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Prognostic implications of modern echocardiographic techniques for the evaluation of the right heart in patients with dilated cardiomyopathy

PHD THESIS SUMMARY

PhD supervisor:

Prof. Dr. Maria Dorobanţu

PhD student: Aura Elena Vîjîiac

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ABBREVIATION LIST

2D – two dimensional
3D – three dimensional
AIV-RV – isovolumic acceleration of the right ventricle
BASI – biatrial stiffness index
CAVCI – combined atrio-ventricular coupling index
GLS-RV –global longitudinal strain of the right ventricle
LA – left atrium
LS-RVFW – longitudinal strain of the right ventricular free wall
LV – left ventricle
LVEF – left ventricular ejection fraction
NYHA – New York Heart Association
PASP – pulmonary artery systolic pressure
RA – right atrium
RACI – right atrial coupling index
$RAEF_{active}$ – active right atrial emptying fraction
$RAEF_{passive}$ – passive right atrial emptying fraction
$RAEF_{total}$ – total right atrial emptying fraction
RAS_{cd} – right atrial conduit strain
RAS_{ct} – right atrial contraction strain
RAS_{res} – right atrial reservoir strain
RASI – right atrial stiffness index
RA V_{active} – right atrial active ejection volume
RA V_{max} – right atrial maximal volume
RA V_{min} – right atrial minimal volume
RA $V_{passive}$ – right atrial passive ejection volume
RA V_{preA} – right atrial pre-A wave volume
RA V_{total} – right atrial total ejection volume
RAVCI – right atrio-ventricular coupling index
RV – right ventricle
RVEF – right ventricular ejection fraction
RVEDV – right ventricular end-diastolic volume
RVESV – right ventricular end-systolic volume
RV-FAC – right ventricular fractional area change
RVOT-SF – right ventricular outflow tract shortening fraction
RVSV – right ventricular stroke volume
STE –speckle tracking echocardiography
TAPSE – tricuspid annular plane systolic excursion

INTRODUCTION

Dilated cardiomyopathy is one of the leading causes of heart failure and the most frequent indication for heart transplantation worldwide. [1] Despite innovative pharmacological and interventional therapies, the 10-year-mortality remains over 40%. [2] Compared with the left ventricle (LV), the right ventricle (RV) has been long considered less important, harder to evaluate by echocardiography and consequently far less studied. Modern echocardiographic techniques such as speckle-tracking echocardiography (STE) and three-dimensional (3D) echocardiography were used in the last decade to evaluate the role of the RV in cardiovascular disease [3, 4], but their clinical impact and prognostic superiority in dilated cardiomyopathy still remain to be clarified.

The right atrium (RA) is a dynamic chamber, with three phasic functions which cand be assessed by STE and 3D echocardiography. However, its characterisation and its role in dilated cardiomyopathy are unknown. An emerging concept in recent literature is the non-invasive evaluation of right ventriculo-arterial coupling, but its importance in dilated cardiomyopathy hasn't been evaluated so far. Currently, there are no published studies comparing various non-invasive estimations of right ventriculo-arterial coupling in the same study population.

Based on this scientific background, the aim of the current PhD thesis was to extensively evaluate the right heart (RA, RV, right ventriculo-arterial coupling) by innovative echocardiographic techniques, in order to enhance the risk stratification for these patients.

CURRENT KNOWLEDGE

CHAPTER 1

Remodelling of the right ventricle in dilated cardiomyopathy

1.1. Anatomy of the right ventricle

Unlike the ellipsoid shape of the LV, the complex shape of the RV renders it difficult to fit any geometrical pattern. Microscopically, the RV has two types of myocardial fibres: a subendocardial longitudinal layer and a subepicardial circumferential layer.

1.2. Physiology of the right ventricle

The contraction of the RV has three components: longitudinal, radial and antero-posterior. [5] The shortening of the longitudinal fibres is responsible for 70% of the ventricular contraction. [6] The RV better accommodates volume overload states, but it is very sensitive to sudden changes in afterload; even a small increase in pulmonary vascular resistance can determine an important reduction of RV output. [7]

1.3. Pathophysiologic changes of the right ventricle in dilated cardiomyopathy

The most common cause of RV failure is left heart failure. [8] Initially, the RV adapts to the increase in afterload by hypertrophy and an increase in contractility, but in time the RV will begin to dilate and systolic and diastolic dysfunction will occur. [8] The RV involvement in dilated cardiomyopathy is not only a consequence of the increased afterload, but it is also due to the ventricular interdependence and to the primary cardiomyopathic process.

1.4. Echocardiographic evaluation of the right ventricle

So far, there is no single ideal parameter for the echocardiographic evaluation of RV function. [9] Therefore, current guidelines recommend an integrative approach, using multiple windows and multiple functional parameters. [10, 11]

1.4.1. Evaluation of the linear dimensions of the right ventricle

The linear dimensions of the RV include the transversal diameters, the longitudinal diameter, the diameter of the RV outflow tract and the RV free wall thickness.

1.4.2. Evaluation of the systolic function of the right ventricle

Conventional parameters include the tricuspid annular plane systolic excursion (TAPSE), the systolic velocity of the lateral tricuspid annulus (S wave), the myocardial acceleration during isovolumic contraction (AIV-RV), the RV outflow tract shortening fraction (RVOT-SF) and the RV fractional area change (RV-FAC). Innovative parameters include global longitudinal strain (GLS-RV), longitudinal strain of the RV free wall (LS-RVFW) and 3D RV ejection fraction (RVEF).

1.4.3. Evaluation of the diastolic function of the right ventricle

The assessment of the diastolic function is based on the diastolic profile of the tricuspid inflow and on the tissular velocities of the lateral tricuspid annulus.

1.4.4. Evaluation of the global function of the right ventricle

The myocardial performance index, also known as Tei index, is a parameter which reflects the global (systolic + diastolic) ventricular function.

1.5. The clinical impact of right ventricular dysfunction in dilated cardiomyopathy

Most of the studies which assessed RV function in dilated cardiomyopathy used conventional echocardiographic parameters [12, 13]. A recent study reported LS-RVFW to be the only event predictor in dilated cardiomyopathy. [14] 3D RVEF was an independent predictor of adverse events in a retrospective study on patients with various cardiovascular disease. [15]

CHAPTER 2
Right ventricular – pulmonary artery coupling

2.1. Physiology and pathophysiology of ventriculo-arterial coupling

The pulmonary circulation can accommodate an important increase of blood flow with minimal increase of the pulmonary artery systolic pressure (PASP). [16] In pulmonary hypertension, the pulmonary circulation will become a high-resistance, low-compliance system, and these changes will lead to ventriculo-arterial decoupling. Although this decoupling ensues after prolonged pressure overload, it precedes clinically overt right heart failure. [16]

2.2. Non-invasive evaluation of right ventriculo-arterial coupling

The estimation of right ventriculo-arterial coupling can be done non-invasively. Several echocardiographic parameters showed good correlation with the gold standard of coupling derived from right heart catheterisation. [17–19]

2.3. The clinical impact of right ventriculo-arterial decoupling

TAPSE/PASP ratio was a predictor of death in patients with left heart failure. [20, 21] In a recent study, TAPSE/PASP was the best predictor of exercise tolerance in patients with reduced LV ejection fraction (LVEF). [22] GLS-RV/PASP and LS-RVFW/PASP ratios were independent predictors of death in patients with left heart failure [23] and of the response to cardiac resynchronisation therapy. [24] In a study enrolling 1004 elderly subjects, each 0.5 unit decrease of the RVEF/PASP ratio was associated with a 65% increase in the risk of death or hospitalisation [25].

CHAPTER 3

Remodelling of the right atrium in dilated cardiomyopathy

3.1. Anatomy of the right atrium

The RA is an ellipsoid structure, located above the RV, with three components: the vestibule, the RA appendage and the venous compartment. [26] The orifice of the RA appendage is larger than the left atrial appendage's; this allows a favourable circulation of blood flow and explains why thrombi are more rarely encountered in the RA appendage than in the left one. [27]

3.2. Physiology of the right atrium

The RA has three phasic functions: (1) the reservoir function, corresponding to the storage of blood coming through the two caval veins to the RA; (2) the conduit function, corresponding to the passive inflow of blood from the RA to the RV; and (3) the contraction function, corresponding to the atrial systole and active pumping of blood into the RV.

3.3. Pathophysiologic changes of the right atrium in dilated cardiomyopathy

In dilated cardiomyopathy, the dilation of the tricuspid annulus secondary to the RV remodelling will determine the distension of the RA, in order to accommodate the volume overload from the tricuspid regurgitant volume. Apart from the volume overload, the RA is exposed to pressure overload as well in dilated cardiomyopathy. A recent study of magnetic resonance showed that all three RA phasic functions are altered in RV pressure overload. [28]

3.4. Echocardiographic evaluation of the right atrium

Modern echocardiographic techniques allow the assessment of RA phasic function. By STE, strain curves are obtained, which are used to measure the maximal longitudinal strain corresponding to the reservoir (RAS_{res}), conduit (RAS_{cd}) and contraction (RAS_{ct}) function. By 3D echocardiography, the RA maximal (RA V_{max} 3D), minimal (RA V_{min} 3D) and pre-A wave (RA V_{preA} 3D) volumes are calculated. Based on these volumes, the total (RA V_{total} 3D), passive (RA $V_{passive}$ 3D) and active (RA V_{active} 3D) ejection volume are calculated, as well as the corresponding emptying fractions ($RAEF_{total}$ 3D, $RAEF_{passive}$ 3D, $RAEF_{active}$ 3D). [29]

3.5. The clinical impact of right atrial dysfunction in dilated cardiomyopathy

2D RA maximal volume was an independent predictor of death, heart transplantation or hospitalization in patients with LVEF<35% [30] and in patients with dilated cardiomyopathy. [31] RA phasic function in patients with heart failure was evaluated by magnetic resonance in a recent study, which reported both reservoir and conduit function to be independent predictors of mortality. [32] So far, RA phasic function assessed with 3D echocardiography was not evaluated in patients with dilated cardiomyopathy. There are no data regarding the prognostic role of RA strain or 3D RA volumes in this disease.

PERSONAL CONTRIBUTIONS

CHAPTER 4

Aims and hypothesis

Since the function of the right heart hasn't been thoroughly studied in dilated cardiomyopathy, the hypothesis of the current research was the following: the extensive evaluation of the right heart by modern echocardiographic techniques will bring important prognostic information, with potential impact on the management of these patients.

The primary aim of the study was to evaluate the relationship between right heart dysfunction (RV, RA, right ventriculo-arterial coupling) and major adverse cardiovascular events, while searching for new prognostic markers.

The secondary aims were the following:

- To evaluate the prevalence of RV dysfunction, RA dysfunction, and right ventriculo-arterial decoupling
- To evaluate whether there are any correlations between right heart dysfunction and symptom severity
- To compare the prognostic impact of modern and conventional echocardiographic techniques

CHAPTER 5

General methodology

This is a prospective study held between January 2019 – December 2021. 173 consecutive patients with dilated cardiomyopathy were screened. The inclusion criteria were: adult patients with dilated LV and LVEF<40%, in the absence of significant coronary artery stenosis or significant preload/ afterload changes. The exclusion criteria were: severe respiratory disease potentially impacting the right heart, atrial fibrillation, poor acoustic window, severe status, comorbidities with life expectancy < 1 year.

The enrolled patients underwent transthoracic echocardiography at baseline (T1) and at 12 months (T2). At baseline, clinical, biological, and electrocardiographic data were also collected. Since the right heart is sensitive to loading conditions and in order to minimize their effect on echocardiographic measurements, echocardiography was performed after stabilisation of congestive symptoms, in patients who had no change in their diuretic dose for the 72 hours prior to echocardiography.

5.1. Assessed parameters

5.1.1. Clinical data

Demographic data, cardiovascular risk factors, NYHA classification and treatment were reported for each patient. At follow-up, the occurrence of any major adverse event was also reported. For the current research, the main composite endpoint consisted of death, heart transplantation, aborted sudden cardiac death or heart failure hospitalization.

5.1.2. Biological data

Blood sugar, creatinine, and natriuretic peptide (NT pro-BNP) were reported.

5.1.3. Electrocardiographic data

The rhythm, the duration of the QRS complex and the presence of left bundle branch block were reported.

5.1.4. Echocardiographic data

For the RV, beside linear dimensions and conventional parameters of systolic function (TAPSE, S wave, AIV-RV, RVOT-SF, RV-FAC), we collected the following modern parameters: GLS-RV, LS-RVFW, RV mechanical dispersion, RV apical traction, end-diastolic volume (RVEDV), end-systolic volume (RVESV), stroke-volume (RVSV) and RVEF.

For right ventriculo-arterial coupling, the following non-invasive estimates were used: TAPSE/PASP ratio, GLS-RV/PASP ratio, LS-RVFW/PASP ratio, RVEF/PASP ratio, RVSV/RVESV ratio.

For the RA, beside 2D volumes and emptying fractions, we collected the following modern parameters: RAS_{res}, RAS_{cd}, RAS_{ct}, RA mechanical dispersion, RA V_{max} 3D, RA V_{min}

3D, RA V_{preA} 3D, RA V_{total} 3D, RA $V_{passive}$ 3D, RA V_{active} 3D, $RAEF_{total}$ 3D, $RAEF_{passive}$ 3D, $RAEF_{active}$ 3D.

We also evaluated novel atrial indices, using formulas which were validated for the left atrium (LA): RA stiffness index (RASI), RA coupling index 3D (RACI), right atrioventricular coupling index 3D (RAVCI). Furthermore, we defined two novel indices: biatrial stiffness index (BASI) (the sum of RASI and LA stiffness index) and combined atrioventricular coupling index (CAVCI) (the sum of RAVCI and left atrioventricular coupling index 3D).

The morphology and function of the LV and LA were evaluated by 2D echocardiography, but also by STE (global longitudinal strain of the LV, LA strain) and 3D echocardiography (3D volumes and corresponding ejection fractions).

5.2. Statistical analysis

Depending on distribution, continuous variables were compared using t test or Mann-Whitney U, categorical variables were compared using chi-square test or Fisher's exact test. To evaluate the associations between parameters, Pearson's or Spearman's correlation coefficients were calculated, depending on the normality of distribution. To evaluate the correlation between functional parameters and NYHA class, the Jonckheere-Terpstra test for trend was used. To assess the ability of different parameters to predict an event, univariable and multivariable Cox regression analysis were used. For survival analysis, Kaplan-Meier curves and log-rank test were used. To assess the accuracy of a certain parameter to predict an event, ROC curves and the corresponding area under the curves (AUC) were used. The cut-off values with optimal discriminatory power for each parameter were chosen based on maximal Youden index. The tested hypotheses were considered statistically significant if $p<0.05$.

CHAPTER 6
Characteristics of the study population

Of the 173 patients initially screened, 52 patients were excluded: 10 with severe respiratory disease, 18 in severe clinical status, 2 with active cancer and life expectancy < 1 year, 15 with persistent atrial fibrillation, 7 with poor acoustic window. The final study population consisted of 121 patients, with mean age 59±14 years and 73.6% men. The mean LVEF was 25±7%. During the mean follow-up period of 19±11 months, 55 patients (45.5%) had major cardiovascular events: there were 26 deaths, one heart transplant, 5 aborted sudden cardiac deaths and 23 heart failure hospitalizations.

CHAPTER 7

Right ventricular dysfunction, its dynamics and prognostic role in patients with dilated cardiomyopathy

7.1. Introduction

The specific aims were: to evaluate the prevalence of RV dysfunction; to evaluate the dynamics of RV dysfunction and of RV reverse-remodelling; to evaluate the prognostic role of RV dysfunction; to evaluate the relationship between RV dysfunction and the severity of heart failure symptoms.

7.2. Material and methods

Patients underwent transthoracic echocardiography at baseline and at 12 months, while various conventional and modern RV functional parameters were collected. The occurrence of any major cardiovascular event was assessed by phone contact, and the event and the date of the event were reported.

7.3. Results

TAPSE, S wave, RV-FAC, GLS-RV, LS-RVFW, RVESV, RVSV and RVEF were significantly more impaired in patients with adverse events. Of the diastolic functional parameters, A_t wave and E_t/A_t ratio were significantly different between patients with and without events. Mean PASP was 41 mm Hg. The prevalence of RV systolic dysfunction was between 31.4% and 56.2% when assessed by conventional techniques, and between 59.5% and 74.4% when assessed by modern techniques. TAPSE, S wave and RVEF had a significant decreasing trend with the increase in NYHA class ($p=0.008$, $p=0.013$ and $p=0.009$, respectively); these were also the only parameters which had significantly different dynamics between patients with and without events. The only parameters which varied significantly from T1 to T2 were RVOT-SF, GLS-RV and RVEF.

Based on univariable Cox regression, the following parameters were significant predictors of the primary endpoint: TAPSE, S wave, RV-FAC, GLS-RV, LS-RVFW, RV apical traction, RVESV, RVSV, RVEF, A_t wave, E_t/A_t ratio, E_t/e'_t ratio. Using ROC curves, RVEF had the best predictive value, with an AUC of 0.88 ($p<0.001$). A RVEF <43% had 86% sensitivity and 77% specificity for the prediction of adverse events. Using cut-offs derived from ROC analysis and Kaplan-Meier curves, patients with TAPSE<17 mm, S wave<9.5 cm/s, RV-FAC<35%, RVEF<43% (log-rank p<0.001 for all), GLS-RV>-9.6% (log-rank p=0.001) and LS-RVFW>-14.9% (log-rank p=0.001) had a worse outcome.

To test the independent predictive value of RV functional parameters, they were introduced in multivariable Cox regression, together with parameters with well-established prognostic role. Three multivariable models were constructed:

- Model 1: age, NYHA class
- Model 2: age, NYHA class, LVEF
- Model 3: age, NYHA class, LVEF, LA maximal volume, PASP

All the six functional parameters, TAPSE, S wave, RV-FAC, GLS-RV, LS-RVFW and RVEF, were independent predictors in all three multivariable models. A RVEF<43% was associated with a ~8 times higher hazard of major events (HR=7.9, 95% CI 3.6–17.1, p<0.001).

7.4. Discussion

In this study, we proved that the prevalence of systolic, diastolic and global RV dysfunction is high among patients with dilated cardiomyopathy. All parameters of systolic function, both conventional and modern, were significantly more impaired in patients with major adverse cardiovascular events. TAPSE, S wave, RV-FAC, GLS-RV, LS-RVFW and RVEF were independent predictors of events. The best prognostic value was found for RVEF, patients with RVEF<43% having a ~8 times higher risk of events.

The prognostic role of conventional parameters such as TAPSE, S wave and RV-FAC in patients with dilated cardiomyopathy is already known [12, 13, 33], the results of this study being in line with published data. In our research, both GLS-RV and LS-RVFW were predictors of the primary endpoint. Recently, two studies have reported the predictive value of LS-RVFW for major events [34] and of GLS-RV and LS-RVFW for mortality [35] in patients with heart failure with reduced LVEF of various etiologies. Another recent study has reported the prognostic role of LS-RVFW in patients with dilated cardiomyopathy. [14]

In our study, RVEF was the best predictor of events. The superiority of RVEF over conventional parameters is most likely due to the fact that RVEF is the only parameter which integrates all three components of RV contraction. Recent literature data highlight the importance of radial and antero-posterior contraction in determining global RV performance. [36] A study from 2021 revealed that the antero-posterior contraction of the RV has an independent prognostic role for death or hospitalization, even when RVEF is preserved. [37]

The prognostic role of 3D RVEF in patients with various cardiovascular disease was reported in several recent studies [15, 38, 39]; however, all these studies were retrospective and they enrolled patients with heart failure of different etiologies. In a recent prospective study, RVEF was an independent predictor of cardiac death or hospitalization in patients with heart failure with preserved LVEF. [40] In a study from 2023, Tokodi et al. used a deep-learning algorithm for measurement of RVEF based on 2D images, which they further validated in a group of patients with various cardiovascular disease, reporting the prognostic role of RVEF [41]. However, the patients were enrolled retrospectively and only 14% of them had a primary cardiomyopathy. Thus, so far, our research remains the only prospective study which evaluated by 3D echocardiography the role of RV dysfunction in dilated cardiomyopathy. [42]

Study limitations

The main limitation is due to the study design – unicentric, with a small number of patients and a relatively short follow-up. Another limitation is a potential selection bias, due to the exclusion of patients with poor acoustic window and atrial fibrillation. So far, there are no reference values for RV strain in dilated cardiomyopathy. For RV strain we used software designed for the LV and adapted for the RV; it is possible that cut-off values derived from ROC analysis are not applicable for other existing software.

7.5. Conclusions

The multi-parametric evaluation of RV function in patients with dilated cardiomyopathy brings important prognostic information. The prognostic role of 3D echocardiography is superior to conventional techniques, RVEF being the parameter with the best predictive value for major adverse cardiovascular events.

CHAPTER 8

Right atrial dysfunction, its dynamics and prognostic role in patients with dilated cardiomyopathy

8.1. Introduction

The specific aims were: to evaluate the prevalence of RA dysfunction; to evaluate the dynamics of RA dysfunction; to evaluate the prognostic role of RA dysfunction.

8.2. Material and methods

Patients underwent transthoracic echocardiography at baseline and at 12 months, while various conventional and modern RA functional parameters were collected.

8.3. Results

The prevalence of RA dilation based on indexed 3D volumes RA V_{max}, RA V_{min}, RA V_{preA}, was 53%, 65% and 60%, respectively. Based on 3D $RAEF_{total,}$ $RAEF_{active}$, and $RAEF_{passive}$, the prevalence of reservoir, conduit and booster pump dysfunction was 76%, 60% and 59%, respectively. Based on atrial strain, 93%, 74% and 89% of the patients had an abnormal RAS_{res}, RAS_{cd}, RAS_{ct}, respectively. Both by STE and 3D echocardiography, RA reservoir function was the most frequently impaired.

The following parameters differed significantly between patients with and without events: all 2D and 3D RA volumes, $RAEF_{total}$ 3D, $RAEF_{passive}$ 3D, RAS_{res}, RAS_{cd}, RAS_{ct}, RACI 2D and 3D, RAVCI, CAVCI, RASI and BASI.

Regarding the dynamics of RA parameters during follow-up, some parameters increased significantly: all 2D atrial volumes, RA V_{max} 3D, RA V_{preA} 3D, RA V_{total} 3D, RA V_{active} 3D, RAVCI, CAVCI, reflecting thus an aggravation of RA dysfunction during follow-up.

Based on univariable Cox regression, the following parameters were significant predictors of the primary endpoint: indexed RA V_{max}, RA V_{min}, RA V_{preA}, both 2D and 3D, RA V_{active}, both 2D and 3D, $RAEF_{total}$ 3D, $RAEF_{passive}$ 3D, RAS_{res}, RAS_{cd}, RAS_{ct}, RA mechanical dispersion, RACI 2D and 3D, RAVCI, CAVCI, RASI and BASI.

Using ROC analysis, 3D volumes had higher AUC than 2D volumes, whereas atrial strain had higher AUC than 3D emptying fractions. The highest AUC corresponded to RAS_{res} and BASI (AUC=0.70 and AUC=0.73, respectively, $p<0.001$ for both). $RAS_{res} < 20\%$ had 86% sensitivity and 53% specificity for prediction of major events, while BASI > 1.70 had 78% sensitivity and 72% specificity for prediction of adverse events.

Using cut-offs derived from ROC analysis and Kaplan-Meier curves, a worse outcome was found for patients with indexed RA $V_{min} > 21$ ml/m^2, indexed RA $V_{preA} > 25$ ml/m^2, RAS_{cd} > -5%, $RAEF_{passive}$ 3D < 17%, RACI 3D > 2.1, RAVCI > 0.21, CAVCI > 0.44 (log-rank p=0.001 for all), RAS_{res} < 20%, RAS_{ct} > -5%, RASI > 0.76, BASI > 1.70 (log-rank p<0.001 for all), $RAEF_{total}$ 3D < 33%, indexed RA $V_{max} > 40$ ml/m^2 (log-rank p=0.005 for both).

To test the independent prognostic value, parameters which were significant in univariable analysis were introduced in multivariable Cox regression, together with parameters with well-established prognostic role. Two multivariable models were constructed:

- Model 1: age, LVEF, LA maximal volume, degree of tricuspid regurgitation
- Model 2: parameters from model 1 and LS-RVFW

RA V_{min} 3D, RA V_{preA} 3D, $RAEF_{passive}$ 3D, RAS_{res}, RACI 3D, RAVCI, CAVCI and BASI remained independent predictors of major events in both multivariable models. RAS_{cd}, RAS_{ct} and RASI kept their prognostic value only in model 1.

8.4. Discussion

In this study, we proved that the prevalence of RA dilation and reservoir, conduit and contraction dysfunction are high among patients with dilated cardiomyopathy. RA dimensions (both 2D and 3D) and most of the functional parameters derived from STE and 3D echocardiography were significantly more impaired in patients with events. RAS_{res}, RAS_{cd}, RAS_{ct}, RA V_{min} 3D, RA V_{preA} 3D and $RAEF_{passive}$ 3D were independent predictors of the primary endpoint after adjustment for age, LVEF, LA maximal volume and the degree of tricuspid regurgitation; except for RAS_{cd} and RAS_{ct}, all remained independent predictors after further adjustment for LS-RVFW. Of all the RA functional parameters, RAS_{res} had the best prognostic value; patients with $RAS_{res} < 20\%$ had a 2.5 times higher risk of events.

Moreover, the atrial indices which were first evaluated in the current study – RACI, BASI, RAVCI, CAVCI – were independent predictors of the primary endpoint in both multivariable models. Of all the atrial indices, BASI had the best prognostic value; patients with BASI > 1.70 had a 2.9 times higher risk of events.

Published data regarding RA function in left heart failure are scarce, and the majority of them used magnetic resonance. Studies reported impairment of RA reservoir [32, 43] and conduit function [32], and also a prognostic role for RAS_{res} and RAS_{cd}. [32, 44]. The current study is the first one to report the impairment of all three RA phasic functions in patients with reduced LVEF [45] and also the first one to report the predictive value of all three phasic functions in dilated cardiomyopathy. It is also the first evaluation of RA morphology and function in patients with dilated cardiomyopathy using both STE and 3D echocardiography in the same population.

Regarding non-invasive RA stiffness, the only published study proved its predictive role for death in patients with systemic sclerosis. [46] The current study is the first to prove the independent prognostic role of non-invasive RA stiffness in dilated cardiomyopathy. Moreover, we proposed a combined stiffness index, which takes into account the stiffness of both atria – this index was the best predictor of the primary endpoint in the current study. Atrial stiffness is a marker of ventricular diastolic dysfunction [47], but, since it takes into account reservoir strain, it will reflect early changes in atrial mechanics, which appear before changes in atrial volumes. This can be a possible explanation for the superior prognostic value of BASI.

In the last two years, some authors evaluated left atrio-ventricular coupling index by magnetic resonance [48] or 2D echocardiography [49], proving its predictive value for incident atrial fibrillation or death. [48, 49] The only study which evaluated RAVCI, using the same formula derived from magnetic resonance, was published in 2023, and reported that this index had a predictive role for malignant arrythmias in a paediatric population with corrected Fallot tetralogy. [50] The current research is the first to evaluate atrio-ventricular coupling in patients with dilated cardiomyopathy and the first evaluation of coupling by 3D echocardiography; it is the first study to evaluate both left and right atrio-ventricular coupling in the same population; moreover, it is the first study to define a combined atrio-ventricular coupling index and to assess its prognostic role. RAVCI and CAVCI were independent predictors of the primary endpoint in the current study. The atrio-ventricular coupling index evaluate the haemodynamic relationship between the atrium and the ventricle in diastole. Recent studies suggest that the end-diastolic atrial volume correlates better with ventricular filling pressures and it is a better prognostic marker than end-systolic atrial volume. [51, 52] This is a possible explanation for the prognostic superiority of CAVCI. Dilated cardiomyopathy, while being primarily a disease of the LV, determines morpho-functional changes in all heart chambers; this can partly explain the prognostic role of CAVCI – an index which combines the haemodynamic interaction between all four heart chambers.

Study limitations

Besides the limitations already mentioned in Chapter 7, it is worth mentioning that the normal values for RA strain have a very wide range, which questions the actual utility of RA strain in clinical practice. [53] So far, there are no reference values for RA strain in patients with dilated cardiomyopathy. Furthermore, there are no normal reference values for the novel indices in the current research (RASI, BASI, RACI, RAVCI, CAVCI).

8.5. Conclusions

All three RA phasic functions are impaired in patients with dilated cardiomyopathy. The prognostic role of modern echocardiographic techniques is superior to conventional ones, RAS_{res} being the parameter with the best predictive value for major adverse cardiovascular events. Both BASI and CAVCI – two indices first defined in the current study – were independent predictors of adverse events.

CHAPTER 9

Non-invasive right ventriculo-arterial coupling in patients with dilated cardiomyopathy

9.1. Introduction

The specific aims were: non-invasive evaluation of right ventriculo-arterial coupling; comparison of various echocardiographic surrogate parameters for right ventriculo-arterial coupling; evaluation of the prognostic role of right ventriculo-arterial decoupling in dilated cardiomyopathy; evaluation of the relationship between right ventriculo-arterial coupling and symptom severity.

9.2. Material and methods

Right ventriculo-arterial coupling was estimated non-invasively using the following five echocardiographic parameters: TAPSE/PASP ratio, GLS-RV/PASP ratio, LS-RVFW/PASP ratio, RVEF/PASP ratio and RVSV/RVESV ratio.

9.3. Results

All five parameters were significantly more impaired among patients with adverse events ($p=0.002$ for GLS-RV/PASP, $p<0.001$ for all the others), reflecting a more severe ventriculo-arterial decoupling. The degree of decoupling was greater when symptoms were more severe, the trend of TAPSE/PASP, RVEF/PASP, RVSV/RVESV decrease and of GLS-RV/PASP, LS-RVFW/PASP increase concomitantly with the increase in NYHA class was statistically significant.

By Cox univariable regression, all five parameters were predictors of events ($p=0.001$ for TAPSE/PASP and GLS-RV/PASP, $p<0.001$ for all the others). In ROC analysis, all five parameters had good predictive values for adverse events, with AUC over 0.68 ($p<0.001$ for all). RVSV/RVESV had the best predictive value for the primary endpoint (AUC=0.88, $p<0.001$), a value under 0.74 having 86% sensitivity and 77% specificity for event prediction.

To test the independent prognostic value of coupling parameters, we used a multivariable model which included age, NYHA class, LVEF and LA maximal volume. All five coupling parameters were independent predictors of major events. A RVSV/RVESV ratio < 0.74 was associated with a 7.5 times higher risk of events (HR=7.5, 95% CI 3.5–16.2, $p<0.001$).

To evaluate the relationship between right ventriculo-arterial coupling and symptom severity, we used multinomial logistic regression, in order to analyse the ability of coupling parameters to determine the NYHA class. The regression model included age, LVEF and LA maximal volume. TAPSE/PASP, RVEF/PASP and RVSV/RVESV were independent predictors of NYHA class in multinomial regression ($p=0.028$, $p=0.013$ and $p=0.011$, respectively).

9.4. Discussion

In the current study, we proved that all five parameters of right ventriculo-arterial coupling were significantly more impaired in patients with adverse events. The degree of decoupling was greater when NYHA class was higher. TAPSE/PASP, RVEF/PASP and RVSV/RVESV were independent predictors of NYHA class. All five coupling parameters were independent predictors of the primary endpoint, after adjustment for age, NYHA class, LVEF and LA maximal volume. RVSV/RVESV had the best predictive value; patients with RVSV/RVESV < 0.74 had a 7.5 times higher risk of major events.

The current study is the first to assess the prognostic value of right ventriculo-arterial coupling in patients with dilated cardiomyopathy and the first to compare various echocardiographic parameters of right ventriculo-arterial coupling in the same study population. The most extensively studied echocardiographic surrogate, TAPSE/PASP ratio, is known to have a prognostic role in heart failure with reduced LVEF. [18, 21, 54] Bosch et al. reported GLS-RV/PASP to be an independent predictor of death or hospitalization in patients with heart failure [21], while another study reported both GLS-RV/PASP and LS-RVFW/PASP to be independent predictors of death in patients with LVEF<45%. [23]

The first study to evaluate RVEF/PASP ratio as a surrogate for right ventriculo-arterial coupling was published in 2018 and included a cohort of elderly patients with heart failure. RVEF/PASP proved to be a predictor of death or hospitalization. [25] The only other study evaluating this ratio enrolled patients with precapillary pulmonary hypertension [55]; hence, the current research is the first to assess the RVEF/PASP ratio in patients with dilated cardiomyopathy. The only study to assess the prognostic role of RVSV/RVESV ratio included paediatric patients with pulmonary hypertension [56]; therefore, so far, the only data regarding the role of this parameter in left heart failure are data from the current research. [57, 58]

Limitele studiului

Besides the limitations already mentioned in Chapters 7 and 8, the main limitation is the lack of validation of the non-invasive coupling parameters against the gold standard derived from right heart catheterization. So far, there are no reference values for right ventriculo-arterial coupling parameters, neither from the general population, nor from patients with dilated cardiomyopathy. Therefore, we cannot establish whether the cut-off values from ROC analysis can be extrapolated to other populations or patient cohorts.

9.5. Conclusions

Right ventriculo-arterial coupling is impaired in patients with dilated cardiomyopathy, and it is an independent predictor of adverse events. Non-invasive evaluation of coupling can be performed by conventional or modern echocardiographic techniques. Of the non-invasive coupling surrogate parameters, the RVSV/RVESV ratio had the best prognostic value.

CHAPTER 10

Conclusions. Personal contributions

10.1. Final conclusions

The current research led to the following conclusions:

1) The prevalence of RV dysfunction in dilated cardiomyopathy is increased, and it is greater when assessed by modern echocardiographic techniques

2) TAPSE, S wave, RV-FAC, GLS-RV, LS-RVFW and RVEF were predictors of major adverse cardiovascular events, independent of age, NYHA class, LV systolic and diastolic function and the degree of pulmonary hypertension

3) Of all RV functional parameters, RVEF was the best predictor of outcome, patients with RVEF<43% having an 8 times higher risk of adverse events

4) The prevalence of RA dilation and of RA reservoir, conduit and contraction dysfunction in dilated cardiomyopathy is increased, and it is greater when assessed by modern echocardiographic techniques

5) RAS_{res}, RAS_{cd}, RAS_{ct}, RA V_{min} 3D, RA V_{preA} 3D and $RAEF_{passive}$ 3D were predictors of major adverse cardiovascular events, independent of age, LVEF, LA maximal volume and the degree of tricuspid regurgitation; RAS_{res}, RA V_{min} 3D, RA V_{preA} 3D and $RAEF_{passive}$ 3D remained independent predictors after further adjustment for LS-RVFW

6) Of all RA functional parameters, RAS_{res} was the best predictor of outcome, patients with RAS_{res} <20% having a 2.5 times higher risk of adverse events

7) The indices of atrial stiffness (RASI and BASI), of atrial coupling (RACI) and of atrio-ventricular coupling (RAVCI and CAVCI) were independent predictors of major adverse cardiovascular events, after adjustment for age, LVEF, LA maximal volume and the degree of tricuspid regurgitation; except for RASI, all the indices remained independent predictors after further adjustment for LS-RVFW

8) Of all atrial indices, BASI was the best predictor of outcome, patients with BASI > 1.70 having a ~3 times higher risk of adverse events

9) TAPSE/PASP, GLS-RV/PASP, LS-RVFW/PASP, RVEF/PASP and RVSV/RVESV were significantly more impaired among patients with adverse events

10) The greater the NYHA class, the greater the degree of right ventriculo-arterial decoupling for all five parameters of coupling

11) TAPSE/PASP, RVEF/PASP and RVSV/RVESV were independent predictors of NYHA class

12) All five parameters of right ventriculo-arterial coupling were independent predictors of major adverse cardiovascular events in multivariable analysis

13) Of all five parameters of coupling, RVSV/RVESV was the best predictor of outcome, patients with RVSV/RVESV < 0.74 having an 8 times higher risk of adverse events

10.2. Personal contributions and original features

The current research has several original directions. First of all, it is the first study to assess in patients with dilated cardiomyopathy both RV function, RA function and right ventriculo-arterial coupling by modern echocardiographic techniques. So far, it is the only prospective study which proved the independent prognostic role of 3D RVEF in dilated cardiomyopathy. The current thesis represents the first evaluation of RA morphology and phasic function in patients with dilated cardiomyopathy using modern echocardiographic techniques (both STE and 3D echocardiography); it is also the first study to report the impairment of all three RA phasic functions in patients with reduced LVEF.

The current research is the first to assess non-invasively RA stiffness in dilated cardiomyopathy, proving its independent prognostic role. Moreover, we defined a combined stiffness index, which considers the stiffness of both atria – this index proved to be an excellent predictor of the primary endpoint. So far, it is the only study to assess the 3D RACI, proving its independent prognostic role. Regarding the assessment of atrio-ventricular coupling, it is the first study to evaluate the atrio-ventricular coupling index in patients with dilated cardiomyopathy; it is the first study to evaluate the atrio-ventricular coupling index by 3D echocardiography; it is the first study to evaluate both left and right atrio-ventricular coupling index in the same study population; and it is the first study to define a combined atrio-ventricular coupling index and assess its prognostic role.

The current research is the first to evaluate and prove the prognostic value of right ventriculo-arterial coupling in patients with dilated cardiomyopathy and the first to compare various echocardiographic methods to estimate coupling non-invasively in the same study population.

Patients with dilated cardiomyopathy need, beyond LV evaluation, an echocardiographic evaluation of RV and RA function, since longitudinal and global RV dysfunction, as well as RA reservoir, conduit and pump dysfunction proved to be independent predictors of major adverse cardiovascular events. If the local equipment and expertise allow it, RV and RA assessment by STE and 3D echocardiography determine an enhanced risk stratification, as modern techniques are able to detect subtle changes of atrial and ventricular function. As a future perspective, RVEF and RAS_{res}, which were the best predictors of events in the current research, should be evaluated and reported in dilated cardiomyopathy, patients with RVEF<43% and RAS_{res}<20% having the most unfavourable outcome.

Therefore, this PhD research met its primary goal, namely, to identify new parameters of unfavourable prognosis in dilated cardiomyopathy – right heart functional parameters derived from modern echocardiographic techniques. The results were published throughout the doctoral research in five scientific articles (four original articles and one review); all of them were published in international journals indexed in ISI Web of Science database, with an impact factor between 1.87 and 3.70.

10.3. Future directions

Recently, dedicated software for RV strain analysis and atrial strain analysis was developed, as well as software for 3D analysis of the RV, atria and a prototype software from GE for the 3D evaluation of the tricuspid annulus. Unfortunately, when patients were enrolled in the current research, such software was unavailable in the Echocardiography Laboratory from the Emergency Clinical Hospital Bucharest. Therefore, the current research can be enhanced in the following directions:

1) Evaluating the reproducibility of the results using dedicated software for RV and RA

2) Long-term follow-up of the patients

3) Evaluation of the dynamics of the tricuspid annulus and its prognostic role in dilated cardiomyopathy

4) Evaluating the reproducibility of the results in patients with dilated cardiomyopathy and mildly reduced LVEF

Since the current research was based on modern echocardiographic techniques, the extrapolation of the results and their clinical usefulness are highly dependent on the facilities of the imaging laboratory where patients are evaluated. Strain imaging and 3D echocardiography have indisputable advantages in clinical practice, especially for the evaluation of the right heart – advantages which are confirmed by the current research as well. However, modern echocardiographic techniques require high costs, and including them into daily practice is not feasible for the moment, at least in our country. Nevertheless, dilated cardiomyopathy is a disease with (still) significant morbidity and mortality (despite important progress in the treatment of heart failure in the last two decades); therefore, a refined risk stratification for these patients will lead implicitly to diminished costs for the health system and to a reduction in morbidity and mortality. In conclusion, research on patients with dilated cardiomyopathy must be continued, having as a future target the inclusion of modern echocardiographic techniques in the routine evaluation of these patients.

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