MINISTRY OF EDUCATION

University of Medicine and Pharmacy of Craiova

DOCTORAL SCHOOL

PHD THESIS

ATRIAL FUNCTIONAL TRICUSPID REGURGITATION: PATHOPHYSIOLOGICAL AND IMAGING CONSIDERATIONS

- SUMMARY -

SCIENTIFIC COORDINATOR:

Professor Dr. Bălșeanu Tudor-Adrian

PHD CANDIDATE:

Dr. Florescu (Hădăreanu) G. Diana-Ruxandra

CRAIOVA

2022

TABLE OF CONTENTS

INTRODUCTION *1*

CURRENT STATE OF KNOWLEDGE *2*

ANATOMY OF THE TRICUSPID VALVE APPARATUS AND PATHOPHYSIOLOGY OF FUNCTIONAL TRICUSPID REGURGITATION *2*

EVALUATION OF FUNCTIONAL TRICUSPID REGURGITATION BY MULTI-MODALITY IMAGING *2*

PERSONAL CONTRIBUTIONS *3*

RIGHT HEART CHAMBERS REMODELING IN THE ATRIAL AND THE VENTRICULAR PHENOTYPES OF FUNCTIONAL TRICUSPID REGURGITATION *3*

HYPOTHESIS AND GENERAL OBJECTIVES **3**

RESEARCH METHODOLOGY **3**

RESULTS **4**

DISCUSSIONS **6**

FUNCTIONAL TRICUSPID REGURGITATION SEVERITY GRADING USING THE CORRECTED PISA METHOD *8*

HYPOTHESIS AND GENERAL OBJECTIVES **8**

RESEARCH METHODOLOGY **8**

RESULTS **10**

DISCUSSIONS **11**

AUTOMATED LEFT ATRIAL VOLUME AND FUNCTION BY TWO-DIMENSIONAL SPECKLE-TRACKING ECOCARDIOGRAPHY *12*

HYPOTHESIS AND GENERAL OBJECTIVES **12**

RESEARCH METHODOLOGY **13**

RESULTS **13**

DISCUSSIONS **14**

CONCLUSIONS**.....*****15***
BIBLIOGRAPHY**.....*****16***

KEYWORDS: *atrial functional tricuspid regurgitation; atrial fibrillation; three-dimensional echocardiography; speckle-tracking echocardiography; tricuspid valve; right ventricle; right atrium.*

INTRODUCTION

Functional tricuspid regurgitation (FTR), secondary to tricuspid annulus (TA) dilation and dysfunction, tricuspid valve (TV) leaflets' tethering, or a combination of both, is a progressive valvular disease (1), accounting for approximately 90% of all cases of FTR (2,3). The general belief has been that FTR is a consequence of right ventricular (RV) dilation and dysfunction, occurring in patients with pulmonary arterial hypertension (PHTN). Furthermore, atrial FTR (A-FTR) has been called "neglected", an "underappreciated cause", "a new entity" (4–9). However, in a significant number of patients with persistent/permanent atrial fibrillation (AF), the dilation and dysfunction of the TA, secondary to right atrial (RA) dilation and dysfunction, lead to the development of significant A-FTR (7,10,11). Nevertheless, all the geometrical and functional changes occurring in AF finally result in TV leaflets' mal-coaptation and A-FTR development, even in the presence of normal/mildly abnormal RV size and function (12,13). Thus, understanding the pathophysiological cascade leading to the development of A-FTR in patients with AF is essential for correctly diagnosing it, assessing its severity by transthoracic echocardiography (TTE) as the imaging method of choice, and distinguishing between the two phenotypes of FTR. However, FTR severity quantification is difficult, and the quantitative parameters recommended by current guidelines in FTR grading have multiple limitations.

Accordingly, our objectives were: (i) to study the geometry and function of the RV, RA and TA in A-FTR by two-dimensional (2DE) and three-dimensional (3DE) TTE, and compare them with those found in ventricular FTR (V-FTR); (ii) to assess the impact of correcting the conventional PISA formula on the accuracy of effective regurgitant orifice area (EROA) and regurgitant volume (RegVol) measurement for FTR grading, and its clinical impact compared to the uncorrected method; and (iii) to evaluate the feasibility, accuracy, and reproducibility of the automated measurement of left atrial (LA)

maximal volume (Vmax) derived from two-dimensional speckle-tracking echocardiography (2DSTE). Each of the three main objectives was concretized in a sub-study of the doctoral thesis.

CURRENT STATE OF KNOWLEDGE

ANATOMY OF THE TRICUSPID VALVE APPARATUS AND PATHOPHYSIOLOGY OF FUNCTIONAL TRICUSPID REGURGITATION

The TV is a complex structure that includes the TA, the TV leaflets, and a sub-valvular apparatus represented by the chordae tendineae and papillary muscles. The anatomical integrity of the TV apparatus and the normal functioning and geometry of the right heart chambers are necessary for the proper functioning of the TV (14–16). A-FTR is still a neglected consequence of persistent/permanent atrial fibrillation (AF), characterized by TA remodeling secondary to RA dilation, and normal/slightly abnormal RV size and function, especially in the early stages of the disease (5,9,17). V-FTR occurs secondary to pathological conditions impacting the geometry, dynamics and/or function of the RV, leading to RV papillary muscles displacement and TV leaflets tethering (5).

EVALUATION OF FUNCTIONAL TRICUSPID REGURGITATION BY MULTI-MODALITY IMAGING

The echocardiographic evaluation of the TV and FTR relies on the following aspects: (1) confirmation of the presence of pathological FTR; (2) morphological assessment of the TV; (3) identification of the mechanisms involved in FTR development (TA dilation, TV leaflets tethering, interference of intracardiac devices, etc.); (4) differentiation between A-FTR and V-FTR; (5) quantification of FTR severity and its hemodynamic impact (18). The recommended first line examination in the routine assessment of patients with FTR is made by 2DE and Doppler TTE and uses a series of parameters (structural, qualitative, semi-quantitative and quantitative) (13,18–20). However,

the most accurate echocardiographic method for assessing the structural parameters (TV morphology, TA, RA and RV dimensions) is 3DE (21,22).

Cardiac nuclear magnetic resonance (CMR) is the reference imaging technique for the assessment of RV size and function. CMR provides can provide an accurate FTR severity grading based on the measurement of the RegVol and regurgitation fraction (RegF). Cardiac computed tomography, characterized by high spatial resolution, is the ideal method for assessing the TA dimensions and cardiac anatomy, and for the direct measurement of the EROA (23–25).

PERSONAL CONTRIBUTIONS

RIGHT HEART CHAMBERS REMODELING IN THE ATRIAL AND THE VENTRICULAR PHENOTYPES OF FUNCTIONAL TRICUSPID REGURGITATION

HYPOTHESIS AND GENERAL OBJECTIVES

A-FTR is a relatively new phenotype of FTR (5). RA dimensions play an important role in determining the changes in the TV complex (6,7). Differently from V-FTR, patients with A-FTR have normal RV size and preserved systolic function (7,26). Yet, the geometry and function of the RV, RA and TA in patients with A-FTR and V-FTR have never been systematically evaluated.

Thus, the objectives of our study were: (i) to study the geometry and function of the RV, RA and TA in A-FTR using 2DE, 2DSTE and 3DE, and (ii) to compare them with those encountered in V-FTR. As a secondary objective, we aimed to evaluate the clinical implications of using 2DE versus 3DE for the evaluation of RV geometry and function in patients with FTR.

RESEARCH METHODOLOGY

We have prospectively included 224 FTR patients evaluated by clinically-indicated 2DE and 3DE using Vivid E9, E90 and E95 scanners between July 2020 and May 2021. The study population was subsequently divided into two groups according to the etiology of FTR (group 1 = persistent/permanent AF,

without pulmonary hypertension (PHTN) and group 2 = PHTN, without AF). The inclusion criteria were: (i) age> 18 years; (ii) qualitative and complete 2DE and 3DE studies for the assessment of the RV, RA and TA; and (iii) correct estimation of systolic pulmonary artery pressure by Doppler echocardiography (27). The subjects included in the control groups were selected from the Padua 3D Echo normal study (2011-2014) (28).

The absence of structural TV disease was assessed by 3DE. For FTR severity staging a multi-parametric algorithm was used as recommended by current guidelines (20,29). The probability of PHTN was determined by using the maximum velocity of the FTR jet and the presence or absence of other echocardiographic signs (27). The dimensions and function of the RA and RV were evaluated by 2DE, 2DSTE and 3DE using the dedicated softwares included in EchoPac v204. Three RV diameters were measured by 2DE and 3DE at end-diastole to describe the morphology of the RV (30). The following ratios between RV linear dimensions were calculated: basal / medium, basal / length, medium / length and sphericity index (mean diameter x length / basal diameter) (31).

The T test for independent variables was used to compare the mean values of the continuous variables, and a p value <0.05 was considered statistically significant. For a correct comparison of the two phenotypes of FTR we used the Z scores by including in the calculation formula the mean and the standard deviation of the parameters of the control groups. A score Z> 2 was considered significantly abnormal. The statistical analysis was performed using SPSS version 23 for Mac (SPSS Inc., IBM Corp., Chicago, IL, USA).

RESULTS

The final study cohort consisted of 113 patients with FTR: 55 patients with persistent / permanent AF (A-FTR, age = 74 ± 8 years, 24 men) and 58 patients with PHTN (V-FTR, age = 61 ± 18 years, 19 men). Patients from the two FTR groups were compared with two different age- (p =.068 and .994) and sex-

matched (p =.920 and p =.987) control groups (45 for A-FTR patients: age = 71 ± 9 years, 20 men and 46 for V-FTR: age = 61 ± 8 years, 15 men).

The distribution of FTR severity grading was similar between the two groups: mild (27 = 49.1% versus 23 = 39.7%), moderate (17 = 30.9% versus 26 = 44.8 %), and severe (11 = 20% versus 9 = 15.5%) (p =.601). Except for the average VC width that was higher in the V-FTR group (p =.037), all other quantitative parameters used for FTR grading (EROA, PISA radius, RegVol, RegF) were similar between the two groups. In addition, patients with V-FTR had increased TV leaflets tethering and higher tenting heights compared to patients with A-FTR. In both FTR groups RA Vmax measured by 3DE and 2DE as well as RA minimum volume (Vmin) measured by 3DE were significantly larger compared to controls.

Patients with A-FTR were characterized by larger RV basal diameters, smaller RV lengths, and larger RV volumes compared to the control group. All RV function parameters had lower values in patients with A-FTR compared to the control group. In addition, these patients had an increased ratio of basal / middle and basal / length diameters, and reduced sphericity index. In contrast, the mid-diameter / length ratio was similar between A-FTR patients and their controls. These described changes are characteristic for the localized basal RV dilation in A-FTR, with the geometric remodeling of the RV resembling a conical pattern. Patients with V-FTR had increased basal and mid-ventricular diameters as well as RV lengths compared to their controls. The RV volumes were larger, and the RV functional parameters lower in V-FTR than in the controls (p <.001). In addition, patients with RTF-V had increased ratios of linear dimensions (basal / mid, basal / length and mid / length) and higher sphericity index (p <.001 for all) compared to the controls (thus developing significant RV dilation at all levels - basal, mid-cavitary and longitudinal). These described changes characterize the spherical or elliptical pattern of RV remodeling in V-FTR.

Patients with A-FTR did not have significantly abnormal RV size and function compared to their controls (all Z scores <2). In contrast, patients with

V-FTR have larger RV volumes and reduced RV function compared to the controls. Thus, all RV Z scores were significantly higher in V-FTR compared to A-FTR ($p < .001$ for all). RA dimensions were significantly abnormal in both FTR groups compared to the controls, but with similar RA Vmax values, and significantly higher RA Vmin values in A-FTR compared to V-FTR. TA areas in mid-systole and tele-diastole were significantly abnormal and larger in V-FTR than in A-FTR ($p = .01$ and $p < .001$). 73% of patients with severe A-FTR and 18% of patients with non-severe A-FTR presented significant RV dilation. Differently from A-FTR, all patients with V-FTR had significant RV dilation regardless of the degree of FTR.

DISCUSSIONS

To the best of our knowledge, this study is the first to use 3DE to provide a systematic comparison of right heart chambers and TA geometry and function in patients with A-FTR and V-FTR with similar degrees of FTR severity. Our results can be summarized as follows: (i) although patients with A-FTR had larger RV basal diameters and lower RV volumes and systolic function compared to their controls, they were not significantly abnormal (all Z scores <2) ; (ii) patients with V-FTR have significantly abnormal RV diameters and volumes (all scores Z> 2) and significantly lower RV function compared to the controls; (iii) the remodeling pattern of the RV in A-FTR corresponds to a conical deformation, characterized by an increase in the ratio of basal / mid diameters as well as basal / length and reduced sphericity index; (iv) the remodeling pattern of the RV in V-FTR is similar to a spherical or elliptical deformation, characterized by an increase in all diameters and sphericity index; (v) the RA is significantly dilated in both FTR phenotypes, patients with A-FTR having significantly higher RA Vmin than those with V-FTR, despite similar RA Vmax; (vi) TA areas, TV leaflet tethering, tenting height and volumes were significantly higher in V-FTR.

FTR has recently been divided into two different phenotypes, with different etiologies and likely different prognosis (5). Topilsky et al. (31) studied

the changes in right heart geometry in patients with idiopathic FTR (i-FTR) and V-FTR. Similar to our study, patients with i-FTR had larger RV basal diameters and shorter RV lengths compared to V-FTR. In contrast, the RV mid diameters were similar in patients with i-FTR and V-FTR. These differences could be explained by the different characteristics of the studied cohorts. The prevalence of AF in the group of patients with i-FTR was 51%, and all three groups included in their study had similar prevalence of AF. In contrast, in our study we selected only patients with long-term persistent / permanent AF to be included in the A-FTR group and only patients with PHTN and sinus rhythm to be included in the V-FTR group. Two different groups of age- and sex-matched healthy subjects sex were selected to be compared with the two subgroups of FTR in order to correctly identify the specific changes of each of them.

By using the linear dimensions derived from 3DE (which have a reproducible spatial orientation in different patients) we demonstrated the existence of different RV remodeling patterns in A-FTR and V-FTR, thus explaining the different TV complex morphologies in these patients. In A-FTR the remodeling pattern is predominantly conical, with an increase in the basal dimensions, and normal RV mid-diameter and length. Thus, the papillary muscles maintain their normal anatomical position, orientation and distance from the TV cusps, causing minimal leaflet tethering. A-FTR is characterized by TA dilation and decreased function, and an imbalance between TA and TV leaflets areas (40). Conversely, the remodeling pattern of the RV in V-FTR is elliptical or spherical, characterized by an increase in the mid-diameter and length, leading to papillary muscles displacement and consequent TV leaflets tethering.

Current guidelines indicate that RV dilation may be suggestive of severe FTR (13,18). However, unlike the classic V-FTR phenotype, patients with A-FTR may have severe FTR and normal RV volumes, or, conversely, patients with non-severe FTR may have RV dilation. Therefore, the absence of RV dilation in A-FTR should not be an indicator of a less severe degree of FTR. Accordingly, current indications for TV surgery in highly symptomatic patients with severe

FTR or in mildly symptomatic patients with progressive RV dysfunction or dilation should be considered differently depending on the etiology of FTR (32).

FUNCTIONAL TRICUSPID REGURGITATION SEVERITY GRADING USING THE CORRECTED PISA METHOD

HYPOTHESIS AND GENERAL OBJECTIVES

EROA and RegVol calculated using the 2D PISA method (18,20) are among the quantitative parameters frequently used in FTR grading. However, the use of the 2D PISA method for FTR quantification has many limitations (33): i. the regurgitation is often a dynamic phenomenon, therefore the calculated EROA may not be equivalent to the average regurgitation orifice throughout the systole (34); ii. blood viscosity may reduce the flow rate (35); iii. the regurgitation orifice is not punctiform, but rather has a finite opening, often characterized by a star-shaped or ellipsoidal morphology (21); iv. both the low pressure and velocity profile of the right heart, and the distortion of the FTR plane that results from the tethering of the TV leaflets could flatten the PISA hemispheres (36). Thus, the use of the 2D PISA method for the quantification of FTR may lead to an underestimation of its severity (37). Applying the correction factors that take into account the angle subtended by the TV leaflets (α / 180 °), and the relatively low velocity of the FTR jet might improve the accuracy of the conventional PISA formula. However, this hypothesis remains to be proven.

Consequently, the aims of our study were to assess: (i) whether correcting the conventional PISA formula by including the angle of the TV leaflets and the velocity of the FTR jet improves the accuracy of EROA and RegVol calculation; (ii) the clinical impact of the corrected 2D PISA method in grading the FTR severity compared to the uncorrected conventional method.

RESEARCH METHODOLOGY

We retrospectively analyzed the echocardiographic studies performed between October 2015 and October 2021. The inclusion criteria were the presence of at least mild FTR and a complete TTE study, including 2DE, Doppler

examination and 3DE. Exclusion criteria were: age <18 years, primary TR, presence of cardiac implantable devices, intra-cardiac shunts, more than mild aortic or mitral regurgitation, and inadequate acoustic window.

Digitally stored 2DE, Doppler, and 3DE datasets were analyzed offline using EchoPAC v204 (GE Vingmed, Horten, Norway). We classified FTR severity based on EROA using the conventional PISA 2D method: mild (<0.2 cm2), moderate (0.2-0.39 cm2), severe (0.4-0.59 cm2), massive (0.6-0.79 cm2) and torrential (> 0.8 cm2). The PISA radius was defined as the largest distance in mm between the aliasing edge and the regurgitant orifice (18,20). The uncorrected conventional EROA was calculated using the formula: 6.28 r2 x Va / Vp, where r = PISA radius, Va = aliasing velocity, Vp = maximum TR jet velocity. RegVol by the PISA method was calculated as: EROA x VTIRT, where VTIRT represents the velocity-time integral of the TR jet continuous wave Doppler tracing. Corrected EROA (EROAc), which takes into account the angle of the TV leaflets (α) and the low jet velocities was calculated as: $6{,}28\ \mathrm{r2} \times \mathrm{Va} \times \left(\frac{\alpha}{180}\right) \times \frac{\frac{\mathrm{Vp}}{\mathrm{Vp}} - \mathrm{Va}}{\mathrm{Vp}}$, where α is the angle determined by the TV cusps. α was measured after removing the color Doppler signal in the same frame in which the PISA radius was calculated. The RegVol by the quantitative 3DE volumetric method (3DEV) = the total RV stroke volume (SV) - total LV SV (30,38), EROA by 3DEV = RegVol / VTIRT, and RegF = RegVol / RV SV (39).

Continuous variables were expressed as median and inter-quartile range (IQR), and categorical variables as numbers or percentages. Categorical and continuous variables were compared using the Chi2 test and the Kruskal-Wallis test. Bland-Altman graphs were plotted to test the accuracy of the calculations using the conventional PISA method and the corrected one with 3DEV. Cohen's K statistic was used to test the agreement between the conventional and the corrected PISA methods and 3DEV used for FTR severity grading. ROC analysis was used to determine the ability of TV characteristics to predict a change in FTR severity. A p value <0.05 was considered statistically significant.

RESULTS

A total of 180 patients were analyzed. We excluded 35 patients due to incomplete TTE examination or inadequate datasets, and 43 due to more than mild mitral and/or aortic insufficiency. The final study cohort consisted of 102 patients divided into 5 groups according to 3DEV EROA. Mild, moderate, severe, massive and torrential FTR were found in 23%, 44%, 15%, 8% and 10% of patients, respectively. No significant differences were observed between the parameters describing LV size and function between the 5 groups. In contrast, the parameters reflecting the geometry of the right heart chambers and the TA were significantly higher, and the RV ejection fraction significantly lower with increasing FTR severity.

Both RegVol by the corrected PISA method (RegVolc) (median = 25 mL, IQR = 5-45 mL) and EROAc (median =.29 cm2, IQR = .03-.55 cm2) were significantly higher than RegVol (median = 19 mL, IQR = 4-33 mL, p <.001) and EROA (median =.22 cm2, IQR =.01-.44 cm2, p <.001). However, PISA underestimated both 3DEV RegVol (median = 28mL, IQR = 9-47 mL, p <.001) and EROA (median =.34, IQR =.06-.62 cm2, p <.001). Bland-Altman graphs showed that RegVolc (bias = -3.7 mL, limits of agreement, LOA = ± 2.8 mL) and EROAc (bias = -0.05 cm2, LOA = ± 0.03 cm2) were more similar to RegVol and EROA calculated by 3DEV than RegVol (bias = -11.3 mL, LOA = ± 13.9 mL) and EROA (bias = -.16 cm2, LOA = ± .30 cm2) by the conventional PISA method. Moreover, EROAc (r = .972) and RegVolc (r = .965) were more closely correlated with the corresponding measurements obtained using 3DEV (p <.05) than EROA (r = .943) and RegVol (r = .921).

Correcting the PISA method by including in the calculation formula the TV tethering angle and the TR jet velocity resulted in a change in FTR severity grading in 38/102 (37%, p <.001) of the patients. Using the parameters obtained by the corrected PISA method resulted in a significant increase in the sensitivity (93.8% [95% CI, 79.7% - 99.2%]), negative predictive value (97.2% [95% CI, 90% - 99.2%]) and the accuracy (98% [95% CI, 93.1% - 99.7%]) of identifying

patients with severe RTF (p <0001 for all), while the specificity and the positive predictive value remained unchanged.

DISCUSSIONS

To the best of our knowledge, our study is the first to evaluate the relative accuracy and clinical impact of RegVol and EROA by the conventional PISA method and the corrected PISA method compared to the volumetric 3DE method by including the impact of TV geometry and FTR flow velocity in FTR severity grading. The results of our study can be summarized as follows: (i) the conventional PISA method underestimated the severity of FTR in 37% of patients; (ii) the correction of the PISA formula improved the concordance between the RegVol and EROA calculated using PISA and 3DEV; (iii) the change in FTR severity was mainly in patients with more than mild FTR.

Current guidelines recommend the 2D PISA method for calculating EROA and RegVol in patients with FTR (18,20). This has led to an underestimation of FTR severity in many patients (40–43), which in turn affects both their prognostic stratification (30,44), and delays the moment of TV intervention (32,45). In our patients EROA and RegVol calculated by the conventional PISA method were 24% and 25% lower than those obtained by 3DEV. By correcting the conventional PISA method for the TV leaflet angle and TR jet velocity, we obtained a significantly better agreement between EROA and RegVol calculated by PISA and 3DEV, with minimal bias and narrow LOA between the two methods. The changes were also clinically significant as they reclassified 37% of our patients, being more frequent in patients with more than mild FTR compared to those with mild FTR (44% versus 27%, respectively; p <.001). This is probably related to the foreseeable increase in the degree TV leaflets restriction and decrease in TR jet velocity in more severe degrees of FTR. Consequently, we obtained that the tenting height, the tenting area and the TV angle above 5.5mm, 1.42cm2 and 217.5° respectively predicts the underestimation of FTR severity by the conventional PISA method.

Finally, our results showing that by the conventional PISA method, both EROA and VolReg are significantly underestimated compared to the corrected PISA method. This might explain the different EROA and RegVol threshold values associated in studies with an negative prognosis in patients with FTR (39,46,47). The use of a corrected formula instead of a fixed correction factor to calculate EROA and RegVol by PISA is essential due to the different degree of TV leaflets tethering in the two phenotypes of FTR (18), and the wide range of RV systolic function that may affect the velocity of the FTR jets.

AUTOMATED LEFT ATRIAL VOLUME AND FUNCTION BY TWO-DIMENSIONAL SPECKLE-TRACKING ECOCARDIOGRAPHY

HYPOTHESIS AND GENERAL OBJECTIVES

LA size and function are key parameters for assessing LV diastolic function (48). Current guidelines recommend quantifying LA volumes by 2DE using either the disc summation method (MOD) or the area-length method, and evaluating LA function by Doppler echocardiography (38). However, using the recommended algorithm, a variable percentage of patients (between 8% and 21%) are classified as having indeterminate diastolic function (49–51), and LV diastolic function evaluation is even more difficult in patients with AF. The LA strain measured by 2DSTE is a relatively new parameter used for LA function assessment, showing increased clinical utility. The LA global longitudinal strain during the reservoir phase has been proposed as a way to reduce the number of patients with indeterminate diastolic function (50,52,53).

A by-product of the 2DSTE analysis of the LA is the automated LA Vmax measurement. However, the feasibility and accuracy of the automated LA Vmax measurement by 2DSTE have never been demonstrated. Therefore, the objectives of this study were: (i) to assess the feasibility of automated LA Vmax measurement by 2DSTE; (ii) to compare the LA Vmax values automatically obtained by 2DSTE with the conventional measurements by 2DE MOD and 3DE;

and (iii) to analyze the accuracy and reproducibility of the three echocardiographic methods used to measure LA Vmax.

RESEARCH METHODOLOGY

We prospectively enrolled 210 consecutive patients evaluated by clinically-indicated TTE. Inclusion criteria were age>17 years and given informed consent to participate in the study. A subgroup of 26 patients who underwent clinically-indicated CMR on the same day with the TTE evaluation constituted the validation cohort. Echocardiographic images were stored in digital format and all 3DE and STE measurements were performed using the dedicated softwares included in EchoPac v204 (GE, Vingmed). Biplane MOD was used to measure LA Vmax by 2DE, as recommended by current guidelines (30). The geometry of the LA was evaluated using the sphericity index, calculated as the ratio between the LA Vmax measured by 3DE and the volume of a sphere whose diameter is the length of the LA measured in end-systole. All CMR examinations were performed using a 1.5 T scanner (Siemens AVANTO, Erlangen, Germany). LA Vmax was measured by MOD using the CMR 42 software, Circle, Canada, version 5.12.1.

Continuous variables were expressed as median and IQR. Categorical variables were reported as percentages. The differences between LA Vmax obtained by 2DE, 2DSTE, 3DE and CMR were compared by the Wilcoxon rank-sum test. The non-parametric Kendall test was used to analyze the correlations between LA Vmax. Bland-Altman plots were used to assess the agreement between the LA Vmax measurements.

RESULTS

The final study population consisted of 198 patients (94% feasibility of LA STE analysis) with various cardiovascular diseases, and a wide range of LA Vmax values (34-197 mL). The validation cohort consisted of 26 consecutive patients (median age 59 years, IQR = 17-83 years; 21 men) who were examined by TTE and CMR on the same day. LA Vmax by CMR (median = 76 mL, IQR

= 59-89 mL) were similar to LA Vmax by 3DE (median = 72 mL, IQR = 57-87 mL, p = .097). In contrast, 2DE (median = 63mL, IQR = 53-78mL, p <.001) and 2DSTE (median = 63 mL, IQR = 51-76 mL, p <.001) underestimated the LA Vmax by CMR. The TTE and CMR measurements of the LA Vmax were strongly correlated with each other. Bland-Altman analysis showed a similar underestimation of LA Vmax by 2DSTE and 2DE compared to CMR (bias = -9.5 mL, LOA ± 16 mL and -8mL, LOA ± 17 mL). In contrast, the LA Vmax by 3DE were similar to those obtained by CMR (bias = -2mL, LOA ± 10 mL). Therefore, the LA Vmax obtained by 3DE was used as the reference methods for comparing the measurements by 2DE and 2DSTE in the clinical cohort.

In the 198 patients included in the study, LA Vmax obtained by 2DE, 2DSTE and 3DE were closely correlated. The LA Vmax measured by 3DE were significantly higher than those obtained by 2DE and 2DSTE (p <.001 for all). Although the Bland-Altman analysis showed that 2DE and 2DSTE underestimated the LA Vmax compared to 3DE, the LA Vmax measured by 2DE and 2DSTE had similar values. The concordance between the LA Vmax measured by the 3 echocardiographic methods was not influenced by LV function. However, the concordance between 2DE and 2DSTE with 3DE was significantly lower in patients with a more spherical LA geometry than in those with a more elliptical LA. In addition, using either 2DE or 2DSTE for the calculation of LA Vmax did not influence the classification of patients as having mildly dilated, moderately dilated or severely dilated LA.

DISCUSSIONS

To the best of our knowledge, this is the first prospective study evaluating the feasibility, accuracy and reproducibility of the automated LA Vmax measurement by 2DSTE. Our results can be summarized as follows: (i) The automated LA Vmax by 2DSTE was highly feasible in a relatively large cohort of patients with a wide range of LA Vmax values evaluated by clinically-indicated TTE; (ii) The automated LA Vmax by 2DSTE were very similar to

those obtained by MSD 2DE; (iii) although LA Vmax by 2DSTE underestimated LA Vmax by 3DE and CMR, the degree of underestimation was similar to the 2DE MSD; (iv) The automated LA Vmax by 2DSTE had excellent intra- and inter-observer reproducibility.

LA remodeling is a common finding, and a sensitive predictor of negative cardiovascular outcomes in various cardiac diseases such as heart failure with reduced (54) or preserved ejection fraction (55), AF (56), and cardiomyopathies (57). Of the various echocardiographic parameters used to measure LA size, the LA Vmax has the highest diagnostic and prognostic value (30), and the importance of reporting LA function along with LA size has been demonstrated in the recent years. However, the feasibility, accuracy and reproducibility of the automated LA Vmax measurement derived from the 2DSTE analysis of the LA were never reported. Our study showed that LA Vmax by 2DE and 2DSTE had similar values. The use of either 2DE or 2DSTE did not influence the staging of LA dilation. However, LA Vmax calculation by 2DSTE has the same limitations as 2DE because it is based on the same algorithm and assumptions on LA geometry (58). Therefore the LA Vmax by 2DE and 2DSTE were significantly lower than those measured by 3DE. 3DE is not influenced by the assumptions related to the geometry of the LA, and is not affected by the LA shortening that is frequently found in the 2DE examination of the LA (59).

CONCLUSIONS

Correctly defining FTR etiology and distinguishing between the two main FTR phenotypes plays a crucial role in the management and selection of patients for TV interventions. The results of our studies provide the necessary information for elucidating the different pathophysiological cascades involved in the development of A-FTR and V-FTR, as well as important implications on the choice of appropriate therapeutic options and timing for each phenotype. Thus, despite similar degrees of FTR severity and similarly and significantly increased RA Vmax, patients with A-FTR have higher RA Vmin and smaller TA areas than

patients with V-FTR. In addition, patients with A-FTR have normal RV size and function as opposed to patients with V-FTR that have significant RV dilation and dysfunction.

Moreover, although the 2D PISA method is currently recommended in the assessment of FTR severity despite its well-known limitations, our study showed that applying a correction formula that takes into account the distortions in the geometry of the TV and the velocity of the FTR jet can substantially reduce the underestimation of FTR severity, reclassifying its grading in 37% of our patients. Because the change in FTR severity grade occurs significantly more frequently in patients with moderate or severe FTR, the use of the corrected PISA method may have an impact on the management and prognosis of these patients.

Finally, we have shown that, provided the 2DE acquisitions are correct, LA Vmax automatically obtained by the 2DSTE analysis of the LA is highly feasible, highly reproductible, and has similar accuracy with the calculation by conventional 2DE MOD. Our results should motivate echocardiographers in including the evaluation of the LA by 2DSTE in daily routine practice as it might help clinicians in the correct assessment of LV diastolic function in AF and FTR, by simultaneously conferring two robust parameters with demonstrated predictive value – LA size and function.

SELECTIVE BIBLIOGRAPHY

1. Badano LP, Muraru D, Enriquez-Sarano M. Assessment of functional tricuspid regurgitation. European Heart Journal. 2013;34(25):1875–84.
2. Asmarats L, Taramasso M, Rodés-Cabau J. Tricuspid valve disease: diagnosis, prognosis and management of a rapidly evolving field. Nat Rev Cardiol. 2019 Sep;16(9):538–54.
3. Prihadi EA, Delgado V, Leon MB, Enriquez-Sarano M, Topilsky Y, Bax JJ. Morphologic Types of Tricuspid Regurgitation: Characteristics and Prognostic Implications. JACC: Cardiovascular Imaging. 2019;12(3):491–9.

4. Silbiger JJ. Atrial functional tricuspid regurgitation: An underappreciated cause of secondary tricuspid regurgitation. Echocardiography. 2019;36(5):954–7.
5. Muraru D, Guta AC, Ochoa-Jimenez RC, Bartos D, Aruta P, Mihaila S, et al. Functional Regurgitation of Atrioventricular Valves and Atrial Fibrillation: An Elusive Pathophysiological Link Deserving Further Attention. Journal of the American Society of Echocardiography [Internet]. 2020;33(1):42–53. Available from: https://doi.org/10.1016/j.echo.2019.08.016
6. Utsunomiya H, Harada Y, Susawa H, Ueda Y, Izumi K, Itakura K, et al. Tricuspid valve geometry and right heart remodelling: Insights into the mechanism of atrial functional tricuspid regurgitation. European Heart Journal Cardiovascular Imaging. 2020;21(10):1068–78.
7. Guta AC, Badano LP, Tomaselli M, Mihalcea D, Bartos D, Parati G, et al. The pathophysiological link between right atrial remodeling and functional tricuspid regurgitation in patients with atrial fibrillation. A three-dimensional echocardiography study. Journal of the American Society of Echocardiography [Internet]. 2021; Available from: http://www.sciencedirect.com/science/article/pii/S0894731721000067
8. Praz F, Muraru D, Kreidel F, Lurz P, Hahn RT, Delgado V, et al. Transcatheter treatment for tricuspid valve disease. EuroIntervention [Internet]. 2021 Nov;17(10):791–808. Available from: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00695
9. Florescu DR, Muraru D, Florescu C, Volpato V, Caravita S, Perger E, et al. Right heart chambers geometry and function in patients with the atrial and the ventricular phenotypes of functional tricuspid regurgitation. European Heart Journal - Cardiovascular Imaging [Internet]. 2021 Nov 8; Available from: https://doi.org/10.1093/ehjci/jeab211
10. Muraru D, Caravita S, Guta AC, Mihalcea D, Branzi G, Parati G, et al. Functional Tricuspid Regurgitation and Atrial Fibrillation: Which Comes First, the Chicken or the Egg? Case [Internet]. 2020; Available from: https://doi.org/10.1016/j.case.2020.04.011
11. Ortiz-Leon XA, Posada-Martinez EL, Trejo-Paredes MC, Ivey-Miranda JB, Pereira J, Crandall I, et al. Understanding tricuspid valve remodelling in atrial fibrillation using three-dimensional echocardiography. Eur Heart J Cardiovasc Imaging. 2020;21(7):747–55.
12. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, et al. European association of echocardiography recommendations for the assessment of valvular regurgitation. Part 2: Mitral and tricuspid regurgitation (native valve disease). European Journal of Echocardiography. 2010;11(4):307–32.
13. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: An executive summary from the European

Association of Cardiovascular Imaging. European Heart Journal Cardiovascular Imaging. 2013;14(7):611–44.
14. Prihadi EA, Delgado V, Hahn RT, Leipsic J, Min JK, Bax JJ. Imaging Needs in Novel Transcatheter Tricuspid Valve Interventions. JACC: Cardiovascular Imaging. 2018;11(5):736–54.
15. Fukuda S, Saracino G, Matsumura Y, Daimon M, Tran H, Greenberg NL, et al. Three-dimensional geometry of the tricuspid annulus in healthy subjects and in patients with functional tricuspid regurgitation: A real-time, 3-dimensional echocardiographic study. Circulation. 2006;114(SUPPL. 1):492–8.
16. Anwar AM, Geleijnse ML, Soliman OII, McGhie JS, Frowijn R, Nemes A, et al. Assessment of normal tricuspid valve anatomy in adults by real-time three-dimensional echocardiography. International Journal of Cardiovascular Imaging. 2007;23(6):717–24.
17. Florescu DR, Muraru D, Volpato V, Gavazzoni M, Caravita S, Tomaselli M, et al. Atrial Functional Tricuspid Regurgitation as a Distinct Pathophysiological and Clinical Entity: No Idiopathic Tricuspid Regurgitation Anymore. Vol. 11, Journal of Clinical Medicine. MDPI; 2022.
18. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. Journal of the American Society of Echocardiography [Internet]. 2017;30(4):303–71. Available from: http://dx.doi.org/10.1016/j.echo.2017.01.007
19. Hahn RT. State-of-the-art review of echocardiographic imaging in the evaluation and treatment of functional tricuspid regurgitation. Circulation: Cardiovascular Imaging. 2016;9(12):1–15.
20. Zaidi A, Oxborough D, Augustine DX, Bedair R, Harkness A, Rana B, et al. Echocardiographic assessment of the tricuspid and pulmonary valves: a practical guideline from the British Society of Echocardiography. Echo Research and Practice. 2020;7(4):G95–122.
21. Hahn RT, Thomas JD, Khalique OK, Cavalcante JL, Praz F, Zoghbi WA. Imaging Assessment of Tricuspid Regurgitation Severity. JACC: Cardiovascular Imaging. 2019;12(3):469–90.
22. Addetia K, Muraru D, Badano LP, Lang RM. New Directions in Right Ventricular Assessment Using 3-Dimensional Echocardiography. JAMA Cardiology. 2019;4(9):936–44.
23. Kabasawa M, Kohno H, Ishizaka T, Ishida K, Funabashi N, Kataoka A, et al. Assessment of functional tricuspid regurgitation using 320-detector-row multislice computed tomography: Risk factor analysis for recurrent regurgitation after tricuspid annuloplasty. Journal of Thoracic and Cardiovascular Surgery [Internet]. 2014;147(1):312–20. Available from: http://dx.doi.org/10.1016/j.jtcvs.2012.11.017

24. Lopes BBC, Hashimoto G, Bapat VN, Sorajja P, Scherer MD, Cavalcante JL. Cardiac Computed Tomography and Magnetic Resonance Imaging of the Tricuspid Valve: Preprocedural Planning and Postprocedural Follow-up. Interventional Cardiology Clinics. 2022 Jan;11(1).
25. Agricola E, Asmarats L, Maisano F, Cavalcante JL, Liu S, Milla F, et al. Imaging for Tricuspid Valve Repair and Replacement. JACC: Cardiovascular Imaging. 2021;14(1):61–111.
26. Muraru D, Addetia K, Guta AC, Roberto C, Genovese D, Veronesi F, et al. Right atrial volume is a major determinant of tricuspid annulus area in functional tricuspid regurgitation: a three-dimensional echocardiographic study. European Heart Journal - Cardiovascular Imaging. 2020;i:1–9.
27. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal. 2016;37(1):67–119.
28. Muraru D, Onciul S, Peluso D, Soriani N, Cucchini U, Aruta P, et al. Sex- and method-specific reference values for right ventricular strain by 2-dimensional speckle-tracking echocardiography. Circulation: Cardiovascular Imaging. 2016;9(2):1–9.
29. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography. Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and . Journal of the American Society of Echocardiography [Internet]. 2010;23(7):685–713. Available from: http://dx.doi.org/10.1016/j.echo.2010.05.010
30. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American society of echocardiography and the European association of cardiovascular imaging. European Heart Journal Cardiovascular Imaging. 2015;16(3):233–71.
31. Topilsky Y, Khanna A, le Toumeau T, Park S, Michelena H, Suri R, et al. Clinical context and mechanism of functional tricuspid regurgitation in patients with and without pulmonary hypertension. Circulation: Cardiovascular Imaging. 2012;5(3):314–23.
32. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. European Heart Journal [Internet]. 2021 Aug 28; Available from: https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab395/6358470
33. Badano LP, Hahn R, Zanella H, Araiza Garaygordobil D, Ochoa-Jimenez RC, Muraru D. Morphological Assessment of the Tricuspid Apparatus and Grading Regurgitation Severity in Patients With Functional Tricuspid

Regurgitation: Thinking Outside the Box. JACC: Cardiovascular Imaging. 2019;12(4):652–64.
34. Rodriguez L, Anconina J, Flachskampf FA, Weyman AE, Levine RA, Thomas JD. Impact of Finite Orifice Size on Proximal Flow Convergence. Implications for Doppler Quantification of Valvular Regurgitation [Internet]. Vol. 70, Circulaion Research. 1992. Available from: http://ahajournals.org
35. Pu M, Vandervoort PM, Griffin BP, Leung DY, Stewart WJ, Cosgrove DM, et al. Quantification of Mitral Regurgitation by the Proximal Convergence Method Using Transesophageal Echocardiography. Circulation [Internet]. 1995 Oct 15;92(8):2169–77. Available from: https://doi.org/10.1161/01.CIR.92.8.2169
36. Rivera JM, Vandervoort PM, Mele D, Siu S, Morris E, Weyman AE, et al. Quantification of tricuspid regurgitation by means of the proximal flow convergence method: A clinical study. American Heart Journal. 1994;May:1354–62.
37. Lang RM, Badano LP, Tsang W, Adams DH, Agricola E, Buck T, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. European Heart Journal Cardiovascular Imaging. 2012;13(1):1–46.
38. Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. European Heart Journal Cardiovascular Imaging. 2017;18(12):1342–3.
39. Muraru D, Previtero M, Ochoa-Jimenez RC, Guta AC, Figliozzi S, Gregori D, et al. Prognostic validation of partition values for quantitative parameters to grade functional tricuspid regurgitation severity by conventional echocardiography. European Heart Journal Cardiovascular Imaging. 2021;22(2):155–65.
40. Hahn RT, Meduri CU, Davidson CJ, Lim S, Nazif TM, Ricciardi MJ, et al. Early Feasibility Study of a Transcatheter Tricuspid Valve Annuloplasty: SCOUT Trial 30-Day Results. J Am Coll Cardiol. 2017;69(14):1795–806.
41. Grossmann G, Stein M, Kochs M, Hö M, Koenig W, Hombach V, et al. Comparison of the proximal flow convergence method and the jet area method for the assessment of the severity of tricuspid regurgitation. Vol. 19, European Heart Journal. 1998.
42. Chen TE, Kwon SH, Enriquez-Sarano M, Wong BF, Mankad S v. Three-dimensional color doppler echocardiographic quantification of tricuspid regurgitation orifice area: Comparison with conventional two-dimensional measures. Journal of the American Society of Echocardiography. 2013 Oct;26(10):1143–52.
43. Abdellaziz D, Geraldine O, Nadira H, Eleonora A, Jing Y, T HR. Quantifying Tricuspid Regurgitation Severity. JACC: Cardiovascular Imaging [Internet]. 2019 Mar 1;12(3):560–2. Available from: https://doi.org/10.1016/j.jcmg.2018.11.015

44. Wang N, Fulcher J, Abeysuriya N, McGrady M, Wilcox I, Celermajer D, et al. Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: A systematic review and meta-analysis. European Heart Journal. 2019;40(5):476–84.
45. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021 Feb 2;77(4):450–500.
46. Peri Y, Sadeh B, Sherez C, Hochstadt A, Biner S, Aviram G, et al. Quantitative assessment of effective regurgitant orifice: Impact on risk stratification, and cut-off for severe and torrential tricuspid regurgitation grade. European Heart Journal Cardiovascular Imaging. 2020;21(7):768–76.
47. Bartko PE, Arfsten H, Frey MK, Heitzinger G, Pavo N, Cho A, et al. Natural History of Functional Tricuspid Regurgitation: Implications of Quantitative Doppler Assessment. JACC: Cardiovascular Imaging. 2019 Mar 1;12(3):389–97.
48. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American society of echocardiography and the European association of cardiovascular imaging. European Heart Journal Cardiovascular Imaging [Internet]. 2016;17(12):1321–60. Available from: http://dx.doi.org/10.1016/j.echo.2016.01.011
49. Singh A, Addetia K, Maffessanti F, Mor-Avi V, Lang RM. LA Strain for Categorization of LV Diastolic Dysfunction. JACC: Cardiovascular Imaging. 2017;10(7):735–43.
50. Morris DA, Belyavskiy E, Aravind-Kumar R, Kropf M, Frydas A, Braunauer K, et al. Potential Usefulness and Clinical Relevance of Adding Left Atrial Strain to Left Atrial Volume Index in the Detection of Left Ventricular Diastolic Dysfunction. JACC: Cardiovascular Imaging. 2018;11(10):1405–15.
51. Inoue K, Khan FH, Remme EW, Ohte N, García-Izquierdo E, Chetrit M, et al. Determinants of left atrial reservoir and pump strain and use of atrial strain for evaluation of left ventricular filling pressure. European Heart Journal - Cardiovascular Imaging. 2021;1–10.
52. Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left Atrial Structure and Function, and Left Ventricular Diastolic Dysfunction: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;73(15):1961–77.
53. Thomas L, Muraru D, Popescu BA, Sitges M, Rosca M, Pedrizzetti G, et al. Evaluation of Left Atrial Size and Function: Relevance for Clinical Practice. Journal of the American Society of Echocardiography [Internet].

2020;33(8):934–52. Available from: https://doi.org/10.1016/j.echo.2020.03.021
54. Carluccio E, Biagioli P, Mengoni A, Francesca Cerasa M, Lauciello R, Zuchi C, et al. Left Atrial Reservoir Function and Outcome in Heart Failure With Reduced Ejection Fraction. Circ Cardiovasc Imaging. 2018;11(11):e007696.
55. Reddy YNV, Obokata M, Egbe A, Yang JH, Pislaru S, Lin G, et al. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. European Journal of Heart Failure. 2019;21(7):891–900.
56. Cameli M, Mandoli GE, Loiacono F, Sparla S, Iardino E, Mondillo S. Left atrial strain: A useful index in atrial fibrillation. International Journal of Cardiology [Internet]. 2016;220:208–13. Available from: http://dx.doi.org/10.1016/j.ijcard.2016.06.197
57. Debonnaire P, Joyce E, Hiemstra Y, Mertens BJ, Atsma DE, Schalij MJ, et al. Left atrial size and function in hypertrophic cardiomyopathy patients and risk of new-onset atrial fibrillation. Circulation: Arrhythmia and Electrophysiology. 2017;10(2):1–10.
58. Mor-Avi V, Yodwut C, Jenkins C, Khl H, Nesser HJ, Marwick TH, et al. Real-time 3D echocardiographic quantification of left atrial volume: Multicenter study for validation with CMR. JACC: Cardiovascular Imaging. 2012;5(8):769–77.
59. Surkova E, Muraru D, Aruta P, Romeo G, Bidviene J, Cherata D, et al. Current Clinical Applications of Three-Dimensional Echocardiography: When the Technique Makes the Difference. Current Cardiology Reports [Internet]. 2016;18(11):109. Available from: https://doi.org/10.1007/s11886-016-0787-9