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Functional tricuspid regurgitation and efficacy of electrical cardioversion in patients with atrial fibrillation and atrial functional mitral regurgitation

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ABSTRACT

Introduction: *Atrial functional mitral regurgitation (afMR) is common in patients with atrial fibrillation (AF). The presence of functional tricuspid regurgitation (fTR), which arises as a secondary effect of afMR, has the potential to impact the effectiveness of procedures aimed at restoring normal heart rhythm. In this study, we sought to evaluate the efficacy of electrical cardioversion (CVE) in AF regarding the presence and degree of fTR in patients with afMR.*

Material and methods: *Retrospective analysis included 521 patients with persistent AF on optimal medical therapy undergoing CVE. 157 (30.1%) patients had afMR (characterized by left ventricle ejection fraction ≥ 50% and LA dilatation) and were divided into 2 groups: the group with fTR (107, 68.2%) and the group without fTR (50, 31.9%).*

Results: *Patients with afMR and fTR had a higher prevalence of metabolic syndrome ($p = 0.02$) and greater right atrial area ($p < 0.01$) compared to patients without fTR. The efficacy of CVE was lower in the group with fTR in comparison to patients with isolated afMR (82.2% vs. 94%; $p = 0.048$) and it was unrelated to the degree of fTR ($p = 0.15$) and RVSP ($p = 0.56$). The energy required for successful CVE was comparable regardless of the presence ($p = 0.26$) or severity of fTR ($p = 0.94$).*

Conclusions: *The fTR frequently coexists with afMR and it significantly diminishes the effectiveness of CVE for treating AF. The degree of fTR does not appear to influence the efficacy of CVE.*

Keywords: electrical cardioversion; atrial fibrillation; functional tricuspid regurgitation; atrial functional mitral regurgitation

Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia [1]. Uncoordinated atrial activity causes atrial emptying disorder with increased atrial pressure, atrial enlargement, therefore, fibrosis and remodeling disrupts atrial electrical function. These functional and morphological changes cause secondary dilatation of the annulus and impaired coaptation of the valve leaflet [2–5], which leads to functional regurgitation of both atrioventricular valves [6].

Current recommendations distinguish atrial functional mitral regurgitation (afMR) - a type of functional MR secondary to left atrial (LA) disease — typically in the setting of AF without left ventricular (LV) dilatation and primary mitral valve disease [2]. Moreover, afMR and its regurgitant jet induce LA remodeling and development of this arrhythmia [7].

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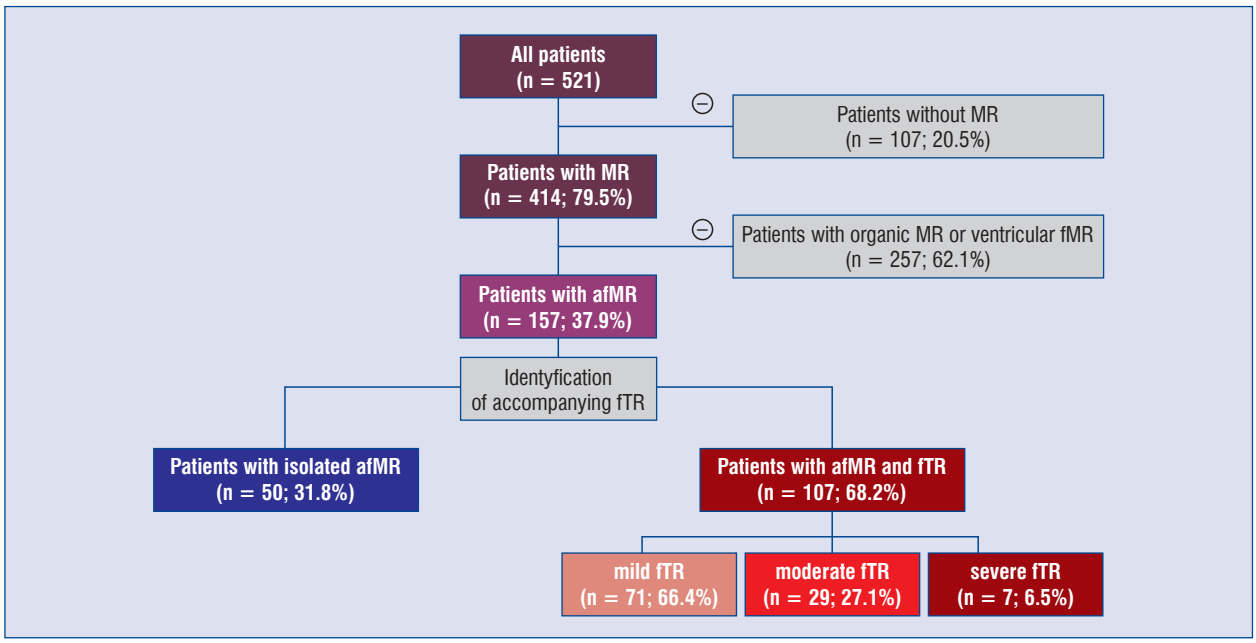

Figure 1. A diagram representing the course of the study. MR — mitral regurgitation; afMR — atrial functional mitral regurgitation, fTR — functional tricuspid regurgitation.

Similarly functional tricuspid regurgitation (fTR) can be caused by chronic AF [6]. However, afMR may underlie fTR. The regurgitant flow over the mitral valve causes pressure overload of the right ventricle (RV), annular dilatation and tethering of the tricuspid valve [8]. TR is an independent risk factor for higher mortality [9] and fTR is related to higher prevalence of right-sided heart failure in a group of patients with chronic AF [10]. More and more attention has been drawn to early indications for tricuspid valve surgery given the serious burden it carries. However, they are still not well established and are applied to patients undergoing left-sided valve surgery or to patients with severe fTR who are symptomatic/ /have RV dilatation [11]. In contrast, ways to treat non-severe or asymptomatic fTR are limited and concern on diuretic treatment or management of PH [12, 13]. More consideration is being given to AF rhythm-control therapy not only because it alleviates symptoms of AF and lowers the risk of adverse outcomes, as confirmed by the EAST--AFNET-4 study [14], but also in order to prevent atrial and annular remodeling [15].

In a previously published study, the relationship between afMR and persistent AF showing that the efficacy of electrical cardioversion (CVE) does not depend on the presence of afMR [16] was discussed. Given the many possible relationships between these pathologies and the paucity of evidence in the literature the present study wanted to verify the co-occurrence of afMR and fTR as well as the efficacy of CVE in AF, which is an effective method when it comes to restoring sinus rhythm (SR) [17].

Material and methods

A retrospective analysis included reviewing the medical records of 521 consecutive patients with persistent AF on optimal medical therapy (OMT) undergoing CVE. Patients were hospitalized between January 2019 – July 2022 at the First Department of Cardiology in Upper-Silesian Medical Center in Katowice. The study follows the principles of the Declaration of Helsinki. All authors have contributed to preparing the manuscript in accordance with the International Committee of Medical Journal Editors (ICMJE) criteria for authorship and obtained Ethics Committee approval ad review for retrospective analysis of data. Based on transthoracic echocardiography (TTE) 414 (79.5%) patients had MR. The analysis distinguished 157 (37.9%) subjects (aged: 67.1 ± 7.8) who met all inclusion (afMR with persistent AF on OMT) and exclusion criteria (organic MR/TR, severe fMR, massive/torrential fTR, LV dysfunction, acute coronary syndrome, congenital heart defect, infective endocarditis, previous heart operation and patients scheduled for valve surgery).

The main objective was to evaluate the comorbidity of fTR along with afMR. Thus, in a group of 157 subjects, 50 (31.8%) patients had isolated afMR, while 107 (68.2%) had accompanying fTR. An additional aim was to evaluate the severity of fTR in a group of 150 patients with fTR and afMR: 71 (66.4%) had mild, 29 (27.1%) moderate and 7 (6.5%) severe degree of fTR (Fig. 1).

Data collection

A retrospective database was created from electronic medical records that included information on patient demographics, comorbidities, risk factors, TTE parameters, and CVE procedure: efficacy — defined as the restoration of SR, the amount of energy required for the procedure and the pharmacological treatment in relation to the presence and degree of fTR.

Definitions

The criterion for the diagnosis of persistent AF was a duration of more than 7 days. Patients with fMR included those in whom organic MR was excluded.

The afMR was defined as fMR without LV dysfunction, with regurgitation caused by atrial dilatation, consequent mitral annular dilatation and inadequate leaflet remodeling. The following echocardiographic criteria were used: 1) normal LV systolic function (LVEF ≥ 50%), 2) normal leaflet motion, 3) central jet, and 4) LA dilatation.

The fTR was characterized by the presence of TR with structurally normal leaflets and chordae, RV volume and/or pressure overload, RV and/or RA dilatation and dysfunction, tricuspid leaflet tethering or tricuspid annular dilatation.

The presence and severity of the fTR was determined by the distal fTR jet area. A mild fTR was defined as a fTR with a distal jet area < 5 cm^2, moderate fTR $\geq 5 - <$ 10 cm^2 and a severe fTR with distal jet area ≥ 10 cm^2.

CVE failure was defined as failure to achieve SR, immediate recurrence or presence of AF while discharge.

Increased RVSP was defined as RVSP > 35 mmHg after substituting into simplified Bernoulli equation a tricuspid regurgitant jet velocity > 2.8 m/s, which increases the risk of pulmonary hypertension (PH), with RA pressure assumed as 5 mmHg.

Kidney failure was defined as an estimated Glomerular Filtration Rate (eGFR) level below 60 mL/min/1.73 m^2.

Metabolic syndrome (MetS) was defined according to the IDF [18]. Patients with drug treatment targeting a given component of the MetS were considered as "treated," regardless of normal values and alignment after treatment initiation. Waist circumference was replaced by the value of body mass index (BMI) due to the retrospective nature of the study. BMI ≥ 25 kg/m^2 was considered to meet the criterion of increased waist circumference.

CVE procedure

Each CVE procedure was performed by an experienced physician under short-term intravenous anesthesia in order to achieve SR (or further attempts to restore it have been abandoned). The starting value of energy used in CVE was 150J and then increased to 200J and then to 360J if needed. No additional antiarrhythmic drugs were administered. CVE was considered successful if sinus rhythm was restored immediately after the procedure and maintained until discharge.

Statistical analysis

To analyze the distribution for quantitative data, the Shapiro-Wilk test was used. Quantitative data with normal distribution were compared using the Student t test and presented as mean ± standard deviation (SD). Quantitative data with a skewed distribution were compared using the Mann-Whitney U test and presented as medians. Chi-square test was used to analyze qualitative data in 3 groups (analysis of the efficacy and amount of energy used for CVE regarding fTR's severity). Statistical significance of qualitative values was determined by Pearson's Chi-2 test. Correlation between increased RVSP and amount of energy required for successful CVE was performed using the Spearman Rank Correlation test. Statistical significance was considered for p-values < 0.05. The analysis was performed with STATISTICA 13.3 PL Software by StatSoft, Medical University of Silesia, Katowice.

Results

Taking into consideration age, height, weight, body surface area (BSA) and body mass index (BMI) of patients with isolated afMR and afMR with fTR (Table 1), there were no statistically significant differences between groups.

The occurrence of hypertension, DM, kidney failure, stroke and transient ischemic attack (TIA), coronary heart disease and current smoking was similar. Considering comorbidities and other risk factors, metabolic syndrome was significantly more frequent in the group with afMR with fTR ($p = 0.02$) (Table 1).

Table 1. Baseline characteristics and comparison of comorbidities and risk factors between groups of patients with isolated afMR and afMR and fTR. afMR — atrial functional mitral regurgitation; fTR — functional tricuspid regurgitation; COPD — chronic obstructive pulmonary disease; TIA — transient ischemic attack; DM — diabetes mellitus

	Isolated afMR (n = 50)	afMR with fTR (n = 107)	p-value
Age [y]	65.6 (± 7.3)	67.7 (± 8)	0.06
Female	18 (36%)	48 (44.9%)	0.29
Height [cm]	172.2 (± 10)	168.2 (± 13.7)	0.12
Weight [kg]	91.2 (± 14.7)	86.9 (± 16.8)	0.07
BSA [m^2]	2.1 (± 0.2)	2 (± 0.2)	0.17
BMI (kg/m^2)	30.8 (± 4.7)	30.3 (± 4.8)	0.52
Concomitant diseases			
COPD	2 (4%)	6 (5.6%)	0.31
History of stroke/TIA	4 (8%)	14 (13.1%)	0.35
Current smoking	9 (18%)	21 (19.6%)	0.81
Hypertension	43 (86%)	91 (85.1%)	0.87
Coronary heart disease	7 (14%)	19 (17.8%)	0.56
DM	15 (30%)	25 (23.4%)	0.37
Metabolic syndrome	20 (40%)	64 (59.8%)	0.02
Kidney failure	8 (16%)	25 (23.4%)	0.29

Table 2. Comparison of echocardiographic parameters between patients with isolated afMR and afMR with fTR. afMR — atrial functional mitral regurgitation; fTR — functional tricuspid regurgitation

	Isolated afMR (n = 50)	afMR with fTR (n = 107)	p-value
LA diameter [mm]	44.1 (± 4.8)	44 (± 4.7)	0.81
LA area [cm^2]	24.7 (± 6.5)	25.8 (± 4.9)	0.07
LV EDD [mm]	50.6 (± 4.5)	50.1 (± 5.5)	0.67
LV ESD [mm]	31.3 (± 5)	30.7 (± 5.2)	0.43
LV EF [%]	55.6 (± 4.6)	54.9 (± 3.4)	0.42
RA area [cm^2]	18.4 (± 3)	20.7 (± 4.5)	0.003
prox-RVOT [cm]	30.2 (± 3.2)	30.9 (± 3.9)	0.37
V-max TR [m/s]	0.6 (± 0.1)	0.6 (± 0.5)	0.54

Groups were comparable considering the results of selected laboratory tests: hemoglobin, white blood count, potassium, LDL, total cholesterol, TSH.

Regarding the selected TTE parameters (Table 2), a statistically significant difference occurred in the RA area, which presumed greater values in patients with afMR with fTR ($p = 0.003$) in comparison to patients with isolated afMR. Other parameters were comparable in both groups. However, in both groups mean values of proximal RVOT exceed the upper limit.

The comparison of the pharmacotherapy did not reveal any significant differences between group of patients with isolated afMR in comparison to patients with afMR and fTR (Table 3).

Efficacy of CVE in study groups

The efficacy of CVE was high and reached 94% in a group of patients with isolated afMR and 82.2% in patients with afMR and fTR. The comparison between groups revealed a statistically significant difference with $p = 0.048$ (Fig. 2).

Table 3. Comparison of drugs used after hospitalization between groups of patients with isolated afMR and afMR with fTR. afMR — atrial functional mitral regurgitation; fTR — functional tricuspid regurgitation

	Isolated afMR (n = 50)	afMR with fTR (n = 107)	p-value
Diuretics	36 (72%)	71 (66.4%)	0.48
Antiarrhythmics — all	26 (52%)	52 (48.6%)	0.69
Digoxin	1 (2%)	3 (2.8%)	0.77
Sotalol	4 (8%)	6 (5.6%)	0.56
Propafenone	4 (8%)	8 (7.5%)	0.91
Amiodarone	17 (34%)	35 (31.8%)	0.87
β-blockers	40 (80%)	85 (79.4%)	0.94
Anticoagulants — all	50 (100%)	107 (100%)	–
ACEI	22 (44%)	52 (48.6%)	0.59
ARB	14 (28%)	21 (19.6%)	0.24

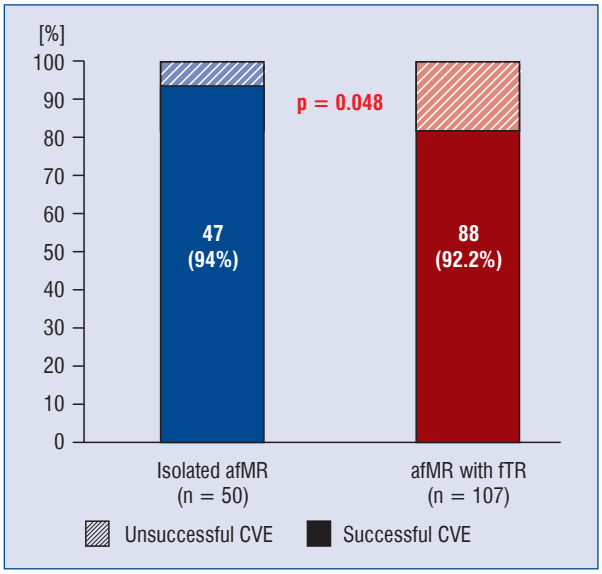

Figure 2. Comparison of the efficacy of CVE between groups of patients with isolated afMR and with afMR and fTR. afMR — atrial functional mitral regurgitation; fTR — functional tricuspid regurgitation; CVE — electrical cardioversion

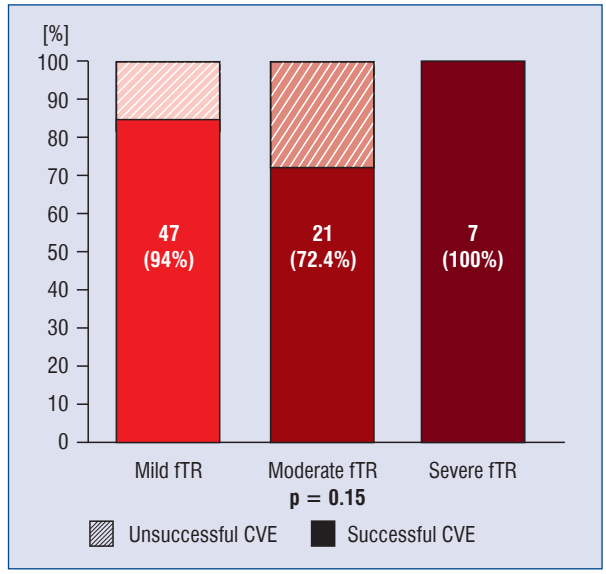

Figure 3. Comparison of CVE results between groups of patients with mild, moderate and severe degree of fTR in a group of patients with afMR and fTR. afMR — atrial functional mitral regurgitation; fTR — functional tricuspid regurgitation; CVE — electrical cardioversion

Among patients with afMR and fTR efficacy of CVE was comparable (p = 0.15) and equaled 84.5% in a group of patients with mild fTR, 72.4% with moderate and 100% in a group of patients with severe degree of fT (Fig. 3).

The amount of energy required for successful CVE did not differ between groups irrespective of presence (p = 0.26), as well as the degree of fTR.

There were no statistically significant differences in the number of patients with or without increased RVSP, in a group of patients with afMR and fTR (p = 0.56) (Fig. 4) and there was no statistically significant correlation between RVSP and the amount of energy required for successful cardioversion in this group (R = –0.12; p = 0.47).

Discussion

Clinical implications

The study presented herein is a continuation of our previous research and summarizes the results of an extensive 3-year experience in performing

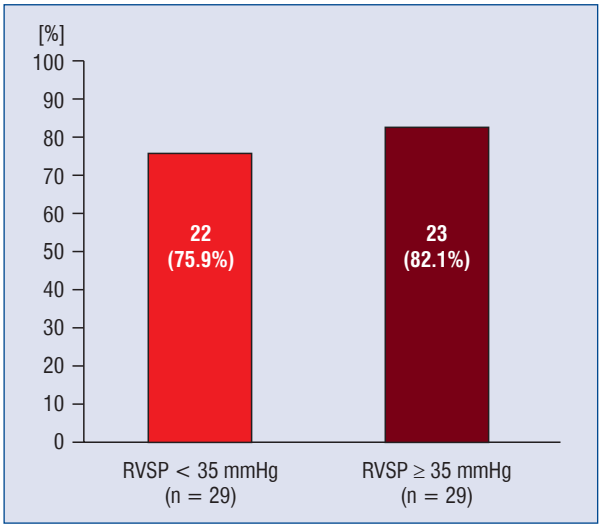

Figure 4. Efficacy of CVE in a group of patients with afMR and fTR in relation to increased RVSP. afMR — atrial functional mitral regurgitation; fTR — functional tricuspid regurgitation; CVE — electrical cardioversion; RVSP — right ventricular systolic pressure

CVE [16]. It shows that afMR is a common finding in patients undergoing CVE of persistent AF and in up to 68% of cases are accompanied by fTR. Studies summarizing a coincidence of both atrioventricular valves regurgitation in AF are still limited and inconsistent. Researchers showed that among patients with AF and preserved LVEF 3.7% patients had both significant afMR and atrial fTR (afTR) [19]. Another study showed that 88% of patients with AF and significant fTR had mild or moderate MR [10]. Currently the number of patients with AF is growing [20], it can therefore be predicted that there will be an increase in both afMR and fTR prevalence.

Attention in the present study was focused on the patients who were not feasible for mitral or tricuspid valve intervention due to the severity of regurgitation, high surgical risk or comorbidities. Patients with severe fMR eligible for cardiac surgery were excluded from the study. Patients undergoing Mitraclip procedure were not analyzed. The study population consisted of patients well prepared for CVE on OMT with a good chance of restoring sinus rhythm. Patients with afTR and afMR caused by AF may benefit more from the strategy of maintaining SR [2, 4]. A month of SR after CVE improves atrial asynchrony, reduces atrial volumes and decreases MR jet area [21] whereas surgical ablation of AF reduces TR progression and right-sided remodeling in patients undergoing mitral valve procedure [22].

Attention to the efficacy of CVE remained due to the unquestionable importance of maintaining SR among those patients. Taking into consideration that treatment options for a patient with non-severe fTR are rather limited, the current study highlights the need to be more vigilant in relation to the applied treatment - especially since the presence of fTR in a group of patients with afMR affects the efficacy of CVE.

Efficacy of ECV

The rate of successful CVEs was high in both groups, reaching 94% in patients with isolated afMR and 82.2% in patients with afMR and fTR. Evaluation of studies regarding the efficacy of CVE is compromised given the multitude of variables affecting the final outcome, however, previous research regarding persistent AF have shown comparable success rates of elective CVE to those presented in the present study [23–26].

It was demonstrated that patients with afMR undergoing CVE of AF who additionally present with fTR have an increased risk of CVE failure. This group showed a favorable trend to a higher mean age, but this difference was not statistically significant ($p = 0.06$). Age of the patient has not been demonstrated to alter the immediate efficacy of the procedure [27], however, it is an important risk factor for the development of severe fTR among patients with AF, which underlines the importance of early intervention in order to prevent the adverse effects of severe fTR [10].

In the current study, RAA was statistically significantly greater in a group with afMR and fTR, where efficacy of CVE was lower. In patients with normal LV function, AF resulted in a greater dilatation of tricuspid annulus rather than mitral annulus, which may indicate a more pronounced impact on RA enlargement [28]. To date, right atrial volume has been proven to be a predictor of AF recurrence in the setting of radiofrequency ablation and might reflect chronicity of disease [29]. Smaller RAA was an independent factor for maintaining SR after 4 weeks of CVE [30]. In contrast, no study was found indicating a direct negative effect of RA enlargement on the effectiveness of CVE in the short term. Further investigation of this parameter would be advisable.

Mean LA diameter values were beyond the upper limit as a consequence of the study design. A tendency was noted however, it did not reach statistical significance ($p = 0.07$), to greater LA area in the group of patients with afMR and fTR. LA enlargement has been proven to increase the

recurrence of AF at long-term follow-up [31, 32] with LA diameter > 4.5 cm being a risk factor for ≥ 2 CVEs in the first year [33]. A potential reason for the present results could have been a more severe degree of afMR with a greater jet volume, as noted by the fact that LA enlargement is correlated with mitral annulus size [34]. However, in a previous study it was proved that type of fMR does not affect the efficacy of the procedure [16].

Despite no difference in BMI between the groups, patients with isolated afMR showed a tendency, but it was not statistically significant ($p = 0.07$), to have a higher body weight. Body weight < 80 kg was proved to be an independent predictor of successful CVE [30]. In both groups, it surpassed this value while, paradoxically, the group with higher efficacy of CVE had a greater mean body mass value. It was believed that this was a single entity and had no impact on the relevance of the final result, especially because the other study showed that SR restoration does not depend on BMI [35].

On the other hand, the analysis showed a greater incidence of MetS in patients with afMR and fTR ($p = 0.02$). MetS is strongly associated with development of AF through electrical or structural remodeling [36]. Despite comparable incidence of the individual components of MetS the final outcome could be determined by cumulative impact of more complex mechanisms, as supported by the fact that role of increased levels of adiponectin, TNF-alpha or leptin signaling has been proved in the pathogenesis of persistent AF [37–39]. Therefore, further analysis may be intriguing in the context of the efficacy of CVE.

In the present research, none of the patients were already diagnosed with PH by right heart catheterization but in some cases TTE showed single parameters suggesting PH. The presence of fTR may be an exponent of pulmonary overload and in patients with chronic AF is related to a higher prevalence of right-sided heart failure [10, 40]. AF is common in patients with PH, worsens its prognosis, results in higher mortality and leads to right ventricle failure [41]. The efficacy of CVE in a group with afMR and fTR did not differ regarding increased RVSP and it was not correlated with a greater amount of energy.

Similar to MR, fTR is proposed to be divided into atrial fTR (afTR) — in the setting of AF [42] and ventricular fTR (vfTR) — mainly associated with left heart disease like MR, ischemic heart disease or PH [6, 43–45]. Enlargement of RV is more pronounced in vfTR, but it can also occur in afTR patients [45]. However, when it comes to determining tricuspid annular enlargement RA dilation plays a greater role [48]. The current study shows that the mean values of RVOT in both groups exceed the upper limit — suggesting RV enlargement. It can be a result of pressure overload and dysfunction of RV [46] caused by increasing LA pressure by afMR [6, 47]. Therefore, the main focus of attention was on fTR, without further division into its subtypes.

Limitations

The current study was conducted in a single center with all the inherent limitations of a retrospective analysis.

The lower success rate of CVE in the group with accompanying fTR may be associated with a potentially longer total history of AF [49, 50]. Short duration of AF is proven to be an independent predictor of successful CVE [30]. A precise determination of the duration of AF could not be done due to the retrospective nature of the study.

Comprehensive evaluation of RV size and function was performed in an insufficient number of patients in order to make a reliable comparison. Therefore, no subtypes of fTR were distinguished and its relation to the efficacy of CVE.

It was not possible to identify each of the semi-quantitative or quantitative criteria of fTR, hence the division into groups by qualitative criteria. Single parameters available were used to exclude patients with massive or torrential fTR. Comparing values and creating detailed cut-off points were not possible due to the heterogeneity of parameters so a simplified definition of fTR and its grading was used, however, it did fulfill all the required criteria for diagnosis. Qualitative and quantitative evaluation of the regurgitant wave was carried out by an experienced echocardiographer, who was well familiar with the abovementioned criteria.

It was surprising that patients with a severe degree of fTR had efficacy of CVE which equaled 100% — it was believed that it was a bias related to the small group size.

This work showed that the amount of energy used for effective CVE did not differ between the study groups. The analysis involved patients hospitalized between 2019 and 2022 and energy of CVE started at 150J and was progressively increased. Current guidelines suggest starting CVE with the maximum-fixed energy because it was more effective and is equally safe [26]. It would be interesting to analyze this strategy whether it yielded different results.

Conclusions

The fTR frequently coexists with afMR. Despite of high efficacy of CVE, in patients with persistent AF and afMR presence of fTR significantly reduces the effectiveness of CVE. However, the degree of fTR does not affect the efficacy of the procedure.

Conflict of interest: None declared

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