

**”VICTOR BABEȘ” UNIVERSITY OF  
MEDICINE AND PHARMACY FROM TIMIȘOARA  
DOCTORAL SCHOOL  
MEDICINE DOMAIN**



**SPECIAL FORMS OF HEART FAILURE  
IN WESTERN ROMANIA**

**ABSTRACT**

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This Habilitation Thesis is the outcome of my academic and scientific efforts over the past 40 years, which have mostly focused on the control of heart disease risk factors and on the reduction of cardiovascular morbidity and mortality.

The thesis is divided into four sections: scientific achievements, academic accomplishments, professional activities, and future academic and scientific goals.

**Scientific achievements.** After the PhD thesis, which referred to the risk of ventricular arrhythmias in heart failure patients, heart failure being a final stage in the evolution of cardiovascular diseases, my research focused on the *early diagnosis of subclinical cardiovascular dysfunction and the predictors of major cardiovascular events in heart failure patients from western Romania*.

Synthetically, the scientific activity materialized through 93 in extenso articles, 79 of them in ISI indexed journals (21 of them as first or principal author), which received a total of 2.832 citations. Thus, a Hirsch Index of 12 in Web of Science was attained, the cumulated impact factor of the published papers in which the candidate is the principal author being 54.242. It is important to be mentioned that the majority of the research work was performed in multidisciplinary teams.

In general, post-doctoral research and professional work reflect a continuation of research from the doctorate stage, with some partnerships broadening the study field while maintaining the emphasis on the evaluation of cardiovascular risk factors that might cause and/or worsen heart failure.

The main research activity was aligned to three main directions related to the evaluation of the cardiovascular risk in patients from western Romania suffering from heart failure.

The first direction consisted in ***the evaluation of cardiovascular morbidity and mortality in elderly patients admitted with heart failure***. We addressed elderly patients with heart failure with reduced left ventricular ejection fraction (LVEF), as well as with preserved LVEF, and analysed the factors associated with in-hospital and 1-year mortality rates.

The second direction was the evaluation ***of the prognosis of acute coronary syndromes in western Romania and the identification of early markers of harmful left ventricular remodeling leading to heart failure***.

The third direction addressed ***the identification of subclinical cardiovascular dysfunction in patients without established cardiovascular disease***, but being at high risk to develop it, due to the presence of ***metabolic syndrome*** or due to the ***treatment with doxorubicin***, a cardiotoxic anticancer agent. We revealed the importance of the early diagnosis of subclinical cardiovascular impairment using modern non-invasive imagistic methods, such as cardiac and vascular two-dimensional *speckle tracking* echography, and identified independent predictors of major cardiovascular events in prospective studies.

The main scientific accomplishments are highlighted here by concisely describing the findings of the most important studies in which I have participated.

In 2015 we published two studies regarding factors associated with prolonged hospitalization, readmission, and death in ***elderly heart failure (HF) patients in western Romania***, and we analysed these factors according to the type of heart failure (with reduced or preserved LVEF). We found that elderly patients are at high risk for prolonged hospitalization, readmission, and death following a first hospitalization for heart failure with reduced ejection fraction. The most powerful predictors for outcomes were the severity of heart failure, the presence of comorbidities, and prolonged hospitalization at baseline. In heart failure patients with preserved ejection fraction aged  $\geq 65$  years, the main cause of rehospitalization during the 1-year follow-up was HF aggravation. The risk of this outcome was independently predicted by increased levels of cardiac peptides, while the risk of no cardiovascular readmissions was predicted by increased levels of inflammatory biomarkers. Increased TNF- $\alpha$  levels predicted both cardiovascular and no cardiovascular readmissions, while increased levels of high-sensitivity C-reactive protein did not predict any of these outcomes in our study.

An important cause of heart failure is represented by coronary artery disease. That's why we continued our research in 2017 including patients with ***acute coronary syndromes***. We studied the clinical characteristics and outcomes in acute myocardial infarction patients from western Romania, analysed the parameters associated with in-hospital mortality after primary percutaneous coronary intervention and evaluated the risk of left ventricular remodeling using the 2D-speckle tracking echocardiography. We

found that reduced values of the global left ventricular longitudinal strain predict accurately the occurrence of post-myocardial infarction heart failure.

In 2018 we included in our research **cancer patients** without established cardiovascular disease and studied the **cardiotoxicity of doxorubicin**. Doxorubicin is an anthracycline widely used in various cytostatic treatment regimens, but has limited applicability, being cardiotoxic. This cardiotoxicity increases the risk of heart failure, increasing the cardiovascular morbidity and mortality. We used new echocardiographic imaging methods, such as *Tissue Doppler*- and *Speckle Tracking Imaging*, in the early recognition of cardiac dysfunction induced by cytostatic treatment, in 60 women, mean age  $52.6 \pm 13$  years, with HER2 negative breast cancer. We also found that Nebivolol had cardioprotective effects and prevented the cardiotoxicity of anthracyclines in the short term (6 months).

Another study, published in Nature, 2020, included 25 patients aged 18–65 years old who received Doxorubicin treatment for hematological malignancies, with a survival probability > 6 months and an LVEF > 50%. This study showed a strong correlation between the genetic Toll-like receptor 4 expression and the myocardial T2\* iron deposition obtained with the CMR technique, corresponding to iron overload in the heart as an immediate side effect of Doxorubicin treatment. LVEF, as an accepted marker for cardiotoxicity, also showed direct relationships with both TLR4 and T2\*. More careful clinical follow-up and the initiation of possible treatments to counteract Doxorubicin cardiotoxicity can be implemented if screenings are conducted early in the disease course.

The **metabolic syndrome** (MS) is a well-known disorder characterized by the coexistence of a number of cardiovascular risk factors, including dyslipidemia, abdominal obesity, hyperglycemia, insulin resistance, and hypertension. It is more prevalent in sedentary and obese individuals and is associated with an increased risk of stroke, diabetes, myocardial infarction, and heart failure. In 2021 we published two studies including adult patients with metabolic syndrome and without established cardiovascular disease. Using 2D-STI we found **subclinical left ventricular and left atrial dysfunction** in these patients.

More-over, in prospective research with a 3-years follow-up period, published in 2022, that enrolled 220 adult MS patients ( $60.7 \pm 7.5$  years old, 53% male), two-dimensional

common carotid artery speckle-tracking ultrasound was used to determine the peak circumferential strain (CS) and the peak circumferential strain rate (CSR). Clinical outcomes were assessed throughout a three-year follow-up period. Carotid CS and CSR were independent predictors of **major cardio- and cerebral-vascular events** (stroke, acute myocardial infarction, death or hospitalization for heart failure). Carotid deformation could be valuable as an early prognostic indicator for the cardiovascular risk in MS patients.

Besides the basic clinical research activities, detailed in this Thesis, I also had some external collaborations in multidisciplinary teams: with the Gastro-Enterology, Neurology and Oncology Departments, with Discipline of Medical Informatics and with the Pharmacy Faculty of our University. I am the coordinator of the Multidisciplinary Heart Research Center of the “Victor Babes” University of Medicine and Pharmacy, Timisoara.

**Academic accomplishments.** I am a member of the academic staff of “Victor Babeș” University of Medicine and Pharmacy Timișoara since 1984. The PhD Thesis, entitled **“Arrhythmias in heart failure: etiopathogenesis, prognostic significance, treatment”** was written under the coordination of Prof. Dr. Costin Carp, from “Carol Davila” University of Medicine and Pharmacy Bucharest, and I obtained the PhD title in 1994. I was permanently concerned to improve the teaching by writing several didactic materials – *handbooks for students and residents, ppt presentations* and a collection of clinical cases. Since 2002, I am Professor, Head of Medical Semiotics Discipline, coordinator of residency in cardiology, and a member of the “Victor Babeș” University of Medicine and Pharmacy Senate. From this position, I tried to harmonize the informative side of education with the formative aspects and involve students and medical residents in research teams. Since 2004, I am scientific coordinator for PhD thesis and I have successfully conducted 18 doctoral theses until now. Since 2016, I am Director of the Doctoral School of Victor Babes University of Medicine and Pharmacy. This Habilitation Thesis is meant to accomplish the actual national standards of being Professor.

**Professional activity.** I am Senior Physician in Internal Medicine (since 1993) and Cardiology (since 2000), and the Head of the Cardiology Clinic of the Timișoara Municipal Emergency Clinical Hospital since 2004. My commitment to the ongoing

improvement of my professional qualifications was an essential component of my day-to-day existence, and it had a tight connection to both academic and scientific endeavors. As a result, I was able to maintain a high standard of clinical practice and care for my patients and students. In this regard, I have authored a total of four monographs within the field of cardiology. Acting as an **expert for project evaluation for the European Commission in Brussels FP6 and FP7 (PHC2 – 2015, Horizon 2020, SC1-BHC-24-2020)** had a significant effect on both my activity level and my professional pathway.

### **Candidate`s future perspectives.**

**On the scientific front**, the results that have been obtained up to this point, the daring themes that are still awaiting deeper investigation, as well as the comfortable and beneficial ambience within the research groups with which I have engaged - all of these things give me concrete arguments to continue the scientific fields that have already been begun, regarding the decline in cardiovascular morbidity and mortality in western Romania, to identify the predictors of a poor outcome, and to initiate a prompt medical intervention.

**On the academic and professional agenda**, new teaching tools and approaches, such as a database of clinical cases that includes images and sounds, or computer-aided interactive clinical stage classes, may be developed as part of the academic and professional agenda.

At the "Victor Babes" University of Medicine and Pharmacy, all of the future research projects that have been outlined call for extensive collaboration with experts from several different academic fields and departments. It is essential to maintain and expand current relationships with academics from other universities or research institutes, both nationally and internationally, in order to broaden the study population while simultaneously increasing the opportunities for financial support. This can be accomplished by maintaining and expanding current relationships. In the subjects of study that are currently being planned for, potential PhD students will be actively involved in cutting-edge medical research, both practically and theoretically.

In addition, I have high hopes that the "Victor Babes" University of Medicine and Pharmacy in Timisoara will be able to meet its long-term growth objectives thanks to the contribution that my work makes.

The teaching profession has a significant impact on society and plays a crucial part in the evolution of human resources and the raising of future generations.

In recent years, Romania's pedagogical mission has distinguished itself, particularly via the development of students' adaptability to the ongoing flow of knowledge and their integration in this moment of change to a globalized education. In this perspective, a successful teacher is one who leaves his mark on his students' education through a variety of personality characteristics and pedagogical approaches.

A professional educator must be innovative, emphasizing the formation of pupils' intellectual, behavioral, moral, and relational abilities rather than solely traditional learning through collecting knowledge.

A qualified teacher must be developmental, which means they ought to place less focus on learning strictly according to the traditional method of acquiring knowledge and more emphasis on developing their students' intellectual abilities, behavioral, emotional, and social skills — or, in the words of the classics, "to include, in addition to the informative knowledge, the formative aspects of the education." This starts with students gaining a thorough understanding of phenomena and processes through enjoyable learning, but it also promotes innovation, collaboration, effective communication, and a patient-centered approach.

A good teacher must also be honest, which means that he or she must uphold the standards set for the students.

Another crucial quality is the ability to adapt, professionally, and in terms of how information is shared.

As a teacher, it's crucial to encourage student teamwork in order to establish a collaborative working style that is built on trust, communication, consistency, adaptability, and respect, in addition to ongoing improvement and flawless personal training.

The following broad goals would be included:

- Continuous development of top competences and abilities in the field of teaching as well as in associated sectors;



- Development of new, current knowledge, skills, and competencies connected to the educational activity within the department
- Putting into practice all of the knowledge obtained and utilizing cutting-edge teaching techniques
- Application and integration of any methodology on the education-research-innovation axis.
- Continuous improvement of pedagogical abilities to enhance the teaching process, pedagogical approaches, and social elements of education.

It is generally acknowledged that a university's reputation heavily depends on its scientific accomplishments. Here, there are two distinct layers:

- (1) the actual research itself, which is typically carried out by diverse teams;
- (2) the participation of students (doctoral, master's, even undergraduate) in research activities; for clinical research, we can even include residents.

Therefore, university clinical disciplines should offer a unique applicability of clinical research in addition to the didactic side. To encourage the growth and tying of academic research to the dynamics of its application in clinical practice, training activities must be developed.

We must also take into account the multidisciplinary and interinstitutional scientific research that is centered on the priorities of the national and European strategy and that will, by tying Romanian research to the vast European research system, by executing joint programs, effectively produce knowledge put at the service of individual and collective health. research collaborations with local and international universities. Creating domestic and worldwide public-private collaborations is helpful for enhancing scientific performance.

On the basis of these assumptions, the following broad goals can be suggested:

- A thorough understanding of the trends in a particular field, a list of "hot concepts," and an updated list of subjects funded by various national or European programs

- A realistic evaluation of how one might approach a contemporary research issue in terms of infrastructure, funding, and documentation.

Building a cooperative, inter-institutional team (of the consortium type), specifically for each project, using the European Commission's (CORDIS) or UEFISCDI's (Brainmap) existing data bases for possible partners. Improving the capacity to write research proposals.

Developing students' abilities and interests in theoretical and applied scientific research in the field of medicine is helpful in terms of the second level. "I don't believe we have any justification for not educating people about scientific procedures, what the best study designs are, and to help them know how to read and count scientifically," the author says. (John Ioannidis, Stanford University) This has an impact on how medical science is understood and developed as well as how we comprehend the information that astounds us every day.

Therefore, it is essential to implement a sophisticated training program in the area of medical scientific research. The most crucial methods for bringing about the essential changes in healthcare and ensuring that the medical field keeps up with patient needs are education and research. The relationship between theory, research, and practice must be established in order for research to advance in the improvement of medical practice.

The development of research abilities in students and residents must meet European standards, and there must be a balance between theoretical and applied instruction.

In order to prepare students, residents, and doctoral students for the research process, the professor must use both formal learning—included in all analytical programs—which is based on a set of objectives, occurs over a specific amount of time, and ends with the certification of knowledge—and non-formal/informal learning (which is carried out within planned activities but does not end with the certification of competencies). Additionally, the young researcher will be positively influenced by a positive and inspiring attitude toward the educational mission and the study.