Left atrial size, function and left ventricular diastolic function in patients with paroxysmal atrial fibrillation and changes after successful and unsuccessful cryoballoon ablation

PhD thesis

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1. INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with an estimated prevalence of 1-2 %, increasing with age to 8% in those older than 80 years. Approximately 40% of AF patients have paroxysmal AF (PAF). AF is associated with increased risk of stroke, other thromboembolic events, heart failure, all-cause mortality and impaired quality of life.

Left atrial and ventricular remodeling

Left atrial (LA) structural remodelling (LA dilatation) is one of the long-term consequences of atrial fibrillation; AF is an independent predictor of left atrial size. Dilated left atrium (increased left atrial volume index; LAVI) is a strong prognostic marker of later cardiovascular events, such as heart failure and stroke. The severely dilated left atrium (LAVI>40 ml/m^2) is associated with an increased risk of mortality in patients with preserved left ventricular (LV) ejection fraction.

Interstitial fibrosis -related to left atrial dilatation- contributes to deterioration of left atrial function (functional remodeling). Impaired LA function also confers a poorer long-term prognosis.

It has been reported that the consequences of atrial fibrillation include not only left ventricular systolic dysfunction but also LV diastolic dysfunction.

Left atrial size, function and left atrial appendage function in patients with paroxysmal atrial fibrillation

In PAF patients left atrial size was reported to be mildly dilated in several studies by LA antero-posterior diameter, left atrial area and also by the most recommended LA volume index, although in other studies LA size was described as moderately-severely enlarged in patients with lone PAF.

Very little information is available about LA function in PAF patients, since complex echocardiographic examination was performed only in a few,

small-scale studies. As opposed to assessment of LA size there is no recommendation for the evaluation of LA function, but mainly different kinds of echocardiographic methods are used. Several LA functional parameters such as left atrial total emptying fraction, LA filling fraction, late diastolic velocities of mitral annulus by pulsed-wave tissue Doppler echocardiography (TDE) were reported to be impaired in patients with paroxysmal atrial fibrillation. It is unknown how often left atrial structural remodeling is associated with functional remodelling in patients with PAF, or how commonly LA function is impaired when the LA is dilated.

Thrombus has a predilection to form in the left atrial appendage (LAA) in AF. LAA function can be assessed by transoesophageal echocardiography (TOE). It has been reported that severely reduced (<20 cm/s) peak left atrial appendage emptying flow velocity (PLAAEFV) increases the risk of LAA thrombus and ischaemic stroke compared to higher velocities. In PAF patients we have practically no information about LAA function, and the relation between LAA and LA function. TOE is routinely performed before AF ablation in PAF patients who are undergoing catheter ablation, to exclude LA and LAA thrombus, so LA function can be compared with LAA function. The LAA and main LA cavity are derived embryologically from different sources. It is controversial in the literature if LAA function is suitable to characterize global LA function or if any LA functional parameter can be used to evaluate LAA function.

Diastolic function in patients with paroxysmal atrial fibrillation

Elevated left ventricular end-diastolic pressure by invasive hemodynamic studies and reduced early diastolic myocardial velocities (Ea) by TDE were reported in lone PAF patients. Left ventricular filling pressure evaluated by E/Ea was increased in PAF patients compared to controls. There is little known about the distribution of different grades of diastolic dysfunction in

patients with atrial fibrillation. Moderate and severe diastolic dysfunction (DD) with elevated LV filling pressure have prognostic implications as they are associated with higher risk of cardiovascular mortality and hospitalization related to heart failure. In PAF patients the occurrence of DD with elevated filling pressure was reported in a few previous studies to be between 16-68%; although grading of DD has never been studied on the basis of the ASE/EAE (American Society of Echocardiography/European Association of Echocardiography) recommendations.

Catheter ablation

None of the pharmacological rate versus rhythm controlled trials demonstrated any difference on mortality between these strategies. Although, a post-hoc on-treatment analysis of the AFFIRM study revealed that the presence of sinus rhythm was associated with a significant reduction in mortality, whereas the use of antiarrhythmic drugs increased mortality. So rhythm control therapy may be preferred if the hemodynamically favourable sinus rhythm could be restored without the proarrhythmic effects and non-cardial toxicity of antiarrhythmic drugs; that is the rational for catheter ablation treatment.

The purpose of ablation treatment is to eliminate foci that trigger and maintain AF and to alter the substrate that sustains AF. The most frequently used energy source is radiofrequency (RF) energy which achieves myocardial ablation by the conduction of alternating electrical current through myocardial tissue as a resistive medium and results in irreversible coagulation necrosis.

The effect of radiofrequency catheter ablation (RFCA) on left atrial size, function and left ventricular diastolic function

Catheter ablation of AF can affect left atrial size, function and LV diastolic function either from the scar caused by the ablation or from reverse atrial remodeling following conversion to normal sinus rhythm or reduction of frequency of AF episodes. In previous studies after successful RFCA of atrial

fibrillation, LA size has been found to decrease and LA function to improve; in contrast, after an unsuccessful catheter ablation, opposite changes were observed. The results of many studies are difficult to interpret, as the effect of ablation was not evaluated separately after successful and unsuccessful treatment.

In PAF patients limited data are available about the change of LA size and function after ablation because the results in patients with paroxysmal and persistent AF were not reported separately in the two groups. After successful RFCA the LA size decreased in some studies while in another studies it did not change or decreased after both successful and unsuccessful RFCA. The results are similarly controversial with regard to left atrial pump and reservoir function.

The effect of RFCA on diastolic function was only investigated in few studies. In PAF patients a few studies after successful RFCA reported improved relaxation, decreased LV filling pressure and reduced degree of DD, however, it was not confirmed by other studies.

Cryoballoon ablation

Cryothermal ablation, as an alternative energy source has several advantages compared to RF ablation: increased catheter stability, less endothelial disruption with lower thromboembolic risk, less generation of inhomogeneous lesions, minimal tissue contraction with healing. Balloon-based cryo-technology potentially offers a simpler and faster means of isolating the pulmonary veins; 3D mapping system is not necessary for the procedure, and it relies less on the dexterity of the operator and causes less scar in the left atrium. A meta-analysis suggests this is a safe and feasible approach with a similar success rate in patients with paroxysmal AF to radiofrequency catheter ablation. The effects of cryoballoon ablation on left atrial structural and functional remodelling and on LV diastolic function have not been examined previously in patients with paroxysmal atrial fibrillation.

2. OBJECTIVES

2.1. Echocardiographic assessment of left atrial size, left atrial and appendage function and left ventricular diastolic function in patients with paroxysmal atrial fibrillation

I. Questions to be answered:

A) How common is the severely dilated left atrium (which is associated with an increased risk of mortality) in patients with PAF?

B) How often is the left atrial structural remodeling associated with LA functional remodelling in patients with PAF?

C) How common is the severely impaired left atrial appendage function (which increases the risk of embolic stroke) in patients with PAF?

D) Is there any correlation between left atrial and left atrial appendage function in patients with PAF?

E) How are the different grades of diastolic dysfunction distributed in patients with atrial fibrillation? How common is the moderate and severe diastolic dysfunction (DD) -which are associated with worse prognosis- on the basis of the ASE/EAE recommendations?

2.2. Left atrial size, function and left ventricular diastolic function after cryoballoon catheter ablation during a one-year follow-up in patients with paroxysmal atrial fibrillation

II. Questions to be answered:

A) Is there reverse left atrial structural remodelling (reduction in LA volume) after successful cryoballoon ablation and further LA dilation (progressing LA remodelling) after unsuccessful ablation?

B) What is the effect of cryoballoon ablation on left atrial function in patients with paroxysmal atrial fibrillation?

C) Do LV diastolic function and the grade of diastolic dysfunction change after cryoballoon ablation in patients with paroxysmal atrial fibrillation?

3. METHODS

3.1. Echocardiographic assessment of left atrial size, left atrial and appendage function and left ventricular diastolic function in patients with paroxysmal atrial fibrillation

Patients

46 consecutive patients with recurrent, symptomatic, non-valvular PAF -all of whom had failed to respond to antiarrhythmic or beta blocker therapy and underwent radiofrequency or cryoballoon ablation- were enrolled in the study between June 2008 and July 2009.

Transthoracic echocardiography

I performed the transthoracic echocardiography examinations before ablation, in sinus rhythm in all patients with the same General Electric Vivid S6 machine.

Left ventricular (LV) global systolic function was assessed by ejection fraction (EF) evaluated by the modified biplane Simpson's rule. LV longitudinal systolic function was assessed by septal and lateral systolic velocities of the mitral annulus (Sa_{sept}, Sa_{lat}) using pulsed-wave TDE. Left ventricular mass index (LVMI) was calculated.

Maximal LA volume (LAV_{max}) was obtained at left ventricular end-systole, minimal LA volume (LAV_{min}) at left ventricular end-diastole. LA volumes were calculated by two-dimensional echocardiography by the biplane area–length method. LA areas (A_1, A_2) and superoinferior longitudinal diameters were measured from apical 4- and 2-chamber views. LA volumes

were calculated : $0.85*A_1*A_2/L$, where L is the shorter superoinferior diameter of the LA. LA volume index (LAVI) was calculated by dividing maximal LA volume by the body surface area (Dubois formula).

In the present study four TTE methods were used in the assessment of LA function. LA booster pump (contractile) function was assessed by:

a) the LA filling fraction (LAFF) which is the ratio of the velocity time integral (VTI) of the late diastolic A wave velocity of mitral inflow to the VTI of the early and late diastolic velocities of mitral inflow ($LAFF=VTI_A/VTI_{E+A}$)

b) septal and lateral velocities of the mitral annulus during atrial contraction (Aa_{sept}, Aa_{lat}), measured by pulsed-wave TDE.

LA reservoir function was assessed by:

a) LA total emptying fraction: $LAEF=(LAV_{max}-LAV_{min})/LAV_{max}$

b) the systolic fraction of pulmonary venous flow which is the ratio of VTI of systolic S wave velocity of pulmonary venous flow to the VTI of the systolic and diastolic velocities of pulmonary venous flow: $PVSF=VTI_S/VTI_{S+D}$. Pulmonary venous flow was measured within right upper pulmonary vein.

In the detailed evaluation of left ventricular diastolic function early (E) and late diastolic (A) velocities of mitral inflow, and deceleration time (DT) were measured by pulsed wave Doppler echocardiography, and E/A ratio was calculated. Septal and lateral early diastolic velocities of the mitral annulus (Ea_{sept}, Ea_{lat}) were measured by TDE, which characterize left ventricular relaxation. In the assessment of mean left ventricular filling pressure E/Ea ratios were calculated, using both the lateral, septal and average Ea velocity. Systolic (S) and diastolic (D) velocities of pulmonary venous flow were measured and S/D ratio was also calculated.

Diastolic dysfunction was graded on the basis of the ASE/EAE recommendations. Definitions of grade I (mild) DD were $Ea_{sept}<8$, $Ea_{lat}<10$, and $E/Ea_{avg}\leq 8$, $E/A<0.8$, $DT>200$ ms, $S>D$. The following attributes were considered characteristic of grade II (moderate) DD: $Ea_{sept}<8$, $Ea_{lat}<10$, the left

atrium is at least moderately dilated (LAVI≥34 ml/m^2) and 8<E/Ea_{avg}<13, and 0.8≤E/A≤1.5, DT: 160-200 ms, S<D. Criteria of grade III (severe) DD were: Ea_{sept}<8, Ea_{lat}<10, LAVI≥34 ml/m^2 and E/Ea_{avg} ≥13, E/A≥2, DT<160 ms, S<D. LV filling pressure was considered elevated when DD was grade II or III.

Transoesophageal echocardiography

Transoesophageal echocardiography was routinely performed in all patients to exclude LA and LAA thrombus with a Philips iE33 machine, all in sinus rhythm. Peak LAA emptying flow velocity was used to assess LAA function; it was obtained by pulsed-wave Doppler interrogation from 1 cm within the orifice of the left atrial appendage. The presence of spontaneous echo contrast (SEC) was assessed on the 2D grey-scale images. TOE and TTE were performed on the same day, within a short time.

3.2. Left atrial size, function and left ventricular diastolic function after cryoballoon catheter ablation during a one-year follow-up in patients with paroxysmal atrial fibrillation

Patients

36 consecutive patients with recurrent, symptomatic, nonvalvular PAF were enrolled in the study between June 2008 and July 2009. All had failed to respond to antiarrhythmic or beta-blocker therapy. They underwent their first catheter ablation by the cryoballoon technique.

Cryoballoon ablation

Cryoballoon ablations were performed in the Electrophysiology Laboratory of György Gottsegen Hungarian Institute of Cardiology as part of the clinical treatment of the patients. All patients were treated with a double lumen cryoballoon (28 mm; Arctic front, Cryocath), after local anaesthesia and under conscious sedation. Transseptal puncture was guided by an intracardiac echocardiography catheter. At least two 5-minute cryo applications per vein

were given to each pulmonary vein (PV). After ablation a circular mapping catheter (Lasso) was positioned in the antrum of each PV to record the presence of pulmonary vein potentials. In case of incomplete PV isolation further cryo applications were delivered by the previously used cryoballoon or by a focal cryo-catheter to complete the lesion.

Study protocol, follow-up

Echocardiography

Comprehensive transthoracic echocardiographic examinations were performed in all patients during sinus rhythm before, and 3, 6 and 12 months after cryoballoon catheter ablation. Transoesophageal echocardiography was performed in all patients before catheter ablation, to exclude LA and LAA thrombus. Transthoracic and transoesophageal echocardiography were performed within a short time, on the same day. The echocardiography machines and the examination protocols were the same as described in detail in the methods of the other study (3.1).

Arrhythmia monitoring

Heart rhythm was recorded during all follow-up echocardiography examinations. Post-ablation follow-up clinical examinations at 1, 3, 6 and 12 months included clinical and arrhythmia history, physical examination and 12-lead ECG. In order to improve arrhythmia monitoring before the 3-month, 6-month and 12-month follow-up visits a 24-hour Holter ECG and / or a 10-day transtelephonic ECG was planned (completed in 81% of the patients).

Definition of success

Based on the definition of the Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, cryoballoon catheter ablation was considered to be clinically successful, if after the initial 3-month blanking period recurrent atrial arrhythmia (>30 s, registered atrial fibrillation or flutter

or tachycardia) was not recognized on clinical, or ECG or Holter ECG, or transtelephonic ECG examinations.

We aimed to evaluate the effect of all episodes of recurrent arrhythmia on the left atrium and left ventricular diastolic function, so recurrences in the first 3 months blanking period were also taken into account for the final analysis. Therefore, two groups of patients were defined: in the arrhythmia-free (AF-free) group there was no recurrence during follow-up. The recurrent group was defined as patients with recurrent atrial arrhythmia at any time during the follow-up.

4. RESULTS

4.1. Echocardiographic assessment of left atrial size, left atrial and appendage function and left ventricular diastolic function in patients with paroxysmal atrial fibrillation

Baseline characteristics

33 out of 46 patients were male; the mean age was 57.7±9.6 (23-77; median: 57) years. The average time period from the first recognition of the AF was 6.9±7.3 (0.5-34; median 5.0) years. 32 patients had hypertension, also 32 had hyperlipidemia. Ischaemic heart disease in 6, thyroid disease in 7 and type 2 diabetes in 5 patients were present. There were no other etiological factors of AF present such as congenital heart disease, significant valvular disease, chronic obstructive pulmonary disease, sleep apnoea syndrome and chronic kidney disease.

Left ventricular size and systolic function

The LV end-diastolic diameter in 4, the end-diastolic volume in 8 patients were above normal values suggesting mildly dilated LV. Left ventricular hypertrophy (septum or posterior wall ≥11 mm) was present in 28 patients; there was no severe hypertrophy (≥17 mm). LVMI was elevated in 16

patients (♀:>96, ♂:>116 g/m2). Left ventricular EF was 62±6%, more than 55% in every patient. LV long-axis systolic function (Sa_{lat} and Sa_{sept}) was preserved in all subjects (>mean value from literature-2 standard deviation).

Left atrial volume in patients with paroxysmal atrial fibrillation

The mean LAVI was 35±10 ml/m^2. LA was dilated in 70% of patients, and was above published normal values (29 ml/m^2) in 32 cases. It was mildly elevated (29 ml/m^2<LAVI<34 ml/m^2) in 11, moderately elevated (34 ml/m^2≤LAVI<40 ml/m^2) in 8 and severely elevated (LAVI≥40 ml/m^2) in 13 cases.

Left atrial and left atrial appendage function in patients with paroxysmal atrial fibrillation

Among the variables of LA pump function the left atrial filling fraction in 5, Aa_{lat} in two, Aa_{sept} in four patients were impaired compared to normal values from literature. Left atrial reservoir function was reduced by pulmonary vein systolic fraction in four, by left atrial total emptying fraction in 9 cases. Overall LA dysfunction was observed in 13 patients. Left atrial pump function in 8, and LA reservoir function in 10 patients were impaired (in 5 subjects both the LA pump and reservoir function were reduced).

Among the 32 patients with dilated LA we found LA dysfunction in 11 cases; impaired LA pump function in 7, and impaired reservoir function in 9 patients (in 5 subjects both LA pump and reservoir function were reduced).

The mean PLAAEFV was 66±21 cm/s. LA appendage function by PLAAEFV was reduced (<50 cm/s) in 10 cases; among these 10 patients, 8 had enlarged left atrium and 6 had impaired LA function. There was no patient with severely reduced (<20 cm/s) PLAAEFV, and there was no SEC in any patient.

Correlations of left atrial and left atrial appendage function in patients with paroxysmal atrial fibrillation

Peak left atrial appendage emptying flow velocity correlated positively with LA pump function (Aa_{lat}: r=0.58; p<0.001; Aa_{szept}: r=0.45; p<0.01) and with reservoir function (LAEF: r=0.49; p<0.001). Aa_{lat} and Aa_{sept} velocity correlated positively with left atrial filling fraction (Aa_{lat}: r=0.53; p<0.001; Aa_{sept}: r=0.43; p<0.05), with left atrial total emptying fraction (Aa_{lat}: r=0.51; p<0.001; Aa_{sept}: r=0.63; p<0.001) and with pulmonary vein systolic fraction (Aa_{lat}: r=0.49; p<0.001; Aa_{sept}: r=0.46; p<0.005).

Left ventricular diastolic function in patients with paroxysmal atrial fibrillation

Ea_{sept} in 21, Ea_{lat} in 18 patients were impaired compared to normal values from recommendations (decreased if Ea_{lat}<10 cm/s, Ea_{sept}<8 cm/s). E/Ea_{avg} was normal (≤8) in 27 patients, and in the intermediate zone (8<$E/Ea_{átl}$<13) in 19 patients, and it was not ≥13 in any patient. E/Ea correlated with age; the highest correlation was with E/Ea_{sept} (r=0.55; p<0.001).

There was normal diastolic function in 17, mild (grade I.) diastolic dysfunction in 10, and moderate (grade II.) diastolic dysfunction in 19 patients. There was no severe (grade III.) DD.

4.2. Left atrial size, function and left ventricular diastolic function after cryoballoon catheter ablation during a one-year follow-up in patients with paroxysmal atrial fibrillation

Outcome of cryoballoon ablation

The clinical success rate was 64%, and there was no severe procedure-related complication. Repeat ablation had not been performed during the first year follow-up. There was no significant AF-related complication during the one-year follow-up.

15 patients (42%) were totally free of arrhythmias throughout the first 12 months of follow-up (the AF-free group). The other 21 patients (the recurrent group) experienced some recurrence of atrial arrhythmias (90% AF, 5-5% atrial tachycardia or flutter) during follow-up. Recurrence only early (within 3 months after treatment) in 8, recurrence only between 3 and 12 months after treatment in 4, and both early and 3 to 12 months recurrences in 9 patients, were detected.

Baseline clinical and echocardiographic characteristics

36 consecutive patients were enrolled in the study; there were 26 males and the mean age was 57.4±8.9 years. Left ventricular EF was 63±5% (55-72%). 27 patients (75%) had hypertension. Hyperlipidemia in 26, ischaemic heart disease in 4, thyroid disease in 6 and type 2 diabetes in 4 patients were present. At baseline, patients' age, gender, prevalence of concomitant diseases such as hypertension, diabetes mellitus, hyperlipidemia and obesity were not significantly different between the recurrent and AF-free groups

The patients who later developed a recurrence (recurrent group), had a longer duration of atrial fibrillation (8.8±8.7 vs 3.8±3.3 years, p<0.05) before cryoballoon catheter ablation.

The longitudinal systolic function by the lateral Sa velocity (8±1.6 vs 9.5±3 cm/s, p<0.05) and the left atrial reservoir function by left atrial total emptying fraction (55±8 vs 48±11 %, p<0.05) were significantly lower in the recurrent group at baseline. The peak left atrial appendage emptying flow velocity was borderline lower in the recurrent group (58±21 vs 73±23 cm/s, p=0.05). The other TTE echocardiographic variables were not different between the groups.

Left atrial size during follow-up

In the recurrent group, at 12 months after ablation, the minimal left atrial volume (38±19 to 44 ±20 ml; p<0.05), the maximal left atrial volume

(73±23 to 81±24 ml; p<0.05), the left atrial volume index (35±10 to 39±11 ml/m2; p=0.01) and the maximal left atrial supero-inferior diameter (55±5 to 59±6 mm; p<0.01) had all increased. In contrast, after successful cryoballoon ablation, LA size had not increased in the AF-free group.

Left atrial function during follow-up

In the recurrent group, at 12 months after ablation, the left atrial reservoir function as assessed by the systolic fraction of pulmonary venous flow (58±9 to 50±10 %; p=0.01) and LA pump function as assessed by left atrial filling fraction (36±7 to 33±8 %; p=0.03) had decreased. In contrast, after successful cryoballoon ablation, LA function had not declined.

Left atrial total emptying fraction, which is a parameter of LA reservoir function, did not change significantly during the follow-up; however, it was significantly lower at all follow-up visits in the recurrent group. Aa_{sept} was significantly lower at 3 and 6 months after ablation in the recurrent group (3. month: 8.3±2.1 vs 10.3±3.1, p<0.05; 6. month: 8.6±1.8 vs 10.4±1.7, p<0.05).

Left ventricular diastolic function during follow-up

Lateral and septal early diastolic velocities did not change significantly during the follow-up. Whereas, $E/Ea_{average}$, which was used to assess the mean LV filling pressure, was increased at one year, from baseline values (7.2±1.8 to 8.5±2.3; p=0.005).

In the recurrent group, at 12 months after ablation, the “mean grade of diastolic dysfunction” increased compared to baseline (0.67±0.91 vs 0.95±1.01; p=0.01), while in the AF-free group it decreased (0.93±0.96 vs 0.53±0.83; p=0.03).

The prevalence of diastolic dysfunction with elevated LV filling pressure (grade II or III) did not change significantly in either group, but at 12 months after ablation it tended to decrease in the AF-free group and to increase

in the recurrent group. In the recurrent group grade III DD was found at the 6 and 12 month follow-up visit.

Left ventricular systolic function during follow-up

Left ventricular global systolic function (EF) did not change significantly during the follow-up in either group. Lateral Sa velocity, a parameter of longitudinal systolic function, was significantly higher in the AF-free group at baseline (9.5±3 vs 8±1.6 cm/s, p<0.05) and at 12 months after ablation (10.7±2.4 vs 8.9±1.3 cm/s, p<0.05).

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5. CONCLUSIONS

I. In patients with paroxysmal atrial fibrillation:

A) The severely dilated left atrium (which is associated with an increased risk of mortality) is not common – even in a mostly hypertensive sample.

B) Left atrial structural remodeling is not always associated with LA functional remodelling.

C) Left atrial appendage function is preserved in most of the patients; severely impaired left atrial appendage function (which increases the risk of embolic stroke) is not common in patients with PAF.

D) Peak left atrial appendage emptying flow velocity correlates with left atrial pump function by late diastolic Aa velocities and with left atrial reservoir function by left atrial total emptying fraction.

E) Left ventricular diastolic dysfunction is common in a mostly hypertensive sample; diastolic dysfunction with elevated filling pressure is more common than relaxation abnormality.

II. In patients whose nonvalvular paroxysmal atrial fibrillation recurred within one year after cryoballoon catheter ablation:

A) Left atrial size increases, while successful cryoballoon catheter ablation prevents progressive left atrial structural remodelling.

B) Left atrial pump and reservoir function decline, while successful cryoballoon catheter ablation prevents progressive left atrial functional remodeling.

C) Left ventricular filling pressure and the severity of diastolic dysfunction by the “mean grade of diastolic dysfunction” increase, whereas after successful ablation they decrease.

6. PUBLICATIONS

6.1 Publications used in the thesis

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