UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE
„CAROL DAVILA” BUCUREȘTI
ȘCOALA DOCTORALĂ
DOMENIUL MEDICINĂ

TEZĂ DE ABILITARE

REZUMAT

CANDIDAT

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Universitatea de Medicină și Farmacie „Carol Davila”, București

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AUTONOMIC NERVOUS SYSTEM DYSFUNCTION IN CARDIOVASCULAR PATHOLOGY; CORRELATIONS WITH METABOLIC RISK FACTORS AND ENDOTHELIAL DYSFUNCTION

ABSTRACT OF THE HABILITATION THESIS

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I practice as a senior in Internal Medicine and a specialist in Cardiology. I have attended several professional training courses, completed with certificates, such as those in echocardiography, general ultrasound, and special functional respiratory investigations. Currently, I am an Assistant Professor in Semiology, with over 30 years of teaching experience and a history of involvement in student training, as evidenced by several diplomas for participation in events of interest to them, as well as by coordinating bachelor's theses.

The research activity is materialised in the doctoral research, “Endothelial dysfunction in experimental and human heart failure”, distinguished with the title Summa cum laude, as well as in several awards granted for scientific research, and my involvement in several grants. The coordination capacity is also evident in the quality of the Head of the Colțea Internal Medicine Department, with the related training and continuous improvement in this regard.

After obtaining the title of Doctor in Medicine, I continued my research activities in several areas of interest, including endothelial dysfunction in diabetes and obesity, the involvement of the autonomic nervous system in normal physiology and inflammation, and the therapeutic effects of certain phytochemicals.

The results obtained from researching endothelial morphology and function in experimental models and in patients with heart failure have led to the expansion of the research team's activities to study the endothelial morphology and function in diabetes mellitus, also in animal models and in patients with diabetes mellitus. We analysed in diabetic rats, such as in heart failure experimental models, the endothelial structural and ultrastructural aspects in mesenteric, coronary, and aorta territories. In diabetic patients, such as in heart failure patients, we analysed the endothelial morphology and ultrastructure in the mesenteric territory, and the endothelial functional response in various territories (brachial artery, superior mesenteric artery, femoral artery). The research on the endothelial structure and function in heart failure and diabetes mellitus has been recognized by several award-winning studies.

The ultrastructural changes suggestive of endothelial activation, such as detachments of endothelial cells from the basement membrane, the presence of caveolae, the abundance of cell organelles in endothelial cells, the densification of abluminal plasma membranes, and the contacts between endothelial cells and smooth muscle cells, were observed exclusively in animals with diabetes. The most extensive vascular changes observed in rats with diabetes were recorded in the mesenteric territory, with the myocardial arteriolar

changes being the next affected site. The changes in large vessels were smaller than in small vessels, similar to those observed in animals with experimental heart failure. The amplitude of endothelial changes correlates with the endothelial activation score. Endothelial ultrastructure changes were less extensive than in animals with experimentally induced heart failure.

Vascular fragments from the superior mesenteric artery territory were analysed in patients with or without diabetes mellitus who underwent surgery. It was found that endothelial ultrastructure changes prevailed in diabetic patients and were inversely correlated with the endothelial functional response in the brachial artery.

We assessed, in diabetic patients, the endothelial vasodilator response in several territories, represented by the brachial, superior mesenteric, and femoral arteries, by quantifying vasodilation in response to controlled ischemia in the brachial artery, in the mesenteric artery after a meal, and the flow in the femoral artery after exercise, respectively. In the study group, which consisted of patients with diabetes and ischemic heart disease, compared to the control group with classic risk factors for coronary heart disease but without diabetes, the endothelium-dependent dilator response in the brachial artery was less pronounced, and flow velocities in the mesenteric artery were significantly reduced in diabetic patients. In diabetic patients, the peak systolic velocity in the femoral artery after walking effort was considerably lower than at rest. Compared to patients with heart failure, the endothelial ultrastructure changes were lower in percentage and less extensive.

The concern for endothelial dysfunction was extended to patients with obesity, as evidenced in a review addressing chronic, low-level inflammation in obesity, underscoring the key role of macrophages in this process. The article was notable for its high number of accumulated citations, receiving the qualities ”highly cited” and ”hot” paper.

Another research topic of interest was the involvement of the autonomic nervous system (ANS) in various pathologies and physiological conditions. Thus, the topic was treated in some reviews centred on gut-brain communication and was also the subject of several conferences.

In one original article, the research team presented the ANS activity evoked by heart rate variability (HRV) in relation to inflammation in patients with viral infections caused by RNA viruses (SARS-CoV-2, measles, and HIV). The study revealed differences between ANS activity with respect to the viral agent, with the most extensive changes in ANS activity in patients with COVID-19. The sympathetic activity was higher in COVID-

19 and measles patients; meanwhile, in patients with HIV, the main trait was the decrease in parasympathetic activity. Inflammation was correlated with sympathetic activation in HIV patients, but not in COVID-19 subjects.

The aspects of HRV in the orthostatic position and during self-regulated breathing, compared to rest, were completed. One study conducted on healthy young people highlighted the fact that heart rate increased in orthostatic conditions in both sexes; meanwhile, total power (TP), low frequency power (LF), and high frequency power (HF) decreased with age in both sexes. LF/HF increased in the orthostatic position compared to rest, mostly in males. Another study on young people, accepted for publication, showed that self-regulated breathing is associated with a decrease in sympathetic tone and an increase in cardiorespiratory coherence. The study also showed an improvement in HRV during self-regulated breathing sessions in females with anxiety, and a better autonomic balance, as indicated by the increase in LF/HF.

Another research, conducted in rats exposed to motion restriction of variable duration, was focused on stress influence on nervous structures, such as the nociceptive neurons and cutaneous nervous fibers originating from them within the glabrous and hairy skin. The study showed that in rats exposed to motion restriction, the nociceptive activity is increased, primarily in primary sensitive neurons.

The third research direction, materialised in review articles, was represented by antimicrobial properties of some phytochemicals, especially against RNA viruses (such as for Kempferol and Capsaicin), and multiresistant bacteria (such as for Capsaicin); the potential antitumoral effects of some phytochemicals (phytocannabinoids or pinosylvin).

I propose, as future directions of research activity, several themes, such as: „Evaluation of subcutaneous and perivisceral fat vessels morphology in overweight and obese patients; correlation of structural and ultrastructural aspects with systemic inflammation and autonomic nervous system markers", „The relationship between heart rate variability, presence of sleep apnea syndrome, and quality of life in patients with heart failure", „The effects of respiratory control (heart-focused breathing) on heart rate variability parameters in patients with heart failure ", „ Autonomic nervous system activity in HIV patients; correlation with cardiovascular risk", „The effects of medication in heart failure with reduced ejection fraction on autonomic nervous system and cognitive function", „Hypocholesterolemic phyochemicals and effcts on higher cognitive processes".