UNIVERSITY OF MEDICINE AND PHARMACY
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MEDICINE

RIGHT-SIDED CARDIAC INVOLVEMENT IN NEUROENDOCRINE TUMOURS, A MAJOR CHALLENGE- FROM CONCEPT TO MULTIDISCIPLINARY APPROACH

PhD THESIS ABSTRACT

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1. Current state of knowledge

Neuroendocrine neoplasms, albeit rare, can beget carcinoid tumors and carcinoid heart disease, with the latter considered a prominent etiology in the field of intrinsic right heart valve disorders, leading to right heart failure and considerable morbidity and mortality. So clinicians need to pay heed to its appropriate diagnosis and prevention [1].

Neuroendocrine neoplasia constitutes infrequent neoplasms that mostly originate from the gastrointestinal tract. They are reported in 2.5-5 persons per 100 000 people. The secretion of vasoactive substances by these tumors is responsible for carcinoid syndrome. Carcinoid tumors usually develop gradually, over years, and are likely to show few or no symptoms until they are bulky enough to be symptomatic or have metastasized, mostly to the liver, followed by the skeletal and pulmonary systems [1,2].

One of the common complications of carcinoid syndrome is cardiac involvement due to the direct action of vasoactive substances. Carcinoid syndrome can occur in up to 60% of cases during the course of the disease, but carcinoid heart disease (CaHD) can be the first manifestation in approximately 20% of patients [3,].

As cardiac manifestations are associated with a poor long-term medical prospect and mortality, the detection of cardiac disease in its early stages has a significant value. Cardiac surgeries such as valve replacement, if performed at the optimal time, significantly contribute to the treatment of symptomatic patients and the improvement of their quality of life [4].

In the primary evaluation of patients with Carcinoid heart disease, the modality of choice is 2D echocardiography in that it can reveal thickness and retraction in the valve leaflets in a semi-open position with reduced mobility, annular constriction, thickness and fusion in the subvalvular apparatus, and finally regurgitation and /or stenosis of various degrees. Severe tricuspid regurgitation results in right ventricle (RV) volume overload and RV/right atrium (RA) dilatation [4,5].

The accuracy of echocardiography as a screening tool can be enhanced through the use of sensitive and specific biochemical markers associated with the

presence and severity of cardiac involvement. Among these useful biomarkers is N-terminal pro-brain natriuretic peptide (NT-proBNP), which is significantly raised in patients with Carcinoid heart disease. This elevation is correlated with disease progression, symptomatic status, and overall survival. An evaluation of NT-proBNP with a cutoff level of 260 pg/mL is recommended as a screening biomarker with 92% sensitivity, 91% specificity, 98% negative predictive value, and 71% positive predictive value [5,6].

The plasma or urinary level of 5-hydroxyindoleacetic acid (5-HIAA), which is a metabolite of serotonin, is higher in cardiac involvement, with an elevated level of this metabolite in excess of 300 mmol/24 h being associated with a two- to threefold increased risk of the progression of carcinoid heart disease [6].

The recognition, diagnosis, and treatment of neuroendocrine tumours and their associated syndromes are a rare but important subset of malignancies capable of affecting the cardiovascular system. Rapid diagnosis utilizing serum studies, CT scans, and echocardiography can help expedite the diagnosis and treatment of such rare conditions, and assist in the avoidance of complications due to the effects of circulating vasoactive substances. Despite its relatively well-recognized clinical symptoms, carcinoid syndrome and its associated heart disease still remains a challenging condition to manage and treat, oftens requiring the input of several subspecialties to treat the condition appropriately [7,8].

Classically, both tricuspid and pulmonary valve leaflets and their corresponding subvalvular apparatus are thickened. Excursion of the leaflets is reduced. Eventually, valve leaflets become retracted, fixed, and noncoapting, leading to the valve remaining in a semiopen position. Functionally, a combination of valvular regurgitation and stenosis occurs . A “dagger-shaped” continuous-wave Doppler profile, resulting from severe tricuspid regurgitation that causes early peak pressure and rapid decline and representing equalization of right atrial and ventricular pressures, is seen in severe disease. The tricuspid valve, with or without pulmonary valve involvement, is involved in most cases of carcinoid heart disease. Indeed, it is the combination of these that creates the most hemodynamic disturbance. Pulmonary stenosis is thought to worsen the severity of tricuspid regurgitation; conversely, the severity of pulmonary stenosis may be underestimated because of low cardiac output and severe tricuspid regurgitation [9,10].

The right atrium and ventricle are typically enlarged. As the ventricle becomes volume overloaded, paradoxical motion of the interventricular septum occurs. Right ventricular function seemingly remains intact until quite late in the disease course. The increasing elevation in right ventricular pressure and increasing size of the right atrium may lead to reopening of patent foramen ovale in severe carcinoid heart disease [11,12].

Tissue Doppler echocardiography, since its introduction more than 2 decades ago, had revolutionized echocardiography. In the quest to directly quantify myocardial function, increase sensitivity to detect early subtle myocardial dysfunction and improve ease of use, tissue Doppler echocardiography has evolved from pulsed wave tissue Doppler, to color-coded tissue Doppler and to 2-dimensional (2D) speckle tracking, and from myocardial velocity to strain/strain rate imaging. Over the years, numerous studies have demonstrated the value of tissue Doppler echocardiography in the diagnosis and risk stratification of a wide range of cardiac diseases. However, each generational change in tissue Doppler echocardiography involves technological software advancements that are not directly comparable to previous generations [13,14,15].

Carcinoid heart disease is the leading source of mortality and morbidity in subjects with carcinoid syndrome. The outcomes without treatment are poor. Fortunately, the prognosis of carcinoid heart disease subjects has significantly improved over the last decades, which is mainly associated with the progress in cardiac imaging modalities, as well as with cardiac valve surgery [15].

2. Personal contribution

2.1. Working hypothesis and general objectives

We aim to present our own experience regarding early myocardial dysfunction in patients with carcinoid syndrome by using predictive neuroendocrine biomarkers and two-dimensional echocardiographic parameters.

2.2. Purpose

This study was conducted in order to identify biochemical and echocardiographic parameters of subclinical myocardial dysfunction and also, establish some possible correlations between them.

2.3. General research methodology

Patients were enrolled regarding both inclusion and exclusion criteria. Study approval was provided by the Ethics Committee of Carol Davila University of Medicine and Pharmacy, Bucharest. All procedures were in agreement with Helsinki declaration concerning ethical principles for medical research involving human subjects.

We used the World Health Organization (WHO) classification scheme that places neuroendocrine tumors (NETs) into three main categories, which emphasize the tumor grade rather than the anatomical origin: well-differentiated neuroendocrine tumours, further subdivided into tumors with benign and those with uncertain behavior, well-differentiated (low grade) neuroendocrine carcinomas with low-grade malignant behavior, poorly differentiated (high grade) neuroendocrine carcinomas, which are the large cell neuroendocrine and small cell carcinomas.

After patient's consent by completing an informed consent, a clinical evaluation and necessary investigation of each patient was carried out.

Diagnosis of carcinoid disease was based on review of outside records, pathology specimens, thoracoabdominal computed tomography, and increased levels of 5-hydroxyindole acetic acid (5-HIAA) in a 24-hour urine sample.

The exclusion criteria were: age under 18 years old, ischemic heart disease, history of percutaneous coronary intervention, arrythmias, congenital heart disease, valvulopathies such as aortic and mitral stenosis, aortic and mitral regurgitation

either rheumatic or degenerative, hypertrophic and restrictive cardiomiopathy, chronic kidney disease, peripheral artery disease, arterial hypertension, diabetes mellitus, Cushing syndrome, acromegaly, pregnancy and lactation, poor transthoracic windows.

To ascertain that the patient had no exclusion criteria, the following prerequisites were performed: clinical evaluation, measurement of blood pressure, 12- leads electrocardiogram, serum creatinine and urea, serum ionogram and echocardiogram.

We studied 64 patients with proven carcinoid syndrome and 64 sex- and age-matched healthy subjects.

Patients were consequently enrolled between October 2017 and June 2021.

The control group comprised adults with no history of cardiovascular disease and normal physical examination, electrocardiography (ECG), and resting echocardiography. The exclusion criteria were the same in both patient and control groups.

2D and Doppler echocardiography was performed with standard techniques and equipment. All studies were performed by experienced sonographers and reviewed by staff cardiologist with advanced training in echocardiography.

All patients underwent comprehensive two-dimensional echocardiography with additional tissue Doppler (TDI) and speckle-tracking techniques, using commercially available echocardiography machines (General Electric Vivid-T8, EchoPac). All patients took the test several times in follow up, minimum 6 months apart, with a total number of explorations of 256 between October 2017 and June 2021 (160 explorations in women, 96 explorations in men).

Valve regurgitation and stenosis severity were assessed according to European Society of Cardiology guidelines.

The parameters also included: systolic velocities of the left ventricle (septal and lateral wall, mean value- S LV), E/e' ratio (assessment of the diastolic function of the left ventricle), global longitudinal strain (GLS LV) using 12 –segment model (adequate two-dimensional images in apical four, three and two chambers), systolic velocity of the free wall of the right ventricle- S RV, E/e' ratio (assessment of the diastolic function of the right ventricle), global longitudinal strain of the right ventricle (GLS RV).

The diagnosis of carcinoid heart disease was based on presence of characteristic thickening, reduced mobility and/or retraction of tricuspid and pulmonary valves leading to dysfunction of the involved valves.

All patients had multiple 24-hour urine samples quantitatively analyzed for 5-HIAA, plasma levels of chromogranin A and serotonin by using enzyme-linked immunosorbent assay (ELISA) technique. For this study, the highest values before or at the time of diagnosis of carcinoid disease were recorded.

Furthermore, a statistical analysis was performed using IBM SPSS Statistics version 29. A simple regression, multinomial regression analysis and correlation tests were performed as appropriate to evaluate the relation between patients' characteristics and echocardiographic and biochemical parameters.

2.4. Results

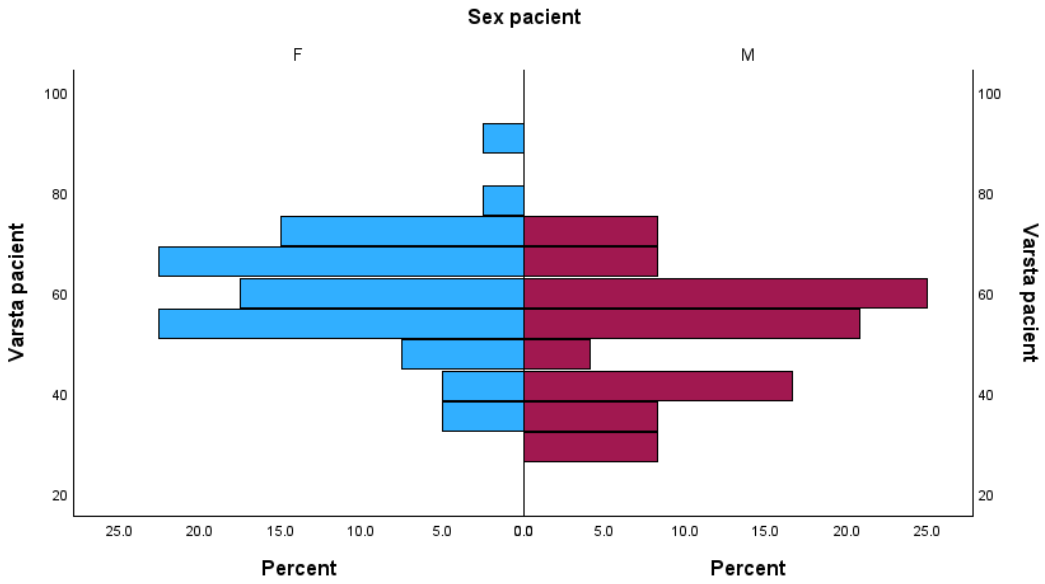

Figure 2.1- Population biology for patients with carcinoid syndrome

We enrolled 64 patients with neuroendocrine tumours (NETs): 24 men (37.5%) and 40 women (62.5%). The average age was 56.98 year-old (*SD* 12.939). For male patients the average alge was 51.5 year-old (*SD* 12.445), while for female patients 60.28 year-old (*SD* 12.226). Population biology is revealed into figure 2.1.

We also studied 64 sex- and age-matched healthy subjects in order to compare echocardiographic parameters regarding tissue Doppler velocities (TDI) and global

longitudinal strain of both left and right ventricles. The feasibility of TDI was better than for all the other methods, particularly for the study of the right ventricle where systolic velocities could be recorded in all patients and healthy subjects. All absolute systolic velocities were lower in patients compared with healthy subjects- table 2.1.

Table 2.1- Mean values of echocardiographic parameters in patients and control subjects

	S LV patient	S LV control subject	S RV patient	S RV control subject	G LS LV patient	G LS LV control subject	G LS RV patient	G LS RV control subject
Mean	9.9688	13.3672	14.06	2.00	18.6219	22.2759	18.4844	22.3767
N	64	64	64	64	64	64	64	64
Std. Deviation	2.36689	1.02447	4.525	1.000	1.17750	1.28785	1.35602	1.23431
Median	9.2500	13.0000	13.00	2.00	18.9500	22.3500	18.8000	22.4250

Among patients, we observed highly statistic correlations between NT-proBNP values and poorly differentiated carcinomas, and also, between global longitudinal strain measured for both ventricles and poorly differentiated carcinomas ($p<0.001$)- figure 2.2., table 2.2.

Moreover, we identified another highly statistic correlation between right ventricle global longitudinal strain (GLS RV) and the presence of hepatic secondary determinations ($p<0.001$)- table 2.3.

In our study, there were also multiple correlations between NT-proBNP, serotonin and 5-hydroxyindole acetic acid levels ($p<0.001$)- table 2.4.

It can be said that poorly differentiated tumoral grade and the presence of hepatic secondary determinations induce poor outcome through early subclinical systolic dysfunction, thus increasing cardiovascular risk in these patients.

There were no statistic associations among various grades of tricuspid regurgitation regarding global longitudinal strain or systolic velocities.

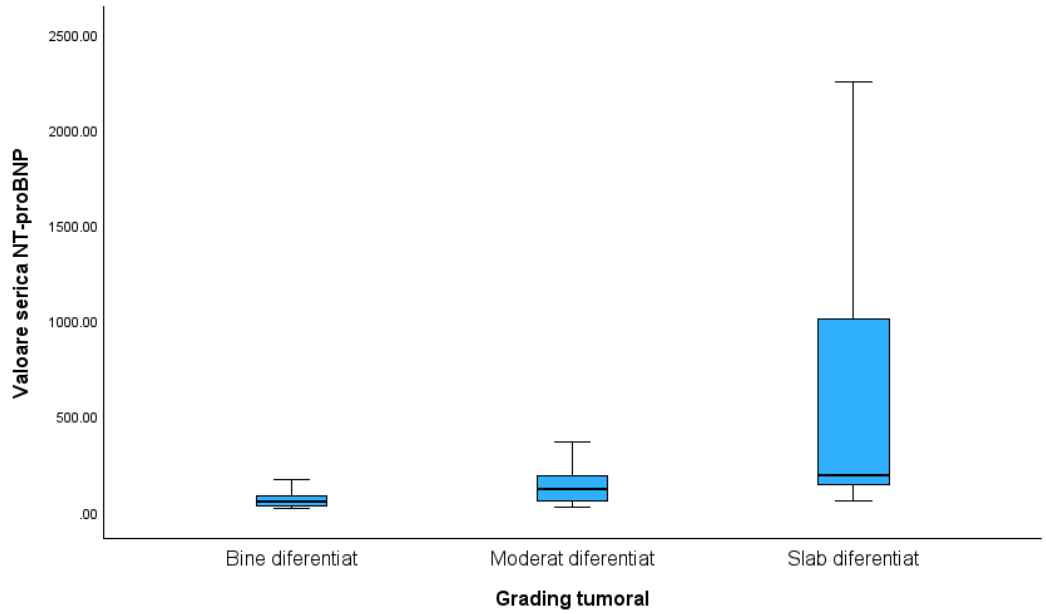

Figure 2.2- Correlation between NT-proBNP values and tumoral grading

Table 2.2- Correlation between global longitudinal strain and tumoral grading

Correlations

		Tumoral Grading	GLS LV	GLS RV
Tumoral Grading	Pearson Correlation	1	-.725**	-.671**
	Sig. (2-tailed)		<.001	<.001
	N	64	64	64
GLS LV	Pearson Correlation	-.725**	1	.990**
	Sig. (2-tailed)	<.001		<.001
	N	64	64	64
GLS RV	Pearson Correlation	-.671**	.990**	1
	Sig. (2-tailed)	<.001	<.001	
	N	64	64	64

**. Correlation is significant at the 0.01 level (2-tailed).

Table 2.3- Correlation between global longitudinal strain and hepatic secondary determinations

Correlations

		GLS RV	Hepatic secondary determinations
Pearson Correlation	GLS RV	1.000	-.476
	Hepatic secondary determinations	-.476	1.000
Sig. (1-tailed)	GLS RV	.	<.001
	Hepatic secondary determinations	.000	.
N	GLS RV	64	64
	Hepatic secondary determinations	64	64

Table 2.4- Multiple correlations

		NT-proBNP	5-HIAA	serotonin
Pearson Correlation	NT-proBNP	1.000	.225	.897
	5-HIAA	.225	1.000	.200
	serotonin	.897	.200	1.000
Sig. (1-tailed)	NT-proBNP	.	.037	<.001
	5-HIAA	.037	.	.057
	serotonin	.000	.057	.
N	NT-proBNP	64	64	64
	5-HIAA	64	64	64
	serotonin	64	64	64

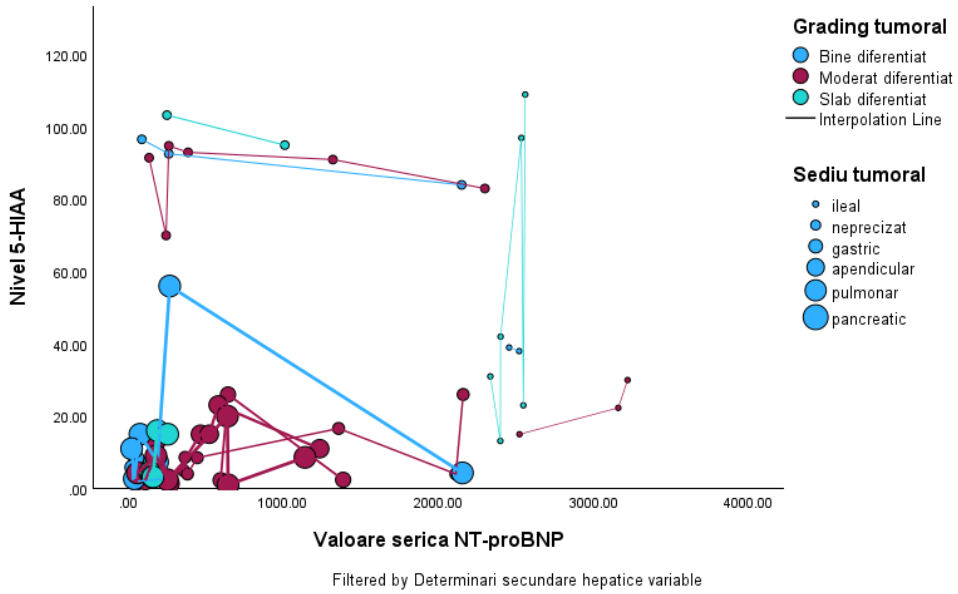

Figure 2.3- Multiple correlations between 5-HIAA, NT-proBNP levels, tumoral grading and primary tumour origin

Patients with ileum tumours, those with poorly differentiated carcinomas and hepatic secondary determinations had the highest levels of NT-proBNP and 5-HIAA, strongly associated with development of carcinoid heart disease ($p<0.001$). These multiple correlations are revealed into figure 2.3.

Regarding the gender-specific differences related to carcinoid syndrome, there was no significant difference between men and women concerning the development of early myocardial dysfunction. There was no association between patients'gender, age, weight or body-mass index and grade of severity among tested patients.

2.5 Conclusions and personal contributions

2.5.1. Conclusions

Despite the fact that carcinoid syndrome is an uncommon cause of valvular heart disease, however, cardiac involvement occurs frequently in patients with this syndrome, adversely affecting prognosis. Echocardiographic assessment of early myocardial dysfunction based on the measurement of systolic and diastolic velocities, as well as the global longitudinal strain of both ventricles, together with specific biomarkers may contribute to better recognition of carcinoid heart disease in clinical practice, but this needs validation through further studies enrolling larger number of patients.

These results indicate that patients with carcinoid syndrome, primary tumour of unknown origin, ileum and high-grade tumour, multiple secondary determinations, may have myocardial dysfunction apparent by tissue Doppler imaging, even if they appear to have normal findings on two-dimensional and conventional Doppler evaluation; these echocardiographic parameters can correlate with specific biomarkers, being of particularly clinical interest in future studies.

There are a few limitations in present study. Firstly, the size of this study to assess the relationship of each factor with myocardial dysfunction was relatively small. Secondly, it is difficult to explain the exact pathophysiologic mechanisms of early myocardial dysfunction.

Thirdly, although all subjects in our study did not have any signs or symptoms of angina, and had normal findings on electrocardiogram and on 2-D echocardiography, we could not completely exclude asymptomatic coronary artery disease.

2.5.2 Personal contributions

Carcinoid syndrome is a rare cause of acquired valvular heart disease. Although the typical echocardiographic features of carcinoid heart disease are well recognized, this study provides new information about unusual manifestations of the disease as well as the role of neuroendocrine biomarkers.

Owing to the rarity of the disease, few studies have investigated the prognosis of patients with carcinoid heart disease. The present study is the first from Romania to assess early myocardial dysfunction by two-dimensional transthoracic echocardiography guided by predictive biomarkers in patients with carcinoid heart disease.

Our results are concordant to other trials and guidelines proposed by European Society of Cardiology regarding Cardio-Oncology field and can be used as a basis for future studies on carcinoid patients.

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[18] **Ileana Nițu**, Roxana Cristina Rimbaș, Livia Florentina Trașcă, Anca Andronic, Dragoș Vinereanu: New Prognostic Model of In-Hospital Mortality in Patients with Acute Heart Failure- 55-th- National Congress of Cardiology, 2016, September Sinaia,

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[20] **Ileana Nițu:** Carcinoid Heart Disease- a Rare Cause of Acquired Right-Sided Valvular Dysfunction- 61-st National Congress of Cardiology, 2022, September, Sinaia

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List of works

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