Catheter ablation for atrial fibrillation in HFpEF patients—A propensity-score-matched analysis

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Abstract

**Background:** Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) are both common conditions associated with high morbidity and mortality, especially if they coexist. Catheter ablation (CA) for AF has been shown recently to induce reverse remodeling and improve symptoms in HFpEF patients. The aim of this study was to compare outcomes of AF patients with HFpEF, who either underwent CA for AF or received medical therapy only.

**Methods and Results:** We included all AF patients with HFpEF according to current guidelines treated at our hospital between 2013 and 2018. Out of 6614 AF patients, we identified 127 with confirmed HFpEF. After applying propensity score matching to balance patient groups, 43 patients treated by CA and 43 patients receiving medical treatment were compared. Patients in the CA group underwent a mean of 1.5 ± 0.8 ablation procedures. Arrhythmia recurrence occurred significantly less frequently in the CA group (hazard ratio [HR]: 0.47; 95% CI: 0.25–0.87; \( p = .016 \)). The primary endpoint, a composite of heart failure hospitalization and death, was reduced significantly by CA compared to medical therapy (HR: 0.30; 95% CI: 0.13–0.67; \( p = .003 \)). This was driven by a decrease in heart failure hospitalization. Clinical and echocardiographic parameters of HFpEF improved significantly only after CA. Remarkably, reassessment of diagnostic HFpEF criteria at the end of follow-up demonstrated HFpEF resolution in 15 out of 43 patients (35%) treated by CA and only 4 out of 43 patients (9%) treated medically (\( p = .008 \)).

**Conclusion:** Catheter ablation for AF in HFpEF patients in comparison to medical therapy decreases heart failure hospitalization, heart failure symptoms, and improves diastolic function. AF ablation should be considered in patients with HFpEF and concomitant AF.

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1 | INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) are both common conditions leading to frequent hospitalization and are associated with high morbidity and mortality, especially if they coexist. \(^1\) Prevalence of HFpEF in AF patients is high (8%–24%) and vice versa (21%–33%), which is in a great part attributable to shared pathomechanisms, but no effective therapies have been established yet. \(^1\) It has been shown that catheter ablation (CA) for AF in heart failure patients with reduced ejection fraction (HFrEF) is able to improve heart failure symptoms, hospitalization rates, and mortality compared to medical therapy. \(^2\) Interestingly, prevalent AF in HFpEF patients hospitalized for heart failure results in an even higher increase of in-hospital mortality than in HFrEF patients. \(^3\) Thus, there is an unmet need for therapeutic strategies in these patients. Previous studies indicated that rhythm control by CA and antiarrhythmic medication may improve left ventricular diastolic function of HFpEF patients. \(^4,5\) We have shown recently, that AF ablation leads to a decrease in heart failure symptoms, left ventricular reverse remodeling, and a decrease of hospitalizations in HFpEF patients if sinus rhythm can be maintained. \(^6\) However, a study evaluating the effect of CA for AF in comparison to medical therapy in HFpEF patients is missing. The present study sought to investigate clinical outcomes of HFpEF patients with concomitant AF treated either by CA for AF or medical therapy.

2 | METHODS

2.1 | Study population

We conducted a case-control study taking into account all patients treated at the Department of Medicine II at Ulm University Medical Center, Ulm, Germany, between 2013 and 2018 with symptomatic heart failure symptoms (at least NYHA class II), AF, and echocardiographic findings of diastolic dysfunction (E/A ratio, E/E’ ratio, septal E’ velocity), according to the current guidelines. \(^1,7,8\) Patients with acutely decompensated heart failure or cardiogenic shock were not eligible. The selection process is depicted in Figure 1 and is comprised of two phases. The first phase targeted at identification of all AF patients with

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FIGURE 1 Patient allocation and analysis. ABL, ablation; AF, atrial fibrillation; BNP, brain natriuretic peptide; HFpEF, heart failure with preserved ejection fraction; HOCM, hypertrophic obstructive cardiomyopathy; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MT, medical therapy; NT-pro BNP, NT-pro brain natriuretic peptide; PS, propensity score
echocardiographic findings of diastolic dysfunction. We excluded patients with left ventricular ejection fraction below 50%, severe valvular heart disease, congenital heart disease, confirmed diagnosis of hypertrophic cardiomyopathy, and amyloidosis. Severe valvular heart disease was defined as a history of aortic or mitral replacement or repair, evidence of severe aortic or mitral regurgitation, severe aortic stenosis, or moderate or severe mitral stenosis. Patients without follow-up data were excluded. In the second phase, in congruence with the guidelines, we excluded patients with NT-pro BNP levels below the recommended cut-off for HFpEF (125 pg/ml or lesser) or neither evidence of left ventricular hypertrophy (LVMI: male: ≤115 g/m²; female: ≤95 g/m²) nor E/E' ratio of 13 or above.\(^7\) Left atrial enlargement, another guideline-accepted criterion of HFpEF, was not considered sufficient to be included in our study, to prevent bias due to the well-established incidence in AF patients even without HFpEF.\(^1\) Additionally, criteria for HFpEF from the "HFA-PEFF diagnostic algorithm" were assessed in all patients.\(^10\) The remaining patients suffering from HFpEF and AF were treated according to current recommendations by either medical rhythm- or rate control therapy or rhythm control strategy by CA.\(^7,9,11,12\) The treatment strategy in each patient was determined according to the attending physician’s discretion, taking into account the patient’s preference. In the CA group, all patients received cryoballoon pulmonary vein isolation as the initial ablation procedure. Repeat ablation procedures due to atrial tachyarrhythmia recurrence were exclusively conducted by irrigated-tip radiofrequency ablation guided by three-dimensional (3D)-mapping systems. If rhythm control by CA was not successful and no further ablation procedure was performed, patients underwent medical rhythm or rate control therapy but remained in the CA group for analysis. In the medical treatment group a target resting heart rate of at least less than 110 bpm for rate control was pursued, however, heart rates of 60–80 bpm were considered as the optimal target in heart failure patients whenever achievable.\(^13\) Baseline and follow-up blood samples were drawn at hospital admission or at presentation at our outpatient clinic for measurements of plasma N-terminal pro-B-type natriuretic peptide levels (Roche Diagnostics). The study complies with the Declaration of Helsinki and was approved by the local ethics committee (Ulm University). The requirement for informed consent was waived.

### 2.2 | Ablation procedure

Preprocedural management was as described before.\(^14,15\) Briefly, left atrial thrombus was ruled out by transesophageal echocardiography in all patients before PVI. Vitamin K antagonists (VKA) were administered uninterruptedly to a target INR of 2.0–2.5 at the time of the procedure. Patients treated with non-VKA oral anticoagulants were advised to hold their anticoagulant 24 h or lesser before the ablation procedure.

In all patients, the index ablation procedure was performed using the second or third generation cryoballoon (Arctic Front Advance or Arctic Front Advance ST). Patients with recurrent atrial tachyarrhythmia, who received repeat ablation procedures, were exclusively treated by irrigated-tip radiofrequency catheter ablation guided by 3D-mapping systems (Carto3; Biosense Webster or NavX Ensite Velocity; St. Jude Medical) under deep conscious sedation. Operators were encouraged to perform PV re-isolation only in case of PV re-conduction. However, additional left or right atrial ablations were permitted in case of documented or present focal, micro- or macro-reentrant tachycardia or at the operator’s discretion. Echocardiography was performed in every patient immediately after the procedure and before hospital discharge to rule out pericardial tamponade or pericardial effusion. Oral anticoagulation was resumed on the day of the ablation procedure. All patients continued oral anticoagulation for at least 2 months and thereafter according to current guidelines.\(^7\)

### 2.3 | Clinical follow-up

Patients were scheduled for outpatient clinic visits including clinical assessment, echocardiography, 12-lead electrocardiogram (ECG), and 7-day Holter monitoring or 24-h Holter monitoring at 1, 3, and 6 months after the procedure and thereafter every 6 months. Patients in the medical therapy group were scheduled for outpatient clinic visits every 6–12 months to ensure appropriate rate- or rhythm control. Drugs for rate control included β-blockers (metoprolol, bisoprolol, nebivolol, and carvedilol) and digoxins. For rhythm control, class III antiarrhythmic drugs (AADs) (amiodarone) were used according to the attending physician’s advice. No patient in the medical therapy group received AF ablation during the follow-up period. Additional medication for HFpEF treatment in both groups including diuretics and mineralocorticoid receptor antagonists was adjusted at the discretion of the attending physician. Recurrence was determined after a 3-month blanking period, beginning on the day of the last ablation procedure. For comparability, patients in the medical therapy group were also attributed a 3-month blanking period beginning at the day of hospital discharge of the index hospitalization or the day of inclusion at the outpatient clinic. Any documented sustained atrial tachyarrhythmia on 12-lead ECG or any tachyarrhythmia of 30 s or longer on Holter ECG after the 3-month blanking period was counted as AT/AF recurrence.

### 2.4 | Transthoracic echocardiography and HFpEF assessment

Transthoracic echocardiography was performed according to a standardized protocol in compliance with the current recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.\(^8\) All echocardiographic examinations were performed by an experienced physician and re-evaluated by an experienced echocardiography investigator during data collection. Additionally, all echocardiographic images were re-evaluated independently by a third echocardiography expert, who was blinded for the treatment regimen (CA or medical therapy), as well as for the rhythm and clinical outcome.
For assessment of echocardiographic HFpEF criteria left ventricular ejection fraction, diastolic interventricular thickness (IVTd), left ventricular diastolic diameter (LVDd), and diastolic left ventricular posterior wall thickness (PWTd) were assessed by the Teichholz monoplane method at baseline and at the end of follow-up. Additionally, E-, A- and E' velocity, E/A ratio, and E/E' ratio were analyzed. Left ventricular mass was estimated by left ventricular cavity dimension and wall thickness at end-diastole and indexed to body surface area. For patients in AF, we assessed echocardiographic parameters by the mean of three consecutive beats. Resolution of HFpEF was accepted in asymptomatic patients (NYHA class I) if both E/E' and wall thickness at end-diastole and indexed to body surface area. For patients in AF, we assessed echocardiographic findings suggestive of diastolic dysfunction and suffered from symptomatic heart failure (NYHA II-IV). Because of reduced left ventricular ejection fraction (LVEF < 50%), thus excluding a diagnosis of HFpEF. 113 patients were excluded. Additionally, 332 patients had severe valvular heart disease and five patients had confirmed hypertrophic obstructive cardiomyopathy and were, therefore, excluded from our study. Moreover, for 123 patients no follow-up data were available. Of the remaining 179 patients, 40 were excluded due to NT-pro BNP levels below 125 pg/ml and 12 because both E/E' ratio and LVM did not meet the required thresholds for HFpEF. Thus, employing the ESC heart failure guidelines, we identified 127 patients with a consistent diagnosis of HFpEF.9 HFpEF diagnosis was reassessed in all patients using the recently introduced “HFA-PEFF” diagnostic algorithm.10 HFA-PEFF score was 5 or above in 98 patients, thus confirming a diagnosis of HFpEF, and 2–4 in 29 patients, thus requiring an additional assessment of left ventricular end-diastolic pressure (LVEDP). All 29 patients had a diagnostic left heart catheterization and an LVEDP of 16 mmHg or above was confirmed in all patients (mean LVEDP 21 ± 4 mmHg). None of the patients had a score of 0 or 1. Thus, assessment of the “HFA-PEFF” diagnostic algorithm confirmed HFpEF in all patients of our cohort. Out of the remaining HFpEF patients, 68 underwent catheter ablation for atrial fibrillation (CA group), whereas 59 received medical treatment only (medical therapy group) by either rate control (n = 53) or rhythm control therapy (n = 6). To account for a potential patient selection bias we conducted a propensity score (PS) matching, which led to the inclusion of 86 patients (43 CA group, 43 medical therapy group) in our study. After PS-matching, except for more frequent use of β-blocker in the medical therapy group, there were no significant differences in any of the assessed baseline characteristics. Baseline characteristics before and after PS-matching are shown in Table 1. Mean follow-up was 35 ± 22 months.

2.5 | Primary and secondary endpoints

The primary endpoint was a composite of the time to death or heart failure hospitalization. Secondary endpoints were a composite of time to death or cardiovascular hospitalization, composite of time to death or all-cause hospitalization, time to death, heart failure symptoms as measured by NYHA class, plasma NT-pro BNP levels, and reassessment of echocardiographic and clinical HFpEF diagnostic criteria. The start of the follow-up period was defined as the day of the last ablation procedure (CA group) or the day of discharge of the index hospitalization or the day of inclusion at the outpatient clinic (medical group).

2.6 | Statistical analysis

The significance of differences of numeric values was calculated by t test if normal distribution with equal variance was given. Numeric variables that were not normally distributed were analyzed by Mann–Whitney rank-sum test and described as median and first to third interquartile range. Categorical variables were described as absolute and relative values and analyzed by χ² test or Fisher’s exact test, as appropriate. Kaplan–Meier analysis was used to assess the time to event and groups were compared using the Cox proportional hazard model. To reduce the treatment-selection bias and potential confounding, we adjusted for age, CHA2DS2-VASc Score, type of AF, and sex with propensity-score (PS) matching. The PS were calculated by logistic regression. For matching a 1:1 nearest neighbor match with a 0.2 caliper and no replacement was used. A p < .05 was considered to be statistically significant. Statistical assessment was performed by SPSS Statistics 25 software (Version 2017; IBM).

3 | RESULTS

3.1 | Study population

We screened 6614 AF patients who were treated at Ulm University Medical Center, Department of Cardiology between January 2013 and December 2018 for concomitant HFpEF. Out of these, 752 patients had echocardiographic findings suggestive of diastolic dysfunction and suffered from symptomatic heart failure (NYHA II-IV). Because of reduced left ventricular ejection fraction (LVEF < 50%), thus excluding a diagnosis of HFpEF. 113 patients were excluded. Additionally, 332 patients had severe valvular heart disease and five patients had confirmed hypertrophic obstructive cardiomyopathy and were, therefore, excluded from our study. Moreover, for 123 patients no follow-up data were available. Of the remaining 179 patients, 40 were excluded due to NT-pro BNP levels below 125 pg/ml and 12 because both E/E' ratio and LVM did not meet the required thresholds for HFpEF. Thus, employing the ESC heart failure guidelines, we identified 127 patients with a consistent diagnosis of HFpEF.9 HFpEF diagnosis was reassessed in all patients using the recently introduced “HFA-PEFF” diagnostic algorithm.10 HFA-PEFF score was 5 or above in 98 patients, thus confirming a diagnosis of HFpEF, and 2–4 in 29 patients, thus requiring an additional assessment of left ventricular end-diastolic pressure (LVEDP). All 29 patients had a diagnostic left heart catheterization and an LVEDP of 16 mmHg or above was confirmed in all patients (mean LVEDP 21 ± 4 mmHg). None of the patients had a score of 0 or 1. Thus, assessment of the “HFA-PEFF” diagnostic algorithm confirmed HFpEF in all patients of our cohort. Out of the remaining HFpEF patients, 68 underwent catheter ablation for atrial fibrillation (CA group), whereas 59 received medical treatment only (medical therapy group) by either rate control (n = 53) or rhythm control therapy (n = 6). To account for a potential patient selection bias we conducted a propensity score (PS) matching, which led to the inclusion of 86 patients (43 CA group, 43 medical therapy group) in our study. After PS-matching, except for more frequent use of β-blocker in the medical therapy group, there were no significant differences in any of the assessed baseline characteristics. Baseline characteristics before and after PS-matching are shown in Table 1. Mean follow-up was 35 ± 22 months.

3.2 | Arrhythmia recurrence

Arrhythmia recurrence was compared between patients undergoing either medical- or CA-therapy for AF. Patients undergoing CA for AF had a mean of 1.5 ± 0.8 ablation procedures. Arrhythmia recurrence was significantly less common in the catheter ablation group (HR: 0.47; 95% CI: 0.25–0.87; p = .016) (Figure 2A). Freedom from any documented AT/AF-recurrence after 1 year was 79% in the medical- and 84% in the ablation-therapy group. Freedom from recurrence after 4 years was 24% in the medical- and 57% in the CA group. None of the patients without recurrence in the CA group received AADs. Two of the five patients treated with AADs in the medical therapy group had AT/AF recurrence.

Remarkably, out of the 26 patients with paroxysmal AF undergoing CA only one (4%) showed progression to persistent AF, whereas six out of 22 paroxysmal AF patients (37%) receiving medical treatment only experienced progression to persistent AF (p = .038) (Figure 2B).
### Table 1 Baseline patient characteristics

|                                  | Before PS matching (n = 127) | After PS matching (n = 86) |
|----------------------------------|------------------------------|----------------------------|
|                                  | Medical Tx (n = 59)          | Ablation (n = 68)          | Medical Tx (n = 43) | Ablation (n = 43) |
| Age (years)                      | 76 ± 8                      | 71 ± 9                     | 74 ± 7              | 73 ± 7              |
|                                  |                              |                            |                      | .747                |
| Female                           | 29 (49)                     | 43 (63)                    | 24 (56)             | 24 (56)             |
|                                  |                              |                            |                      | 1                   |
| BMI (kg/m²)                      | 29 [25; 32]                 | 29 [26; 32]                | 29 [25; 31]         | 28 [26; 30]         |
|                                  |                              |                            |                      | .468                |
| Paroxysmal AF                    | 39 (66)                     | 45 (66)                    | 22 (51)             | 26 (60)             |
|                                  |                              |                            |                      | .385                |
| Previous stroke/TIA             | 4 (7)                       | 7 (10)                     | 2 (5)               | 7 (16)              |
|                                  |                              |                            |                      | .156                |
| Hypertension                     | 54 (92)                     | 60 (88)                    | 39 (91)             | 39 (91)             |
|                                  |                              |                            |                      | 1                   |
| Diabetes mellitus                | 18 (31)                     | 14 (21)                    | 11 (26)             | 10 (23)             |
|                                  |                              |                            |                      | .802                |
| CAD                              | 40 (69)                     | 37 (54)                    | 27 (63)             | 28 (65)             |
|                                  |                              |                            |                      | .822                |
| Myocardial infarction            | 12 (20)                     | 7 (10)                     | 8 (19)              | 5 (12)              |
|                                  |                              |                            |                      | .391                |
| PAD                              | 10 (17)                     | 17 (25)                    | 8 (19)              | 12 (28)             |
|                                  |                              |                            |                      | .307                |
| Dyslipidemia                     | 43 (73)                     | 47 (69)                    | 29 (67)             | 30 (70)             |
|                                  |                              |                            |                      | .816                |
| OSAS                             | 9 (15)                      | 7 (10)                     | 4 (9)               | 5 (12)              |
|                                  |                              |                            |                      | 1                   |
| PHT                              | 17 (29)                     | 12 (18)                    | 10 (23)             | 6 (14)              |
|                                  |                              |                            |                      | .268                |
| CKD                              | 29 (49)                     | 27 (40)                    | 18 (42)             | 18 (42)             |
|                                  |                              |                            |                      | 1                   |
| eGFR (ml/min)                    | 50 [37; 72]                 | 61 [47; 73]                | 50 [39; 69]         | 58 [46; 70]         |
|                                  |                              |                            |                      | .349                |
| CHA²DS²VASc                      | 5 [3; 5]                    | 4 [2; 5]                   | 4 [3; 5]            | 4 [3; 5]            |
|                                  |                              |                            |                      | .757                |
| NT-pro BNP (pg/ml)               | 2728 ± 3277                 | 2176 ± 3058                | 2906 ± 3623         | 2605 ± 3457         |
|                                  |                              |                            |                      | .695                |
| NYHA class                       | 2 [2; 3]                    | 2 [2; 3]                   | 2 [2; 3]            | 2 [2; 3]            |
|                                  |                              |                            |                      | .769                |
| Medication                       |                              |                            |                      |                     |
| AAD                              | 6 (10)                      | 1 (1)                      | 5 (12)              | 1 (2)               |
|                                  |                              |                            |                      | .202                |
| β-Blocker                        | 58 (98)                     | 56 (82)                    | 42 (98)             | 34 (79)             |
|                                  |                              |                            |                      | .015                |
| Digitalis glycosides             | 5 (8)                       | 1 (1)                      | 4 (9)               | 1 (2)               |
|                                  |                              |                            |                      | .360                |
| Oral anticoagulants              | 46 (78)                     | 61 (90)                    | 35 (81)             | 38 (88)             |
|                                  |                              |                            |                      | .366                |
| Diuretics                        | 46 (78)                     | 42 (62)                    | 32 (74)             | 28 (65)             |
|                                  |                              |                            |                      | .348                |
| ACE-I or ARB                     | 46 (78)                     | 52 (76)                    | 33 (76)             | 35 (81)             |
|                                  |                              |                            |                      | .596                |
| Statins                          | 43 (73)                     | 42 (62)                    | 29 (67)             | 30 (70)             |
|                                  |                              |                            |                      | .816                |

Note: Baseline characteristics are shown as mean ± SD, median [IQR], or as number (%). Abbreviations: AAD, antiarrhythmic drugs; ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEDP, left ventricular end-diastolic pressure; NT-pro BNP, NT-pro brain natriuretic peptide; NYHA, New York Heart Association; OSAS, obstructive sleep apnea syndrome; PAD, peripheral arterial disease; PHT, pulmonary hypertension; PS, propensity score; TIA, transitory ischemic attack.

### 3.3 Outcome: Heart failure hospitalization and mortality

Time to first heart failure hospitalization was significantly longer in the CA group than in the medical therapy group (HR: 0.30; 95% CI: 0.13–0.67; p = .003) (Figure 3A).

Cardiovascular hospitalization (HR: 0.53; 95% CI: 0.30–0.95; p = .034) and all-cause hospitalization (HR: 0.56; 95% CI: 0.33–0.96; p = .033) were also significantly less frequent in the CA group (Figure 3B, C). In the CA group there were two fatalities, whereas in the medical treatment group there was one (Figure 3D). All deaths occurred after a hospitalization event, thus, death did not contribute to the combined primary endpoint and to the combined secondary endpoints.

### 3.4 Reverse remodeling

To analyze the impact of ablation in comparison to medical therapy relevant echocardiographic parameters of diastolic function...
were assessed and compared at baseline and at the end of follow-up.

Although there were no differences at baseline between both treatment groups, at the end of follow-up there was a significant difference in the mitral peak A-wave velocity (medical therapy: 83.0 ± 29.0 cm/s, ablation: 65.7 ± 22.7 cm/s; \( p = .012 \)), mitral peak E-wave velocity (medical therapy: 103.9 ± 29.8 cm/s, ablation: 88.3 ± 22.1 cm/s; \( p = .015 \)), E/E’ ratio (medical therapy: 12.8 [9.8, 16.0], ablation: 10.0 [8.1, 12.7]; \( p = .005 \)), LVMI (medical therapy: 123 [103; 155] g/m², ablation: 105 [93; 124] g/m²; \( p = .015 \)) and IVTd (medical therapy: 12.1 ± 2.6, ablation: 11.1 ± 1.9; \( p = .038 \)).

Comparing echocardiographic parameters of diastolic function at baseline and at the end of follow-up within the treatment groups, we observed a significant decrease in E/E’ ratio (baseline: 12.8 [9.7, 15.7], follow-up: 10.0 [8.1, 12.7]; \( p = .005 \)), mitral peak A-wave velocity (baseline: 74.0 ± 21.5 cm/s, follow-up: 65.7 ± 22.7 cm/s, \( p = .008 \)), LVMI (baseline: 126 [108, 148] g/m², follow-up: 105 [93, 124] g/m²; \( p = .001 \)), IVTd (baseline: 12.0 ± 1.8, follow-up: 11.1 ± 1.9; \( p = .018 \)), and in LVDd (baseline: 53.7 ± 7.6 mm, follow-up: 50.7 ± 6.2 mm; \( p = .017 \)) in the CA-group, whereas in the medical therapy group we did not find any improvement in diastolic function. Detailed results are shown in Table 2.

3.5 | Heart failure

To evaluate the effect of the treatment regimen on heart failure symptoms, we compared patients’ NYHA class at baseline and at the end of follow-up (Figure 4). Initially, all patients suffered from heart failure symptoms and there was no difference between both groups (medical therapy: 2 [2, 3] ablation: 2 [2, 3]; \( p = .769 \)). By contrast, at the end of follow-up, there was a significant difference in the median NYHA class (medical therapy: 3 [2, 3] ablation: 1 [1, 2]; \( p < .001 \)). Patients who underwent CA showed a significant decrease in median NYHA class (baseline: 2 [2, 3], follow-up: 1 [1, 2]; \( p < .001 \)), whereas NYHA-class in the medical therapy group increased, although only by trend (baseline: 2 [2, 3], follow-up: 3 [2, 3]; \( p = .102 \)) (Figure 4). NT-pro BNP levels decreased significantly in the CA group (baseline: 2605 ± 3457 pg/ml, follow-up 1228 ± 1893 pg/ml; \( p = .001 \)), but did not change under medical therapy (baseline: 2906 ± 3623 pg/ml, follow-up: 3736 ± 5964 pg/ml; \( p = .114 \)) (Figure 5A). Remarkably, reassessment of diagnostic HFpEF criteria at the end of follow-up demonstrated resolution of HFpEF in 15 out of 43 patients (35%) treated by CA and only four out of 43 patients (9%) treated medically (\( p = .008 \)) (Figure 5B).
DISCUSSION

AF and heart failure often interdepend resulting in a poor prognosis. Although effective therapies for AF with HFrEF, which lead to a reduction of hospitalizations and mortality, have been established, current guidelines only offer treatment strategies based on expert opinion alleviating patients’ symptoms by rate- or fluid control for AF with HFpEF. As a consequence, there is an unmet need for the development of treatment options that can improve symptoms and reduce adverse clinical outcomes of patients with AF and concomitant HFpEF. Catheter ablation for AF has been shown to decrease the burden of AF, subsequently leading to a reduction of heart failure hospitalizations and mortality in HFrEF patients. In contrast, data on the effect of AF ablation on HFpEF is sparse. Previous studies have shown that CA of AF for HFpEF is safe and that a rhythm-control approach by AADs and single or multiple ablation procedures is able to induce reverse remodeling of HFpEF. However, there has been no comprehensive study comparing the effect of catheter ablation versus medical therapy on HFpEF. To the best of our knowledge, this is the first study comparing the impact of CA to medical therapy on clinical outcomes and echocardiographic parameters of diastolic function in patients with HFpEF and AF.

Previous studies on AF patients with concomitant HFpEF have shown an improvement of echocardiographic HFpEF parameters following rhythm control if sinus rhythm could be maintained. In our study, after 1 year, 79% of patients in the medical treatment group were still free from any atrial arrhythmia recurrence compared to 84% of patients in the ablation group, whereas after 4 years, only 24% in the medical therapy group and 57% in the CA group were still free from any arrhythmia recurrence. This difference is statistically significant, nevertheless, it may be underestimated because patients undergoing CA for rhythm control of AF received a much tighter rhythm monitoring than patients on medical rhythm control therapy or patients on rate control therapy. Thus, it is possible or even likely that we have missed recurrence of atrial tachyarrhythmia much more commonly in the medical treatment group than in the ablation group, possibly underestimating the true difference between both groups. As a consequence, the true freedom from atrial arrhythmia recurrence rate in the medical treatment group is likely much lower than the indicated 79% after 1 year and 24% after 4 years. Nevertheless, our results underscore the superiority of CA over medical therapy for rhythm control in AF patients with HFpEF.

HFpEF in AF patients is associated with an increase in heart failure symptoms, higher hospitalization rates, morbidity, and mortality compared to AF alone, which is thought to be related to a more
| TABLE 2  Echocardiographic parameters in patients with HFpEF undergoing either medical therapy or catheter ablation |
|-------------------------------------------------------------|
| **Before PS matching (n = 127)**                           | **After PS matching (n = 84)** |
| **Medical Tx (n = 59)**                                    | **Ablation (n = 68)**          | **Medical Tx (n = 43)**       | **Ablation (n = 43)**          | **p Value** |
| LVEF (%)                                                   |                                |                                |                                |                        |
| Baseline                                                  | 65.5 [58.4; 71.9]              | 65.3 [57.0; 70.8]              | 65.6 [58.6; 72.2]              | 65.3 [55.0; 68.0]       | .439        |
| Follow-up                                                 | 63.9 [55.0; 70.1]              | 66.7 [58.1; 73.5]              | 64.5 [52.8; 71.2]              | 65.6 [56.8; 73.7]       | .308        |
| Mitral peak A-wave velocity (cm/s)                        |                                |                                |                                |                        |
| Baseline                                                  | 84.5 ± 35.3                    | 78.9 ± 23.6                    | 87.5 ± 35.7                    | 74.0 ± 21.5             | .087        |
| Follow-up                                                 | 80.7 ± 29.4*                   | 67.8 ± 23.2*                   | 83.0 ± 29.0                    | 65.7 ± 22.7*            | .012        |
| Mitral peak E-wave velocity (cm/s)                        |                                |                                |                                |                        |
| Baseline                                                  | 102.5 ± 28.2                   | 95.0 ± 30.3                    | 101.8 ± 30.5                   | 92.7 ± 29.9             | .182        |
| Follow-up                                                 | 106.7 ± 29.4                   | 86.2 ± 22.7**                  | 103.9 ± 29.8                   | 88.3 ± 22.1             | .015        |
| E/A ratio                                                 |                                |                                |                                |                        |
| Baseline                                                  | 1.0 [0.8; 1.9]                 | 1.1 [0.8; 1.7]                 | 1.0 [0.8; 1.6]                 | 1.1 [0.8; 1.8]          | .907        |
| Follow-up                                                 | 1.4 [1.1; 1.8]                 | 1.2 [0.9; 2.0]                 | 1.4 [1.0; 1.7]                 | 1.3 [1.0; 2.2]          | .625        |
| E’ (cm/s)                                                  |                                |                                |                                |                        |
| Baseline                                                  | 8.3 ± 3.1                      | 7.9 ± 2.5                      | 8.5 ± 3.2                      | 7.8 ± 2.4              | .287        |
| Follow-up                                                 | 8.8 ± 2.6                      | 9.0 ± 2.7**                    | 8.8 ± 2.6                      | 9.3 ± 2.9              | .477        |
| E/E’ ratio                                                |                                |                                |                                |                        |
| Baseline                                                  | 13.2 [9.6; 16.4]               | 12.5 [9.9; 14.9]               | 12.5 [8.1; 16.0]               | 12.8 [9.7; 15.7]       | .908        |
| Follow-up                                                 | 12.9 [10.3; 15.7]              | 10.1 [8.1; 12.7]**             | 12.8 [9.8; 16.0]               | 10.0 [8.1; 2.7]**      | .006        |
| LV mass index (g/m²)                                      |                                |                                |                                |                        |
| Baseline                                                  | 124 [102; 145]                 | 120 [107; 137]                 | 121 [100; 156]                 | 126 [108; 148]         | .841        |
| Follow-up                                                 | 118 [96; 156]                  | 104 [94; 125]**                | 123 [103; 155]                 | 105 [93; 124]**        | .015        |
| PWTd (mm)                                                 |                                |                                |                                |                        |
| Baseline                                                  | 11.5 ± 1.9                     | 11.3 ± 1.8                     | 11.7 ± 1.9                     | 11.2 ± 1.9             | .234        |
| Follow-up                                                 | 11.7 ± 2.2                     | 11.1 ± 2.2                     | 11.8 ± 2.5                     | 11.2 ± 2.6             | .277        |
| IVTd (mm)                                                 |                                |                                |                                |                        |
| Baseline                                                  | 11.7 ± 2.5                     | 11.8 ± 1.7                     | 12.0 ± 2.7                     | 12.0 ± 1.8             | .955        |
| Follow-up                                                 | 12.1 ± 3.0                     | 11.2 ± 1.9**                   | 12.1 ± 2.6                     | 11.1 ± 1.9**           | .038        |
| LVDd (mm)                                                 |                                |                                |                                |                        |
| Baseline                                                  | 53.2 ± 7.5                     | 52.7 ± 7.5                     | 52.5 ± 8.1                     | 53.7 ± 7.6             | .479        |
| Follow-up                                                 | 52.4 ± 7.6                     | 50.4 ± 6.4**                   | 53.0 ± 7.3                     | 50.7 ± 6.2**           | .121        |
| LAD (mm)                                                  |                                |                                |                                |                        |
| Baseline                                                  | 48.8 ± 7.3                     | 46.6 ± 7.1                     | 48.2 ± 7.5                     | 46.7 ± 7.4             | .362        |
| Follow-up                                                 | 48.3 ± 8.4                     | 46.7 ± 5.9                     | 48.0 ± 7.8                     | 46.5 ± 5.5             | .310        |

Note: Values are shown as mean ± SD or median [IQR].
Abbreviations: HFpEF, heart failure with preserved ejection fraction; IQR, interquartile range; IVTd, diastolic interventricular thickness; LAD, left atrial diameter; LV, left ventricular; LVDd, diastolic left ventricular diameter; LVEF, left ventricular ejection fraction; PS, propensity score; PWTd, diastolic posterior wall thickness.

*p < .05 versus baseline; **p < .01 versus baseline; ***p < .001 versus baseline.
vulnerable hemodynamic state caused by left ventricular diastolic dysfunction. Evaluation of hospitalization showed significantly lower event rates after CA, indicating that resolution of HFpEF may decrease morbidity. In addition, we found that heart failure symptoms as measured by NYHA-class significantly improved after CA, but showed a trend towards aggravation in the medical treatment group, suggesting a beneficial effect of CA on heart failure in HFpEF patients with AF. This finding is also underscored by the significant decrease of NT-pro BNP levels following CA.

\[ \beta \]-Blocker treatment differed significantly between CA and the medical treatment group at baseline. The explanation for this difference is simple: For patients undergoing rate control, \( \beta \)-blockers are the first choice treatment, whereas successful rhythm control may leave \( \beta \)-blockers dispensable. The question is whether this difference may have an impact on HFpEF and heart failure hospitalization. Evidence for \( \beta \)-blockers in HFpEF is limited. A meta-analysis of two randomized controlled trials (RCTs) and 15 observational studies found an association of \( \beta \)-blocker treatment with lower all-cause mortality but no effect on heart failure hospitalization. However, if only the RCTs were included in the meta-analysis, there was no effect on either heart failure hospitalization or all-cause mortality. In contrast, a recent secondary analysis of the TOPCAT trial found an association of \( \beta \)-blocker treatment with increased heart failure hospitalizations in HFpEF patients. Thus, we cannot exclude the possibility, that differences in baseline \( \beta \)-blocker treatment may have influenced our outcomes, but the contradictory results on \( \beta \)-blocker treatment in HFpEF make it difficult to draw definite conclusions.

Despite the improvement in symptoms and diastolic function in the CA group, there was no difference in mortality between both groups, which might be related to the low mortality rate and possibly to the relatively small sample size. In addition, CA in HFrEF patients leads to an almost immediate decrease in hospitalization but survival curves separate only after 3 years in the CASTLE-AF trial. Thus, it is possible that our mean follow-up of almost 3 years is still too short to detect a difference in mortality. Nevertheless, in conclusion, our results suggest that AF ablation may prevent heart failure rehospitalization in HFpEF patients.

**FIGURE 4** Patients' NYHA class at baseline and at the end of follow-up in the medical therapy and ablation therapy groups. While in patients receiving medical therapy median NYHA-class increased (baseline: 2 [2, 3], follow-up: 3 [2, 3]; \( p = .102 \)), NYHA-class after catheter ablation significantly decreased (baseline: 2 [2, 3], follow-up: 1 [1, 2]; \( p < .001 \)). IQR, interquartile range; NYHA, New York Heart Association

**FIGURE 5** NT-pro BNP levels at baseline and at the end of follow-up and reassessment of diagnostic HFpEF criteria at the end of follow-up. (A) Logarithmic view of patients' plasma NT-pro BNP levels at baseline and follow-up in the medical and ablation therapy group. (B) Schematic view of the reassessment of diagnostic HFpEF criteria, demonstrating significant resolution of HFpEF diagnostic only in the ablation group. HFpEF, heart failure with preserved ejection fraction; NT-pro BNP, NT-pro brain natriuretic peptide.
Patients receiving CA progressed from paroxysmal to persistent AF significantly less frequently than medically treated patients. It is known that AF progression is associated with a higher symptomatic burden, more frequent hospital admissions, and major adverse cardiovascular events. As heart failure has been identified as an important risk factor for AF progression, patients with HFrEF supposedly are more prone to progression of AF than those without. Interestingly, only one out of 26 patients in the CA group had progression from paroxysmal to persistent AF, compared to six out of 22 patients in the medical treatment group, suggesting that rhythm control by CA might have a protective effect on atrial pathology in HFrEF patients preventing progression of AF.

It is challenging to assess an improvement or progression of heart failure in HFrEF patients with AF because the typical complaints of both conditions overlap. To account for this issue and add confidence to our clinical results, we evaluated objective HFrEF criteria before inclusion and at the end of follow-up. We observed a significant decrease in mitral peak E-wave velocity, IVTd, LVDd, E/E' ratio, and LVMI in patients undergoing CA, whereas those receiving medical treatment showed no difference, indicating improvement of diastolic function only by CA. Finally, we reassessed the ESC diagnostic criteria for HFrEF at the end of follow-up and found that patients receiving CA for AF experienced resolution of HFrEF significantly more often than those treated medically. These results suggest that CA, but not medical rate or rhythm control, is able to induce reverse remodeling in HFrEF patients.

5 | LIMITATIONS

This is a single-center case-control study comparing the effects of CA and medical therapy on echocardiographic and clinical outcomes of HFrEF patients with concomitant AF. In the CA group, the index ablation procedure was exclusively carried out as a cryoballoon PVI-only ablation procedure and, therefore, our results cannot necessarily be generalized to patients undergoing point-by-point radiofrequency ablation as the index procedure. RCTs are warranted for verification of our results. Nevertheless, propensity score matching was applied to balance both treatment groups. Assuming that we have not missed any important characteristics for propensity score matching in our patients, we achieved two treatment groups without significant differences in any of the recorded relevant baseline characteristics, except β-blocker treatment, but the effects of β-blockers on HFrEF are controversial in the literature.

6 | CONCLUSION

This is the first study evaluating the effects of CA for AF in comparison to medical therapy in patients with concomitant HFrEF. CA, but not medical therapy, led to an improvement of diastolic function, heart failure symptoms, and clinical outcomes. As a result, AF ablation should be considered in patients with HFrEF and concomitant AF.

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DATA AVAILABILITY STATEMENT

Data are available upon reasonable request.

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