueminet S, Rouzet F et al. Intensive cardiovascular risk factors therapy and prevalence of silent myocardial ischaemia in patients with type 2 diabetes. *Arch Cardiovasc Dis* 2008; 101(9): 539-46.
30. Bassett DS, Bullmore ET. Small-World Brain Networks Revisited. *Neuroscientist* 2017; 23(5): 499–516.
31. Bazot M, Darai E, Hourani R, et al. Deep pelvic endometriosis: MR imaging for diagnosis and prediction of extension of disease. *Radiology* 2004; 232 : 379–389.
32. Bazot M, Fiori O, Darai E. Adenomyosis in endometriosis—prevalence and impact on fertility. Evidence from magnetic resonance imaging. *Hum Reprod* 2006; 21 : 1101–2.
33. Beck AT, Emery G, Greenberg RL. *Anxiety Disorders and Phobias: A Cognitive Perspective.* New York: Basic Books, 1985.
34. Bellhouse B, Bellhouse F. Fluid mechanics of model normal and stenosed aortic valves. *Circ Res* 1969; 25(6):693-704.
35. Benedetto U, Raja SG, Albanese A et al. Searching for the second-best graft for coronary artery bypass surgery: a network meta-analysis of randomized controlled trials. *Eur J Cardiothorac Surg* 2014; 47: 59–65.
36. Bennett SH, Kirby AJ, Finnerty GT. Rewiring the connectome: Evidence and effects. *Neurosci Biobehav Rev* 2018; 88: 51–62.
37. Bhat RY, Rao A. Cantrell syndrome in one set of monozytic twins. *Singapore Med J* 2006;47:1087–8.
38. Birks EJ, Webb C, Child A et al. Early and long-term results of a valve-sparing operation for Marfan syndrome. *Cir culation* 1999; 100(19 Suppl): II29-35.
39. Bittmann S, Ulus H, Springer A. Combined pentalogy of Cantrell with tetralogy of Fallot, gallbladder agenesis, and polysplenia: a case report. *J Pediatr Surg* 2004;39:107–9.
40. Bittner A, Mönnig G, Vagt AJ et al. Pulmonary vein variants predispose to atrial fibrillation: a case-control study using multislice contrast-enhanced computed tomography. *Europace* 2011; 13: 1394-400.
41. Bojar RM. *Manual of Perioperative Care in Adult Cardiac Surgery*, 5th Edition. Wiley-Blackwell, 2011.
42. Bonert M, Myers JG, Fremes S et al. A Numerical Study of Blood Flow in Coronary Artery Bypass Graft Side-to-Side Anastomoses. *Ann Biomed Eng* 2002; 30: 599–611.
43. Boston PF, Dursun SM, Reveley MA. Cholesterol and mental disorder. *Br J Psychiatry* 1996;169(6):682-9.

44. Brash JC, Jamieson EB, eds. *Cunningham's manual of practical anatomy*. New York: Oxford University Press, 1947.
45. Buse JB, Ginsberg HN, Bakris GL et al. American Heart Association; American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation* 2007;115(1):114-26.
46. Buxton BF, Hayward PA. The art of arterial revascularization-total arterial revascularization in patients with triple vessel coronary artery disease. *Ann Cardiothorac Surg* 2013; 2(4): 543-51.
47. Cahn W, van Haren NE, Hulshoff Pol HE et al. Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. *Br J Psychiatry* 2006; 189: 381-2.
48. Calafiore AM, Contini M, Vitolla G et al. Bilateral internal thoracic artery grafting: Long-term clinical and angiographic results of in situ versus Y grafts. *J Thorac Cardiovasc Surg* 2000; 120: 990–8.
49. Cameron AA, Green GE, Brogno DA et al. Internal thoracic artery grafts: 20-year clinical follow-up. *J Am Coll Cardiol* 1995; 25(1): 188-92.
50. Cantrell JR, Haller JA, Ravitch MM. A syndrome of congenital defects involving the abdominal wall, sternum, diaphragm, pericardium, and heart. *Surg Gynecol* 1958;107:602–14.
51. Carmi R, Boughman JA. Pentalogy of Cantrell and associated midline anomalies: a possible ventral midline developmental field. *Am J Med Genet* 1992;42:90–5.
52. Carpenter WT, Heinrichs DW, Wagman AM. Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry* 1988; 145: 578-83.
53. Carpentier A, Guermonprez JL, Deloche A et al. The aorta-to-coronary radial artery bypass graft: a technique avoiding pathological changes in grafts. *Ann Thorac Surg* 1973; 16:111–21.
54. Carpentier A. Cardiac valve surgery-the "French correction". *J Thorac Cardiovasc Surg* 1983; 86(3): 323-37.
55. Carranza CL, Ballegaard M, Werner MU et al. Endoscopic versus open radial artery harvest and mammario-radial versus aorto-radial grafting in patients undergoing coronary artery bypass surgery: protocol for the 2 × 2 factorial designed randomised NEO trial. *Trials* 2014;15:135.
56. Chang K, Barnea-Goraly N, Karchemskiy A et al. Cortical magnetic resonance imaging findings in familial pediatric bipolar disorder. *Biol Psychiatry* 2005; 58: 197–203.
57. Chapron C, Fauconnier A, Vieira M et al. Anatomical distribution of deeply infiltrating endometriosis: surgical implications and proposition for a classification. *Hum Reprod* 2003; 18(1) : 157–61.
58. Chen BK, Sassi R, Axelson D et al. Cross-sectional study of abnormal amygdala development in adolescents and young adults with bipolar disorder. *Biol Psychiatry* 2004; 56(6): 399-405.
59. Chen CP. Syndromes and disorders associated with omphalocele(II): OEIS complex and pentalogy of Cantrell. *Taiwan J Obstet Gynecol* 2007;46:103–10.
60. Chiu C-J. Why do radial artery grafts for aortocoronary bypass fail? A reappraisal. *Ann Thorac Surg* 1976; 22:520–3
61. Christo MC. Partial splenectomies in hematologic diseases. *Chirurg Gastroenterol* 1993; 9 (Suppl 2): 23-29.
62. Clark EB, Nakazawa M, Takao A, eds. *Etiology and morphogenesis of congenital heart disease.* Mount Kisco, NY: Futura Publishing Company, 2000.
63. Coleman S, Anson B. Arterial patterns in the hand based upon a study of 650 specimens. *Surgery, Gynecology & Obstetrics* 1961; 113(4):409-24.

64. Cronin P, Sneider MB, Kazerooni EA et al. MDCT of the left atrium and pulmonary veins in planning radiofrequency ablation for atrial fibrillation: a how-to guide. *AJR Am J Roentgenol* 2004; 183: 767-78.
65. Curtis JJ, Stoney WS, Alford WC Jr et al. Intimal hyperplasia: a cause of radial artery aortocoronary bypass graft failure. *Ann Thorac Surg* 1975; 20: 628–35.
66. Cuschieri A. *Development of the heart and cardio- vascular system* [article online]. http://staff.um.edu.mt/acus1/Heart-a.htm. Accessed March 24, 2016.
67. David TE, David CM, Feindel CM, Manlhiot C. Reimplantation of the aortic valve at 20 years. *J Thorac Cardiovasc Surg* 2017; 153(2):232-238.
68. David TE. Aortic valve sparing operations: a review. *Korean J Thorac Cardiovasc Surg* 2012; 45(4):205–212.
69. Davis SW, Dennis NA, Daselaar SM et al. Que PASA? The posterior-anterior shift in aging. *Cereb Cortex* 2008; 18(5): 1201–1209.
70. de Silva TS, Patil A, Lawrence RN. Acute presentation of a benign cystadenofibroma of the fallopian tube: a case re-port. *J Med Case Rep* 2010;4:181.
71. Deac R. http://www.paginamedicala.ro/stiri-medicale/Incepand-cu-1-octombrie_-copiii-cu-malformatii-cardiace-nu-vor-mai-fi-operati-in-Romania_17779/
72. Deisenhammer EA, Kramer-Reinstadler K, Liensberger D et al. No evidence for an association between serum cholesterol and the course of depression and suicidality. *Psychiatry Res* 2004; 121(3): 253-61.
73. Del Frate C, Girometti R, Pittino M et al. Deep retroperitoneal pelvic endometriosis: MR imaging appearance with laparoscopic correlation. *Radiographics* 2006; 26 : 1705–1718.
74. Di Biase L, Santangeli P, Anselmino M et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. *J Am Coll Cardiol* 2012; 60: 531-8.
75. Didio LJA. Anatomicosurgical segmentation as principle of construction of human body and its clinical applications. *Verhandl Anat Gesellsch Anat anz* 1989; 164:737-743.
76. Ding J, Liu Y, Wang F, Bai F. Impact of Competitive Flow on Hemodynamics in Coronary Surgery: Numerical Study of ITA-LAD Model. *Comput Math Methods Med* 2012; 2012: 1–7.
77. Dion R, Glineur D, Derouck D et al. Long-term clinical and angiographic follow-up of sequential internal thoracic artery grafting. *Eur J Cardiothorac Surg* 17: 407-14, 2000.
78. Donofrio MT, Moon-Grady AJ, Hornberger L et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. *Circulation* 2014; 129(21): 2183-242.
79. Dorobantu M, Tautu O-F. *Proiecte romanesti de cercetare a factorilor de risc cardiovascular.* http://www.societate-hipertensiune.ro/articole-proiecte-romanesti-de-cercetare-a-factorilor-de-risc-cardiovascular-societatea-romana-de-hipertensiune.php [accessed August 31st 2017]
80. Drouin A, Noiseux N, Chartrand-Lefebvre C et al. Composite versus conventional coronary artery bypass grafting strategy for the anterolateral territory: study protocol for a randomized controlled trial. *Trials* 2013; 14: 270.
81. Dubertstein PR, Conwell Y, Conner KR et al. Suicide at 50 years of age and older: perceived illness, family discord and financial strain. *Psychol Med* 2004; 34: 137-46.
82. Duerinckx AJ, Vanovermeire O. Accessory appendages of the left atrium as seen during 64-slice coronary CT angiography. *Int J Cardiovasc Imaging* 2008; 24: 215-21.
83. Duran CG. Reconstructive techniques for rheumatic aortic valve disease. *J Card Surg* 1988; 3:23-8.
84. Durand X, Daligand H, Aubert P, Baranger B. Endométriose de la paroi abdominale.

Journal de Chirurgie Viscérale 2010; 147 : 354—359.
85. Ehrlich S, Noam GG, Lyoo IK et al. White matter hyperintensities and their associations with suicidality in psychiatrically hospitalized children and adolescents. *J Am Acad Child Adolesc Psychiatry* 2004; 43: 770-6.
86. El Khoury G, de Kerchove L. Principles of aortic valve repair. *J Thorac Cardiovasc Surg* 2013; 145(3 Suppl): S26-9.
87. Erbel R, Aboyans V, Boileau C et al; ESC Committee for Practice Guidelines. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2014; 35(41): 2873-926.
88. European Society of Cardiology: *ESC/EACTS Guidelines in Myocardial Revascularisation*, 2014. http://eurheartj.oxfordjournals.org/content/ehj/35/37/2541.full.pdf [accessed August 31st 2017]
89. Eurostat - *Cardiovascular diseases statistics* (accessed 31 August 2017). Available from: http://ec.europa.eu/eurostat/statistics-explained/index.php/Cardiovascular_diseases_statistics
90. Eurostat - *Surgical operations and procedures statistics* (accessed 31 August 2017). Available from: http://ec.europa.eu/eurostat/statistics-explained/index.php/Surgical_operations_and_procedures_statistics
91. Fawcett J, Scheftner WA, Fogg L et al. Time-related predictors of suicide in patients with major affective disorder. *Am J Psychiatry* 1990; 147: 1189-94.
92. Fazekas F, Kleiner R, Offenbacher H et al. The morphologic correlate of incidental punctate white matter hyperintensities on MR images. *AJNR Am J Neuroradiol* 1991; 12: 915–921.
93. Fei DY, Thomas JD, Rittgers SE. The effect of angle and flow rate upon hemodynamics in distal vascular graft anastomoses: a numerical model study. *J Biomech Eng* 1994; 116: 331–336.
94. Figuera JR, Cruz EF, Garcia LD et al. Cardiac malformations in patients with pentalogy of Cantrell and ectopia cordis. *Rev Esp Cardiol* 2011;64:615–8.
95. Fisk RL, Brooks CH, Callaghan JC, Dvorkin J. Experience with the radial artery graft for coronary artery bypass. *Ann Thorac Surg* 1976; 21: 513–8
96. Flaum M, O'Leary DS, Swayze VW, Miller DD. Symptom dimensions and brain morphology in schizophrenia and related psychotic disorders. *J Psychiatr Res* 1995; 29(4): 261-276.
97. Fox JE, Gloster ES, Mirchandani R. Trisomy 18 with Cantrell pentalogy in a stillborn infant. *Am J Med Genet* 1988;31:391–4.
98. Frank L, Dillman JR, Parish V et al. Cardiovascular MR imaging of conotruncal anomalies. *Radiographics* 30(4):1069-94, 2010.
99. Frauenfelder T, Boutsianis E, Schertler T et al. Flow and wall shear stress in end-to-side and side-to-side anastomosis of venous coronary artery bypass grafts. Biomed Eng Online 2007; 6: 35.
100. Fukui S, Fukuda H, Toda K et al. Remodeling of the radial artery anastomosed to the internal thoracic artery as a composite straight graft. *J Thorac Cardiovasc Surg* 2007; 134: 1136-42.
101. Georghiou GP, Vidne BA, Dunning J. Does the radial artery provide better long-term patency than the saphenous vein? *Interact Cardiovasc Thorac Surg* 2005; 4(4): 304-10.

102. Ghanta RK, Kaneko T, Gammie JS et al. Evolving trends of reoperative coronary artery bypass grafting: an analysis of the Society of Thoracic Surgeons Adult Cardiac Surgery Database. *J Thorac Cardiovasc Surg* 2013; 145(2): 364-72.
103. Ghista DN, Kabinejadian F. Coronary artery bypass grafting hemodynamics and anastomosis design: a biomedical engineering review. *BioMedical Engineering OnLine* 2013;12:129.
104. Glineur D, Papadatos S, Grau JB et al. Complete myocardial revascularization using only bilateral internal thoracic arteries provides a low-risk and durable 10-year clinical outcome. *Eur J Cardiothorac Surg* 2016; 50(4): 735-741.
105. Go JL, Kim PE, Zee CS, The trigeminal nerve. *Semin Ultrasound CT MR* 2001; 22(6):502–520.
106. Goldberg TE, Torrey EF, Berman KF, Weinberger DR. Relations between neuropsychological performance and brain morphological and physiological measures in monozygotic twins discordant for schizophrenia. *Psychiatry Res* 1994; 55(1): 51-61.
107. Goldman S, Zadina K, Moritz T et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery. *J Am Coll Cardiol* 2004; 44: 2149–56.
108. Goraya TY, Leibson CL, Palumbo PJ et al. Coronary atherosclerosis in diabetes mellitus: a population-based autopsy study. *J Am Coll Cardiol* 2002; 40: 946 –953.
109. Grethel EJ, Hornberger LK, Farmenr DL. Prenatal and postnatal management of a patient with pentalogy of Cantrell and left ventricular aneurysm. A case report and literature review. *Fetal Diag Ther* 2007;22:269–73.
110. Grigore M, Iliev G, Gafitanu D et al. The fetal abdominal wall defects using 2D and 3D ultrasound. Pictorial essay. *Med Ultrason* 2012; 14:341–7.
111. Grigore M, Iliev G. Diagnosis of sacrococcygeal teratoma using two and three-dimensional ultrasonography: two cases reported and a literature review. *Med Ultrason* 2014;16:274–7.
112. Gurbuz Y, Ozkara SK. Immunohistochemical profile of serous papillary cystadenofibroma of the fallopian tube: a clue of paramesonephritic origin. *Appl Immunohistochem Mol Morphol* 2003;11:153-155.
113. Habib RH, Schwann TA, Engoren M. Late Effects of Radial Artery Versus Saphenous Vein Grafting in Patients Aged 70 Years or Older. *Ann Thorac Surg* 2012; 94: 1478–84.
114. Hadamitzky M, Hein F, Meyer T et al. Prognostic value of coronary computed tomographic angiography in diabetic patients without known coronary artery disease. *Diabetes Care* 2010; 33(6):1358-63.
115. Hajek T, Carrey N, Alda M. Neuroanatomical abnormalities as risk factors for bipolar disorder. *Bipolar Disord* 2005; 7: 393–403.
116. Haller JA Jr. The Roger Sherman Lecture. The current status of nonoperative management of abdominal injuries in children and young adults. *American Surgeon* 1998; 64(10):24–7.
117. Haznedar MM, Roversi F, Pallanti S et al. Fronto-thalamo-striatal gray and white matter volumes and anisotropy of their connections in bipolar spectrum illnesses. *Biol Psychiatry* 2005;57(7):733-42.
118. Hess CN, Lopes RD, Gibson CM et al. Saphenous Vein Graft Failure after Coronary Artery Bypass Surgery: Insights from PREVENT IV. *Circulation* 2014; 130: 1445-51.
119. Hetzer R, Komoda S, Komoda T. Remodeling of aortic root by annular reconstruction and plication of sinuses of Valsalva. *J Card Surg* 2008; 23:49–51.
120. Hetzer R, Pasic M, Eichstädt H. Chirurgie des aorta ascendens und des Aortenbogens. *Herzmedizin* 2007; 4:175–82.

121. Hetzer R, Solowjowa N, Knosalla C et al. Surgical correction of ascending aortic aneurysm and aortic valve incompetence by relocation of the aortic valve plane using a short aortic replacement graft. *Ann Thorac Surg* 2012;94(6):1983-8.
122. Hetzer R, Solowjowa N, Kuckuka M et al. Correction of aortic valve incompetence combined with ascending aortic aneurysm by relocation of the aortic valve plane through a short-length aortic graft replacement in Yankah CA, Weng Y, Hetzer R. (eds) *Aortic Root Surgery*. Steinkopff, 2010, 178-184.
123. Hewitson J. Congenital heart surgery: what we do to our patients. *CME* 2011; 29(11-12): 467-470.
124. Hoffmann S, Falkenstein M. Aging and error processing: age related increase in the variability of the error-negativity is not accompanied by increase in response variability. *PLoS One* 2011; 6(2): e17482.
125. Hou YJ, Chen FL, Ng YY et al. Trisomy 18 syndrome with incomplete Cantrell. *Pediatr Neotal* 2008;49:84–7.
126. Hummelshoj L, Prentice A, Groothuis P. Update on endometriosis. *Women's Health* 2006; 2(1) : 53–6.
127. Husum B, Palm T. Arterial dominance in the hand. *Br J Anaesth* 1978; 50: 913–6.
128. Incedayi M, Öztürk E, Sonmez G et al. The incidence of left atrial diverticula in coronary CT angiography. *Diagn Interv Radiol* 2012; 18: 542-6.
129. Iwanow WM. Cystadenofibroma papilliferum tubae Fallopie. *Zentalbl Gynaekol* 1909; 33:745.
130. Jacobs JP, Jacobs ML, Maruszewski B et al. Current status of the European Association for Cardio-Thoracic Surgery and the Society of Thoracic Surgeons Congenital Heart Surgery Database. *Ann Thorac Surg* 2005;80(6):2278-83.
131. Johnson WH, Cromartie RS, Arrants JE et al. Simplified method for candidate selection for radial artery harvesting. *Ann Thorac Surg* 1998; 65: 1167.
132. Jones J. *Spiritualism: The Work of Demons*. Liverpool: Howell, 1871.
133. Joo HC, Chang BC, Youn YN et al. Clinical experience with the Bentall procedure: 28 years. *Yonsei Med J* 2012; 53(5):915-23.
134. Jung SH, Song H, Choo SJ et al. Comparison of radial artery patency according to proximal anastomosis site: Direct aorta to radial artery anastomosis is superior to radial artery composite grafting. *J Thorac Cardiovasc Surg* 2009; 138: 76–83.
135. Kamimura M, Moroi M, Isobe M, Hiroe M. Role of coronary CT angiography in asymptomatic patients with type 2 diabetes mellitus. *Int Heart J* 2012; 53(1): 23-8.
136. Kandel ER, Schwartz JH, Jessell TM. *Principles of Neural Science 3rd ed.,* Prentice-Hall International Inc., London, 1991.
137. Kari FA, Beyersdorf F, Rylski B et al. David I reimplantation procedure for aortic root replacement in Marfan patients: medium-term outcome. *Interact Cardiovasc Thorac Surg* 2014; 19(5):743-8.
138. Kaseno K, Tada H, Koyama K et al. Prevalence and characterization of pulmonary vein variants in patients with atrial fibrillation determined using 3-dimensional computed tomography. *Am J Cardiol* 2008; 101: 1638-42.
139. Kataoka ML, Togashi K, Yamaoka T et al. Posterior cul - de- sac obliteration associated with endometriosis: MR imaging evaluation. *Radiology* 2005; 234 : 815–823.
140. Kato R, Lickfett L, Meininger G et al. Pulmonary vein anatomy in patients undergoing catheter ablation of atrial fibrillation: lessons learned by use of magnetic resonance imaging. *Circulation* 2003; 107: 2004-10.
141. Kawamura M, Nakajima H, Kobayashi J et al. Patency rate of the internal thoracic artery to the left anterior descending artery bypass is reduced by competitive flow from the

concomitant saphenous vein graft in the left coronary artery. *Eur J Cardiothorac Surg* 2008; 34: 833–8.
142. Khairy P, Ionescu-Ittu R, Mackie AS et al. Changing mortality in congenital heart disease. *J Am Coll Cardiol* 2010; 56(14): 1149-57.
143. Killeen RP, Ryan R, MacErlane A et al. Accessory left atrial diverticulae: contractile properties depicted with 64-slice cine-cardiac CT. *Int J Cardiovasc Imaging* 2010; 26: 241–8.
144. Kim J, Kwag HJ, Yoo SM et al. Discrepancies between coronary CT angiography and invasive coronary angiography with focus on culprit lesions which cause future cardiac events. *Eur Radiol* 2018; 28: 1356-1364.
145. Kim J, Yun S, Lim J et al. Long-Term Survival Following Coronary Artery Bypass Grafting: Off-Pump Versus On-Pump Strategies. *J Am Coll Cardiol* 2014; 63(21): 2280-2288.
146. Kimura T, Takatsuki S, Inagawa K et al. Anatomical characteristics of the left atrial appendage in cardiogenic stroke with low CHADS2 scores. *Heart Rhythm* 2013; 10: 921-5.
147. Kinkel K, Frei KA, Balleyguier C et al. Diagnosis of endometriosis with imaging: a review. Eur Radiol 2006 ; 16 : 285- 298.
148. Koman LA, Urbaniak JR. Ulnar artery insufficiency: a guide to treatment. *J Hand Surg* 1981; 6: 16–24.
149. Kraepelin E. Dementia Praecox and Paraphrenia. From *Kraepelin Textbook of Psychiatry* 8th ed. RM Barclay, Edinburgh, Livingstone, 1919.
150. Kriegeskorte N, Goebel R, Bandettini P. Information-based functional brain mapping. *Proc Natl Acad Sci U S A.* 2006; 103(10): 3863–3868.
151. Kroll J, Bachrach B. *The mystic mind: the psychology of medieval mystics and ascetics*. New York and London: Routledge, 2005.
152. Kunugi H, Takei N, Aoki H, Nanko S. Low serum cholesterol in suicide attempters. *Biol Psychiatry* 1997;41(2):196-200.
153. Kunz G, Beil D, Huppert P et al. Adenomyosis in endometriosis—prevalence and impact on fertility. Evidence from magnetic resonance imaging. *Hum Reprod* 2005; 20 : 2309–16.
154. Kute SM, Vorp DA. The effect of proximal artery flow on the hemodynamics at the distal anastomosis of a vascular bypass graft: Computational study. *J Biomech Eng* 2001; 123: 277–283.
155. Lacomis JM, Wigginton W, Fuhrman C et al. Multi-detector row CT of the left atrium and pulmonary veins before radio-frequency catheter ablation for atrial fibrillation. *Radiographics* 2003; 23: S35-48.
156. Lalit M, Harbans SA, Sanjay P. Questionnaire based study showing role of anatomy in post-graduate courses in clinical subjects. National *J Clin Anat* 2016; 05(01): 005-010.
157. Lansac E, Di Centa I, Sleilaty G et al. Long-term results of external aortic ring annuloplasty for aortic valve repair. *Eur J Cardiothorac Surg* 2016; 50(2): 350-60.
158. Lapierre C, Déry J, Guérin R et al. Segmental approach to imaging of congenital heart disease. *Radiographics* 2010; 30(2): 397-411.
159. Larsen SB, Lundorf E, Forman A, Dueholm M. Adenomyosis and junctional zone changes in patients with endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2011; 157 : 206–211.
160. Law MR, Wald NJ. Serum cholesterol concentrations in parasuicide. Depression may cause low cholesterol. *BMJ* 1995; 311(7008): 807.
161. Lazoura O, Reddy T, Shriharan M et al. Prevalence of left atrial anatomical abnormalities in patients with recurrent atrial fibrillation compared with patients in sinus rhythm using multi-slice CT. *J Cardiovasc Comput Tomogr* 2012; 6: 268-73.

162. Lee WJ, Chen SJ, Wang TD. Multiple accessory left atrial appendages along a semi-circular path. *Eur Heart J* 2008; 29: 2447.
163. Leyendecker G, Wildt L, Mall G. The pathophysiology of endometriosis and adenomyosis: tissue injury and repair. *Arch Gynecol Obstet* 2009;280(4):529-38.
164. Li H, Xie B, Gu C et al. Distal end side-to-side anastomoses of sequential vein graft to small target coronary arteries improve intraoperative graft flow. *BMC Cardiovascular Disorders* 2014; 14: 65.
165. Liang RI, Huang SE, Chang FM. Prenatal diagnosis of ectopia cordis at 10 weeks of gestation using two-dimensional and three-dimensional ultrasonography. *Ultrasound Obstet Gynecol* 1997;10:137–9.
166. Liao L, Kong DF, Shaw LK et al. A new anatomic score for prognosis after cardiac catheterization in patients with previous bypass surgery. *J Am Coll Cardiol* 2005; 46(9): 1684-92.
167. Ludolph E, Hinrichsen K. Das Milzverlustsyndrom– einschatung der MdE, *Aktuel Chir* 1990; 25: 181–184.
168. Madžarac V, Matijevic R, Skrtic A, et al. Pentalogy of Cantrell with unilateral kidney evisceration: a case report and review of the literature. *Fetal Pediatr Pathol* 2016;35:43–9.
169. Majoie CB, Verbeeten B Jr, Dol JA, Peeters FL. Trigeminal neuropathy: evaluation with MR imaging. *Radiographics* 1995; 15(4):795–811.
170. Maniar HS, Sundt TM, Barner HB et al. Effect of target stenosis and location on radial artery graft patency. *J Thorac Cardiovasc Surg* 2002; 123: 45–52.
171. Männer J. The anatomy of cardiac looping: a step towards the understanding of the morphogenesis of several forms of congenital cardiac malformations. *Clin Anat* 2009; 22(1):21–35,.
172. Mansour M, Holmvang G, Sosnovik D et al. Assessment of pulmonary vein anatomic variability by magnetic resonance imaging: implications for catheter ablation techniques for atrial fibrillation. *J Cardiovasc Electrophysiol* 2004; 15: 387-93.
173. Marcal L, Nothaft MA, Coelho F, Choi H. Deep pelvic endometriosis: MR imaging. *Abdom Imaging* 2010; 35 : 708–715.
174. Marino AL, Levy RJ, Berger JT et al. Pentalogy of Cantrell with a single- ventricle cardiac defect: collaborative management of a complex disease. *Pediatr Cardiol* 2011;32:498–502.
175. Maris RW. Suicide. *Lancet* 2002; 360: 319-26.
176. McCormack LJ, Caulwell EW, Anson BJ. Braquial and antebraquial arterial patterns. *Surgery, Gynecology &Obstetrics* 1953; 96:43-54.
177. McMinn RMH, Hutchings RT, eds. *Color atlas of human anatomy*. Chicago: Year Book Medical, 1977.
178. Melby SJ, Saint LL, Balsara K et al. Complete Coronary Revascularization Improves Survival in Octogenarians. *Ann Thorac Surg* 2016; 102(2): 505-11.
179. Menzies AW. *Demonic Possession in the New Testament: Its Relations Historical, Medical and Theological*. Edinburgh: Clark, 1902.
180. Miller AV. *Sermons on Modern Spiritualism*. London: Kegan Paul, 1908.
181. Monkul ES, Spence S, Nicoletti Ma et al. Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorders. *Mol Psychiatry* 2007; 12: 360-6.
182. Morales JM, Patel SG, Duff JA et al. Ectopia cordis and other midline defects. *Ann Thorac Surg* 2000;70:111–4.
183. Moreno-Cabral RJ, Mamiya RT et al. Ventricular septal defect and aortic insufficiency. *J Thorac Cardiovasc Surg* 1977; 73:358-65.

184. Morritt D, Shah S, Morritt A, Kaul P. Acute transection of the left internal mammary artery remote from the anastomosis following coronary artery bypass surgery. *Interact CardioVasc Thorac Surg* 2004; 3: 653–5.
185. Mukherjee D, Cheriyan J, Kourliouros A, Athanasiou T. Does the right internal thoracic artery or saphenous vein graft offer superior revascularization of the right coronary artery? Interact Cardiovasc *Thorac Surg* 2012; 15: 244-247.
186. Mulder DG, Kattus AA, Longmire, WP. The treatment of acquired aortic stenosis by valvuloplasty. *J Thorac Cardiovasc Surg* 1960; 40: 731–743.
187. Munro JC, Russell AJ, Murray RM. IQ in childhood psychiatric attendees predicts outcome of later schizophrenia at 21 year follow-up. *Acta Psychiatr Scand* 2002; 106: 139-42.
188. Murphy DA, Craver JM, Jones EL et al. Recognition And Management Of Ascending Aortic Dissection Complicating Cardiac Surgical Operations. *J Thorac Cardiovasc Surg* 1983; 85(2):247–56.
189. Murray RM, Sham P, Van Os J et al. A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophr Res* 2004; 71: 405-16.
190. Mushtaq S, Andreini D, Pontone G et al. Prognostic value of coronary CTA in coronary bypass patients: a long-term follow-up study. *JACC Cardiovasc Imaging* 2014; 7(6): 580-9.
191. Natale A, Raviele A, Arentz T et al. Venice Chart international consensus document on atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2007; 18: 560-80.
192. Ohira S, Doi K, Okawa K et al. Safety and Efficacy of Sequential Left Internal Thoracic Artery Grafting to Left Circumflex Area. *Ann Thorac Surg* 2016; 102(3): 766-73.
193. Oldham S, Fornito A. The development of brain network hubs. *Dev Cogn Neurosci* 2019; 36: 100607.
194. Otsuka F, Yahagi K, Sakakura K, Virmani R. Why is the mammary artery so special and what protects it from atherosclerosis? *Ann Cardiothorac Surg* 2013; 2: 519-526.
195. Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry* 2005; 62: 247-53.
196. Pansky B, House EL, eds. *Review of gross anatomy: a dynamic approach*. New York: Macmillan, 1964.
197. Parissis H, Ramesh BC, Al-Alao B. Which is the best graft for the right coronary artery? *Asian Cardiovasc Thorac Ann* 2014; 23: 100–13.
198. Patel FR, Dehmer GJ, Hirshfeld JW et al. ACCF/SCAI/STS/AATS/AHA/ ASNC/HFSA/SCCT 2012 Appropriate Use Criteria for Coronary Revascularization Focused Update 2012. *J Thorac Cardiovasc Surg* 2012;143(4):780-803.
199. Patel M, Mehta VS, Venuraju S et al. An evaluation of coronary artery plaque burden in asymptomatic type 2 diabetics using dual-source CT coronary angiography. *BMC Proceedings* 2012; 6(Suppl 4):O20.
200. Patel N, Balady G. Diagnostic and prognostic testing to evaluate coronary artery disease in patients with diabetes mellitus. *Rev Endocr Metab Disord* 2010; 11:11–20.
201. Patel SN, French A, Mathias H et al. Presence of left atrial diverticula, accessory appendages, and normal variant pulmonary venous anatomy diagnosed using MDCT and adverse outcomes following radiofrequency catheter ablation therapy in patients with drug-refractory atrial fibrillation: an exploratory study. *Clin Radiol* 2013; 68: 762-9.
202. Patil CV, Nikolsky E, Boulos M et al. Multivessel coronary artery disease: current revascularization strategies. *Eur Heart J* 2001; 22: 1183-1197.
203. Peng LQ, Yu JQ, Yang ZG et al. Left atrial diverticula in patients referred for radiofrequency ablation of atrial fibrillation: assessment of prevalence and morphologic

characteristics by dual-source computed tomography. *Circ Arrhythm Electrophysiol* 2012; 5: 345-50.
204. Petrovic I, Nezic D, Peric M et al. Radial artery vs saphenous vein graft used as the second conduit for surgical myocardial revascularization: long-term clinical follow-up. *J Cardiothor Surg* 2015; 10: 127.
205. Pliatsikas C, Veríssimo J, Babcock L et al. Working memory in older adults declines with age, but is modulated by sex and education. *Q J Exp Psychol (Hove)* 2019; 72(6): 1308-1327.
206. Poh AC, Juraszek AL, Ersoy H et al. Endocardial irregularities of the left atrial roof as seen on coronary CT angiography. *Int J Cardiovasc Imaging* 2008; 24: 729 –734.
207. Polat I, Gul A, Cebeci A et al. Prenatal diagnosis of pentalogy Cantrell in three cases, two with craniorachishisis. *J Clin Ultrasound* 2007;33: 308–11.
208. Pompili M, Ehrlich S, De Pisa E et al. White matter hyperintensities and their associations with suicidality in patients with major affective disorders. *Eur Arch Psychiatry Clin Neurosci* 2007; 257: 494–9.
209. Pompili M, Innamorati M, Mann JJ et al. Periventricular white matter hyperintensities as predictors of suicide attempts in bipolar disorders and unipolar depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; 32(6):1501–1507
210. Porto I, Gaudino M, De Maria GL et al. Long-term morphofunctional remodeling of internal thoracic artery grafts: a frequency-domain optical coherence tomography study. *Circ Cardiovasc Interv* 2013; 6: 269-76.
211. Pundziute G, Schuijf JD, Jukema JW et al. Noninvasive assessment of plaque characteristics with multislice computed tomography coronary angiography in symptomatic diabetic patients. *Diabetes Care* 2007; 30: 1113—9.
212. Qiang F, Yanwen B, Jianmin Y et al. Effects of competitive blood flow from differently stenotic coronary artery on internal mammary artery graft flow. *J Shandong Univ* 2006; 44: 364–367.
213. Qu W, Le TT, Azen SP et al. Value of coronary artery calcium scanning by computed tomography for predicting coronary heart disease in diabetics subjects. *Diabetes Care* 2003; 26:905-910.
214. Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. J Am Coll Cardiol. 2004; 43(9):1663-69.
215. Reyes AT, Frame R, Brodman RF. Technique for harvesting the radial artery as a coronary artery bypass graft. *Ann Thorac Surg* 1995; 59: 118–126
216. Rickert-Sperling S, Kelly R, Driscoll DJ eds. *Congenital Heart Diseases: The Broken Heart.* Springer Verlag, 2015.
217. Risteski L. The radial artery conduit for coronary artery bypass. *Anadolu Kardiyol Derg* 2005; 5: 153-62
218. Robicsek F, Thubrikar MJ. Role of sinus wall compliance in aortic leaflet function. *Am J Cardiol* 1999; 84:944 – 46.
219. Roth JA, Cukingnan RA, Brown BG et al. Factors influencing patency of saphenous vein grafts. *Ann Thorac Surg* 1979; 28: 176-83.
220. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage* 2010;52(3):1059-69.
221. Sabik JF. Understanding saphenous vein graft patency. *Circulation* 2011;124(3):273-5.
222. Sadock BJ, Alcott Sadock Virginia, Ruiz P. *Kaplan and Sadock's Comprehensive Textbook of Psychiatry*. Lippincott Williams and Wilkins, Philadelphia, 2009.
223. Sakalihasan DN, Kuivaniemi H, Michel JB. *Aortic aneurysms - new insights into an old problem*. Liege: Editions de l'Universite de Liege, 2008.

224. Sarsam MA, Yacoub M. Remodeling of the aortic valve annulus. J *Thorac Cardiovasc Surg* 1993; 105:435–8.
225. Schallert EK, Danton GH, Kardon R, Young DA. Describing congenital heart disease by using three-part segmental notation. *Radiographics* 2013; 33(2):E33-46.
226. Schoenhagen P. Osteopontin, coronary calcification, and cardiovascular events: future diagnostic and therapeutic targets for disease prevention? *Eur Heart J* 2006; 27(7): 766-7.
227. Scripcaru Gh. *Medicina legala* [Forensic medicine]. Bucuresti: Ed. didactica si pedagogica, 1993.
228. Sherwin SJ, Doorly DJ, Franke P, Peiro J. Unsteady near wall residence times and shear exposure in model distal arterial bypass grafts. *Biorheology* 2002; 39: 365–371.
229. Shin SY, Kwon SH, Oh JH. Anatomical analysis of incidental left atrial diverticula in patients with suspected coronary artery disease using 64-channel multidetector CT. *Clin Radiol* 2011; 66: 961-5.
230. Siever LJ. Neurobiology of aggression and violence. *Am J Psychiatry* 2008 Apr;165(4):429-42.
231. Siles C, Boyd PA, Maninning N. Omphalocele and pericardial effusion: possible sonographic markers for the pentalogy of Cantrell or its variants. *Obstet Gynecol* 1996;87:840–2.
232. Silva Guisasola J, Alvarez-Cabo R, Hernández-Vaquero D, Méndez RD. Ascending aorta reinterventions. *J Thorac Dis* 2017; 9(Suppl 6): S448–S453.
233. Simpson D. Phrenology and the neurosciences: contributions of F. J. Gall and J. G. Spurzheim. *ANZ J Surg* 2005; 75(6): 475-82.
234. Soares JC, Mann JJ. The anatomy of mood disorders—review of structural neuroimaging studies. *Biol Psychiatry* 1997; 41: 86–106.
235. Song MH, Sato M, Ueda Y. Three-dimensional simulation of coronary artery bypass grafting with the use of computational fluid dynamics. *Surg Today* 30: 993-8, 2000.
236. Sporns O. Graph theory methods: applications in brain networks. *Dialogues Clin Neurosci* 2018; 20(2): 111–121.
237. Sporns O. Structure and function of complex brain networks. *Dialogues Clin Neurosci* 2013;15(3):247–262.
238. Staalsen NH, Ulrich M, Winther J et al. The anastomosis angle does change the flow fields at vascular end-to-side anastomoses in vivo. *J Vasc Surg* 1995; 21: 460-71.
239. Starzl TE, Cruzat EP, Walker FB. A technique for bicuspidization of the aortic valve. *J Thorac Cardiovasc Surg* 1959; 38:262–270.
240. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet* 2001; 358(9285): 870-5.
241. Taggart DP. Current status of arterial grafts for coronary artery bypass grafting. Ann *Cardiothorac Surg* 2013; 2: 427-430.
242. Tash RR, Sze G, Leslie DR. Trigeminal neuralgia: MR imaging features. *Radiology* 1989; 172(3):767–770.
243. Tatoulis J, Buxton BF, Fuller JA. Patencies of 2127 arterial to coronary conduits over 15 years. *Ann Thorac Surg* 2004;77(1): 93-101.
244. Taylor WD, Steffens DC, MacFall JR et al. White matter hyperintensity progression and late-life depression outcomes. *Arch Gen Psychiatry* 2003; 60:1090–1096.
245. Thiene G, Frescura C. Anatomical and pathophysiological classification of congenital heart disease. *Cardiovasc Pathol* 2010; 19(5): 259-74.
246. Thomas AJ, Perry R, Barber R et al. Pathologies and pathological mechanisms for white matter hyperintensities in depression. *Ann N Y Acad Sci* 2002; 977:333–339.

247. Thompson GR, Partridge J. Coronary calcification score: the coronary-risk impact factor. *Lancet* 2004; 363(9408):557-9.
248. Tian D, Rahnavardi M, Yan TD. Aortic valve sparing operations in aortic root aneurysms: remodeling or reimplantation? *Ann Cardiothorac Surg* 2013; 2(1):44–52.
249. Toyama WM. Combined congenital defects of the anterior wall, sternum, diaphragm, pericardium and heart: a case report and review of the syndrome. *Pediatrics* 1972;50:778–92.
250. Tremblay JA, Stevens LM, Chandonnet M et al. A morphometric 3D model of coronary artery bypass graft dysfunction with multidetector computed tomography. *Clinical Imaging* 2015; 39: 1006-1011.
251. Troupis J, Crossett M, Scneider-Kolsky M, Nandurkar D. Presence of accessory left atrial appendage/diverticula in a population with atrial fibrillation compared with those in sinus rhythm: a retrospective review. *Int J Cardiovasc Imaging* 2012; 28: 375-80.
252. Tsao HM, Wu MH, Yu WC et al. Role of right middle pulmonary vein in patients with paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2001; 12: 1353–1357.
253. Tucker FD, Morris JK; JRC Management Committee et al. EUROCAT: an update on its functions and activities. *J Community Genet* 2018; 9(4): 407–410.
254. Tuffier T. Etat actuel de la chiurgie intrathorcique. *XVII International Congress of Medicine,* Section VII Part II. London, 1913, 247-9.
255. Umansky F, Nathan H. The lateral wall of the cavernous sinus. With special reference to the nerves related to it. *J Neurosurg* 1982; 56(2):228–234.
256. Uygur D, Kis S, Sener E et al. An infant with pentalogy of Cantrell and limb defects diagnosed prenatally. *Clin Dysmorphol* 2004;13:57–8.
257. van Hoorn JH, Moonen RM, Huysentruyt JR et al. Pentalogy of Cantrell: two patients and a review to determine prognostic factors for optimal approach. *Eur J Pediatr* 2008;167:29–35.
258. Van Praagh R, Van Praagh S. Anatomically corrected transposition of the great arteries. *Br Heart J* 1967; 29(1):112–119.
259. Van Praagh R. The segmental approach clarified [letter]. *Cardiovasc Intervent Radiol* 1984; 7(6): 320–325,.
260. Van Praagh R. The segmental approach to diagnosis in congenital heart disease. In: Bergsma D, ed. *Birth defects original article series*, vol. 8, no. 5. National Foundation—March of Dimes. Baltimore: Williams & Wilkins, 4–23, 1972.
261. Van Son JAM, Smedts F. Revival of the radial artery for coronary artery bypass grafting: l'histoire se repète [Letter]. *Ann Thorac Surg* 1993; 55: 1596–8
262. Varlam H, Francu LL, Antohe D St et al. *Anatomie regionala si aplicata. Membre.* Junimea, Iasi, 2004.
263. Velakoulis D, Wood SJ, Wong MT. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first episode psychosis, and ultra-high-risk individuals. *Arch Gen Psychiatry* 2006; 63: 139-49.
264. Vlad I, Popa AR. Epidemiology of diabetes mellitus: a current review. *Rom J Diabetes Nutr Metab Dis 2012*; 19(4):433-440
265. Voucharas C, Bisbos A, Zandes N. Plication of the right atrium in order to confront a right coronary artery under tension graft. *Updates Surg* 2011; 63: 209–11.
266. Wackers FJ, Chyun DA, Young LH et al. Detection of Ischemia in Asymptomatic Diabetics (DIAD) Investigators. Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. *Diabetes Care* 2007; 30:2892-8.

267. Wan Y, He Z, Zhang L et al. The anatomical study of left atrium diverticulum by multi-detector row CT. *Surg Radiol Anat* 2009; 31: 191-8.
268. Wang Y, Di Biase L, Horton RP et al. Left atrial appendage studied by computed tomography to help planning for appendage closure device placement. *J Cardiovasc Electrophysiol* 2010; 21: 973-82.
269. Windecker S, Kolh P, Alfonso F et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014; 35: 2541-619.
270. Woolfall P, Coulthard A. Pictorial review: Trigeminal nerve: anatomy and pathology. *Br J Radiol* 2001; 74(881):458–467.
271. Wright IC, Rabe-Hesketh S, Woodruff PW. Meta-analysis of regional brain volumes in schizophrenia. *Am J Psychiatry* 2000; 157: 16-25.
272. Young LH, Wackers FJ, Chyun DA; DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA* 2009; 301: 1547-55.
273. Yu AC, Sweeney PJ. Cranial neuropathies. In: Katirji B, Kaminski HJ, Preston DC, Ruff RL, Shapiro B (eds). *Neuromuscular disorders in clinical practice*. Butterworth Heinemann, Boston–Oxford, 2002, 820–827.
274. Zidere V, Allan LD. Changing findings in pentalogy of Cantrell in fetal life. *Ultrasound Obstet Gynecol* 2008;32:835–7.