

of the time constant of left ventricular relaxation increases through all stage of diastolic dysfunction, so that isovolumic relaxation time becomes prolonged with abnormal relaxation. Shortened ejection time with premature mitral valve closure and prolongation of isovolumic contraction time compensate for increased left ventricular filling pressure. As a result, MPI increases and provides functional information. The advantages of this index are reported to be less dependence on the heart rate and blood pressure, no influence of geometric changes of the ventricle, easy quantitative assessment, suitability for follow up studies, and cost effectiveness. However, the MPI is unsuitable for the evaluation of left ventricular function in patients with atrial fibrillation, atrial flutter, atrioventricular block, severe mitral or aortic valvar disease, and severe pericardial effusion because these factors significantly influence the patterns of left ventricular inflow and outflow [27-29]. European Guidelines (2008) emphasized the role of Natriuretic Peptides (NP) as potential markers for heart failure. Therefore, NPs seem to be independent mortality predictors in patients with carcinoid heart disease. Although most studies showed that brain natriuretic peptide (BNP) is a marker with a higher sensitivity and specificity; however the application of this analysis in clinical practice is often limited by the absence of a universally accepted normal range. A single determination of NT-proBNP at any time during the progression of carcinoid syndrome is a clinically useful tool for risk stratification. The hypothesis that repeated measurements could carry prognostic information beyond a single measure was confirmed in different settings. The importance of repeated determinations is in monitoring the progression of disease and in evaluating the clinical effects of medical therapy [28]. Arterial hypertension is accompanied by higher levels of NT-pro BNP, a reliable indicator of LV pressure and/or volume overload. NT-proBNP levels are closely associated with LV hypertrophy and filling impairment and may be used to facilitate the diagnosis of LV diastolic dysfunction in hypertensives [28]. Wall thickness during arterial hypertension is the major compensatory mechanism to pressure overload and it is often associated with myocardial fibrosis collagen deposition and reduction in LV relaxation and distensibility. Experimental studies demonstrated that the genetic expression of NT-proBNP in myocardial tissue is one of the most important early indicators of LV pressure overload and it occurs before LV Hypertrophy (LVH) development [29].

Contemporary heart failure guidelines recommend natriuretic peptides as the biomarker of choice in diagnostic work-up of patients with heart failure [25]. In this regard, the diagnostic role of NT-proBNP is predominantly to exclude heart failure in carcinoid patients. In this present study, we confirmed NT-pro BNP, more stable counterpart of BNP as both diagnostic and prognostic marker that can largely influence decision making in framing treatment regimens

for patients. NT-proBNP, 76 amino acid biologically inert molecule is generated by proteolytic cleavage by furin and corin, produced due to cardiomyocyte stress [23]. Inflammation, increased levels of oxidative stress and systemic angiogenic imbalance appear to play a crucial role in the pathophysiology of carcinoid heart disease. Through unknown mechanisms, increased levels of oxidative stress cause a cleavage of prolactin into a 16-kDa fragment, which causes endothelial dysfunction and induces cardiomyocyte apoptosis [23]. When interpreting NT-proBNP levels in heart failure, various clinical factors need to be considered. The level of natriuretic peptides increases with age, and therefore, higher cut-off values are suggested for the elderly. Whereas obesity lowers the concentration of natriuretic peptides, renal disease and atrial arrhythmias (Atrial Fibrillation (AF) in particular) are associated with higher NT-proBNP levels. None of the patients in this cohort had AF; this was not surprising, as AF has previously been described to be rare in carcinoid disease [23]. This will enable clinicians to start early and more specifically targeted treatment regimen. In addition to clinical judgement, NT-proBNP measurement may lead to a more effective combinational therapy. High serum NT-proBNP being indicative of increased risk of future cardiac dysfunction may enable clinicians to streamline more target oriented treatment, later followed by regular monitoring of clinical parameters. Although the left ventricle is considered the most important contractility chamber, several recent studies have shown the pivotal importance of RV function. Although initial studies showed that increased NT-proBNP levels were associated with the severity of LV dysfunction some authors have recently shown that patients with both RV and LV dysfunction have increased levels [29]. In our study carcinoid patients without hypertension have similar MPI values when compared with carcinoid syndrome and hypertension with no significant difference in parameters in patients with and without HTN. These results suggest that the contributing effect of hypertension on RV function in carcinoid patients is not more than the effect of carcinoid syndrome alone on RV function. The significant difference in MPI between CS and control group is indicative of the impairment of both RV systolic and diastolic functions in non-hypertensive carcinoid and carcinoid hypertensive patients. So in patients with early subclinical carcinoid heart disease, myocardial dysfunction is not confined to the right ventricle, but also involves the left ventricle, and the impairment of RV function encompasses both systolic and diastolic abnormalities. Increased NT-proBNP levels are associated with LV remodeling [24]. In this cohort, elevated levels of NT-proBNP tended to be associated with a higher MPI. Therefore, NT-proBNP bedside testing in patients with CS is an exciting prospect, especially in health care centres in low- and middle-income countries, where echocardiography is not readily available [29]. Because levels of brain natriuretic peptides are elevated significantly not only in pathologic conditions that affect the left ventricle

but also in clinical conditions that lead to isolated acute or chronic right ventricular overload, it could be proposed that these peptides should not only be regarded as biomarkers of congestive heart failure, but also as indicators of carcinoid cardiovascular outcome [28,29]. The pathophysiological background of cardiac dysfunction in CS is multifactorial and may include both functional and structural alterations in heart muscle [28]. In the present study, we have not found significant correlation between the duration of HTN and the RV and LV MPI. This study has some limitations. One is that the RV systolic function was evaluated with transthoracic echocardiography. Other more accurate and objective methods to estimate RV systolic function, such as Magnetic Resonance Imaging (MRI), would have increased this study's reliability. The other limitation is the study's small population. Also data from large scale epidemiological studies regarding the application of Tei index are lacking.

Conclusion

The simple and easily obtained non-geometric MPI might be a strong predictor of subclinical myocardial dysfunction in patients with carcinoid syndrome; this echocardiographic parameter even correlates with cardiac biomarkers (NT-proBNP) in patients with neuroendocrine tumours, so this present study indicates the clinical feasibility and utility of MPI for assessing global right and left ventricular performance, incorporating both systolic and diastolic function. NT-proBNP can facilitate diagnosis and guides carcinoid heart disease therapy. Its increase is directly related to more advanced NYHA classes and to poor prognosis. However, the clinical application of these results requires further validation.

Declarations

Funding

No funding was received for conducting this study.

Conflicts of interest/Competing interests

The authors declare that there is no conflict of interest.

Ethics Approval

Study approval was provided by the Ethics Committee of "Carol Davila" University of Medicine and Pharmacy, Bucharest

Consent to participate

A written informed consent was obtained from each participant

Consent for publication

Not applicable

Availability of data and material

All data generated or analyzed during this study are included in the published article.

Code of availability

Not applicable

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