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The Impact of Known Heart Disease on Long-Term Outcomes of Catheter Ablation in Patients with Atrial Fibrillation and Left Ventricular Systolic Dysfunction: A Multicenter International Study

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Brief Title

The impact of Known Heart Disease on AF Ablation Outcomes

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Abstract

Background

Catheter ablation for AF is an effective treatment for patients with AF and systolic LV dysfunction; however, the clinical outcome is variable. We evaluated the impact of cardiomyopathy etiology on long-term outcomes post catheter ablation.

Methods

Patients undergoing AF ablation across 3 centers (2 Australian, 1 UK) from 2002-2014, with LVEF<45% were evaluated. Patients were stratified into those with known heart disease as a cause of cardiomyopathy (KHD), and those with idiopathic dilated cardiomyopathy (IDCM).

Results

101 patients (IdCM=77, KHD=24) with AF and LVEF <45% underwent AF ablation. The KHD group (ischemic HD in 67%) were older (61±7 vs. 55±11 years, p=0.005), with a higher CHADS2 score ((2.0±0.8 vs. 1.6±0.7, p=0.016), but otherwise well matched. After mean follow-up of 36±23 months, AF control was greater in the IDCM group (82% vs. 50% in KHD, p<0.001). On multivariate analysis IDCM was associated with long-term AF control (p=0.033). The IDCM group had less functional impairment at follow-up (NYHA class 1.5±0.7 vs 2.0±0.8, p=0.005) and improved LVEF (50±11% vs. 38±10%, p<0.001). Super-responders, (EF improvement >15%), were overwhelmingly in the IDCM group (94% vs. 6%, p<0.001) with greater AF control (89% vs. 61%, p<0.001). All-cause mortality was significantly higher in the KHD group (17% vs. 1.3%, p=0.002)

Conclusion

IDCM was associated with greater AF control, and improvement in symptoms and LVEF compared to patients with KHD post AF ablation. AF is an important reversible cause of HF in patients with an unexplained CM and catheter ablation an effective treatment option.

Keywords

Atrial fibrillation

Known heart disease

Catheter ablation

Idiopathic Cardiomyopathy

Coronary artery disease

Abbreviations

AF	Atrial fibrillation
AMI	Acute Myocardial Infarction
BHR	Baseline heart rate
CRT	Cardiac resynchronisation therapy
CMR	Cardiac Magnetic Resonance
HF	Heart failure
IDCM	Idiopathic cardiomyopathy

KHD	Known heart disease
LV	Left ventricular
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
PV	Pulmonary vein

Introduction

Atrial fibrillation (AF) and heart failure (HF) are growing epidemics in most developed countries. A complex interplay of clinical and physiological factors characterize the relationship of AF and HF, with each condition promoting the progression of the other[1, 2]. The poor efficacy of pharmacological approaches in restoring and maintaining sinus rhythm has confounded the ability to demonstrate a benefit of rhythm control in this patient population[3]. Randomized studies have shown improvements in left ventricular function, heart failure symptoms and VO2 max in patients with LV dysfunction who undergo catheter ablation compared to medical therapy[4-7]. Importantly, these benefits are predicated on successful restoration of sinus rhythm following catheter ablation; thus, factors influencing the effectiveness of AF ablation in HF warrant exploration. A recent meta-analysis highlighted the role of pre-existing known heart disease (KHD) on the efficacy of catheter ablation in HF, yet the impact of this factor on HF outcomes (such as LV ejection fraction [LVEF] and functional capacity) has not been systematically evaluated. The aim of the present study was to evaluate the impact of the etiology of the cardiomyopathy on freedom from AF, LVEF and New York Heart Association (NYHA) functional class following catheter ablation.

We hypothesised that patients with a so called idiopathic cardiomyopathy were more likely to have an arrhythmia-mediated mechanism underlying the cardiomyopathy and consequently obtain greatest benefit from catheter ablation.

Methods

Patient selection

The study population included consecutive patients with AF referred for catheter ablation between 2002 to 2014. Patients were included if aged >18 years, NYHA class ≥ 2 on optimal medical therapy with adequate rate control. Patients were excluded for analysis if had had

previous left atrial ablation, or an intervening procedure (such as revascularization or CRT) that may have impacted upon LVEF improvement. The study was approved by the institutional ethics bodies of the Alfred Hospital Melbourne, Royal Melbourne Hospital and St Bartholomews Hospital, London, United Kingdom.

Definitions

Patients were classified based on the presence or absence of a known cause for the LV dysfunction. Known heart disease was defined as a recognized cause of left ventricular dysfunction such as myocardial infarction, valvular heart disease or hypertrophic cardiomyopathy (HCM). Ischemic heart disease was defined by the presence of regional wall motion abnormalities consistent with a prior myocardial infarction represented on echo, nuclear or cardiac magnetic resonance (CMR) imaging in the presence of documented occlusive coronary disease. Valvular heart disease was defined by standard echocardiographic evidence of severe valvular dysfunction considered primarily responsible for the left ventricular dysfunction. Hypertrophic cardiomyopathy was defined according to standard criteria with concurrent left ventricular dysfunction[8]. Although other less common causes of left ventricular dysfunction were recognized, only ischemic, valvular and HCM were present in the study population. IDCM was defined as no recognized cause of LV dysfunction, with a typical imaging appearance of global systolic impairment, in the absence of valvular or occlusive coronary disease. Secondary causes were excluded as per current heart failure management guidelines[9].

A super response was defined as an absolute improvement in LVEF of 15% or greater from the pre-procedural assessment. Baseline NYHA class was determined at time of initial pre-procedural clinical review and follow-up as documented at the last clinical review.

Ablation procedure

Individual ablation practices differed between centers, however consisted of the following general approaches. Transesophageal echocardiography was performed to exclude intra-cardiac thrombus. Anticoagulation was ceased 2-5 days prior to ablation or continued (in the case of vitamin K antagonists) at operator discretion, with intravenous heparin utilized intra-procedurally. Ablation was performed with a 4mm irrigated ablation catheter (Biosense Webster Inc. or St Jude Medical) with 3D electroanatomical mapping CARTO3 (Biosense Webster Inc.) or Ensite Velocity (St Jude Medical), with a multipolar catheter utilized to confirm PV isolation. PV isolation with bidirectional block was the procedural endpoint in all cases with additional ablation for substrate modification or the treatment of organized atrial arrhythmias performed at the discretion of the operator. A 3-month blanking period post procedure for arrhythmia monitoring was observed.

Follow-up

Patients were routinely reviewed at 6 weeks then every 6 months with a combination of (1) ECG, (2) 24-hour holter monitoring, (3) interrogation of dual lead implantable device or implantable loop recorder where available.

AF control was defined as freedom from AF or marked (>90%) reduction in AF burden on or off previously ineffective antiarrhythmic therapy[10]. LVEF assessment was determined by echocardiography, cardiac MRI or gated blood pool scan. Echocardiographic LV assessment was performed using the Simpson's biplane technique utilizing 4-chamber and 2-chamber LV views. CMR LVEF assessment was performed via the summation of disc methods. Only patients with pre- and post-ablation LVEF assessments utilizing the same modality were included to avoid the

impact of discrepancies between different modalities in the measurement of LVEF. Follow-up LVEF was performed a minimum of 6 months post index ablation procedure.

Statistical analysis

Data are expressed as mean±standard deviation (SD) unless otherwise indicated. After assessment of normal distribution with the Kolmogorov–Smirnov test, two-group comparisons were made using Student's t test for continuous variables, or the Chi-squared test for categorical variables. The independent samples Mann-Whitney U test was used for non-normally distributed variables. Binary logistic regression analysis was utilized to assess the association of continuous and categorical variables with multi-procedural freedom from AF and greater than 15% absolute LVEF improvement at follow-up in univariable and multivariable models. A two-tailed p value of <0.05 was considered significant. Analyses were conducted using SPSS software (version 23, IBM, Chicago, Illinois).

Results

Study Population (table 1)

A total of 2,484 patients were screened across the 3 centers with 118 patients meeting the inclusion criteria. A consort diagram is presented in figure 1. Seventeen patients were excluded due to incomplete clinical records, with 101 patients (IDCM in 77 and KHD in 24 patients) included. In the KHD group myocardial infarction was present in 16 (68%), HCM in 4 (16%), and severe valvular disease in 4 (mitral regurgitation in 2 and aortic valvular disease in 2).

Patients in the KHD were significantly older (61±7 vs. 55±11 years, p=0.005), with more coronary artery disease (67% vs. 12%, p<0.001) and a higher average $CHADS_2$ score (2.0±0.8 vs. 1.6±0.7, p=0.016). In addition, the KHD group were more likely to be prescribed amiodarone (54% vs. 31%, p=0.041), and ACE inhibitors (83% vs. 57%, p=0.021) at baseline, and more likely to have an implantable cardiac defibrillator (38% v 9%, p<0.001). In the present study, a rhythm control strategy using cardioversion and/or amiodarone had been instituted in 76% the IDCM group and 83% in the SHD group (p=0.41).

Implantable cardiac devices capable of detecting atrial arrhythmia (ILR or any implantable device with a functioning atrial lead) were present in 42% of the KHD group and 18% of the (p=0.018).

The groups were otherwise well matched including for duration of continuous AF, AF type, LA dimensions and NYHA class. Patients in the IDCM group were far more likely to be co-diagnosed with HF and AF on initial presentation (49% vs. 17%, p=0.004). CMR imaging was performed at baseline in 26% of patients in the IDCM group and 13% in the KHD group (p=0.17), and at follow-up in 9% of the IDCM group and in none of the KHD group (p=0.13). In the present study, a rhythm control strategy using cardioversion and/or amiodarone had been previously instituted in 76% the IDCM group and 83% in the KHD group (p=0.41).

Procedural Characteristics (table 2)

Pulmonary vein isolation was successfully achieved in 100 of 101 patients. Additional substrate modification did not differ significantly between the two groups (IDCM in 77% and KHD in 83%, p=0.49 see table 2). Procedure duration (IDCM vs KHD; 240±86 minutes vs 256±111 minutes, p=0.54) and radiation doses (22745±26998 vs 12903±15465 DAP $mGycm^2$, p=0.16) did not differ significantly between the two groups.

AF control

After a mean follow-up of 36 ± 22months multi-procedural AF control was documented in 82% in the IDCM group vs. 50% in KHD group (p=0.002). The mean number of procedures was 1.6±0.75 in the IDCM group and 1.8±0.9 in the KHD group (p=0.13).

Univariate analysis identified age, coronary artery disease, myocardial infarction, KHD, CHADS2 score, initial AF and HF co-diagnosis, amiodarone and ACE inhibitor therapy as predictive of AF control. Following a binary logistical regression model the absence of KHD was the only predictor of AF control at final follow-up (p=0.033).

The two groups were well matched for follow-up duration (IDCM: 35±22 months vs KHD: 33±19 months, p=0.81).

Functional Status Post Ablation (Figure 3)

There was no significant difference in baseline NYHA functional class between the groups. Both groups demonstrated a significant improvement in average NYHA functional class from baseline to last follow-up post ablation. At follow-up, those without KHD had a significantly lower degree of function limitation than those with IDCM (mean NYHA Class 2.0±0.8 vs 1.5±0.7, p=0.005).

Left Ventricular Ejection Fraction (Figures 5A, 5B and Table 3)

At baseline the LVEF did not differ between the groups (IDCM vs. SHD, 36±8% vs. 35±8%, p=0.59). However, at follow-up those with IDCM had a significantly greater LVEF than those with KHD (mean LVEF 50±11% vs 38±10%, p<0.001). The absolute improvement in LVEF in the

IDCM group was 14% (p<0.001) compared to 3% in the KHD group (p=0.25, Figure 4). Furthermore, significantly more patients had a normalized LVEF (≥55%) post ablation in the IDCM (38%) compared to the KHD group (6%, p=0.0015). In the IDCM group, there was no significant difference in LVEF improvement when stratified according to baseline heart rates of greater than (Δ average LVEF: +16%) vs less than 100bpm (+14%, p=0.64, See Table 3). After exclusion of patients with baseline resting heart rates >100bpm, (23 patients in the IDCM group, 7 in the KHD group), AF control (85% vs 41%, p=0.0017) and LVEF improvement (+13.4% vs +4.5%, p<0.001) remained significantly greater in the IDCM group. The degree of dyspnea (as estimated by NYHA class) or palpitations on presentation were not predictive of the adequacy of rate control in the IDCM group (See table 3).

The lack of improvement in LVEF in the SHD group at final follow-up, was independent of AF control (KHD group with AF control: (n=12) Δ average LVEF=+1.8% [p=0.67], KHD group without AF control: (n=12) Δ average LVEF= +4.6% [p=0.24]). Super responders were more likely to have IDCM (p<0.001), a reduced baseline LA diameter (45±5mm vs 48±7mm, p=0.022) and lower baseline LVEF (33±9% vs 37±7%, p=0.014). A significant reduction in LA diameter was noted in the super responders at follow-up assessment (45±5mm vs 42±7mm, p=0.04). On multivariate analysis, the presence of IDCM was the only significant predictor of super responder status (p=0.008, Figure 5A). Super responders were associated with a significantly greater AF control than the rest of the study cohort (89% vs. 61% in LVEF improvement<15%, p<0.001, Figure 5B).

Twenty-two of 77 patients in the IDCM group, (28.5%) underwent CMR data, of which only 5 (23%) had late gadolinium enhancement (LGE). All LGE was localized to the mid wall, a common association with idiopathic cardiomyopathy[11]. Two of 24 patients in the KHD group underwent CMR data. Both patients had hypertrophic cardiomyopathy with transmural mid

wall enhancement. Fifteen patients in the KHD group (62.5%) who did not undergo CMR had evidence of a myocardial infarction on echocardiography.

There was a significant improvement in LVEF in the LGE positive (n=5: 34% to 44%, p=0.03) and LGE negative groups n=17: 37.2% to 51.5%, p<0.001).

Mortality

All cause mortality was significantly higher in the KHD group (17% vs. 1.3%, p=0.002). There were 5 deaths in total - 4 deaths in the KHD group and 1 death in the IdCM group. The single death in the IdCM group was from an electro-mechanical dissociative (EMD) arrest. In the KHD group, one death was an EMD arrest, another from malignancy and remaining two from unknown causes. No deaths occurred within 30 days of an index or redo AF ablation procedure.

Discussion

Catheter ablation offers the potential benefits of restoring sinus rhythm without the deleterious effects of antiarrhythmic medications in patients with atrial fibrillation and left ventricular dysfunction. However, there is significant variation in procedural outcomes and the impact on heart failure symptoms and LV function. In this multicenter international study, we evaluated the outcomes of a cohort of patients with concurrent LV dysfunction and AF undergoing catheter ablation stratified according to the presence of known heart disease. Patients with AF and an unexplained or IDCM demonstrated:

1. a significantly higher AF control (82%) compared with known heart disease (50%, p=0.0017) at a mean follow up of 3 years;

2. a significantly greater improvement in NYHA functional class;
3. an absolute improvement in LVEF of 14% (p<0.001);compared with 3% in KHD group (p=0.25);
4. a lower total mortality (1.3%) compared with 17% in the KHD group (p=0.002).

Freedom from AF and Structural Heart Disease

Catheter ablation has become an important strategy for the management of atrial fibrillation in heart failure. A large randomized multicenter study did not support a pharmacologic strategy of rhythm control over rate control; however, catheter ablation was not included[3, 12]. Haissaiguerre and co-workers reported substantial improvements in heart failure symptoms and LV function in 58 patients with an average LVEF or 35±7%, of which 26 patients were categorized as KHD. There was no significant difference in multi-procedural freedom of AF at an average of 12±7 months post ablation to those with 'dilated cardiomyopathy alone' (73% vs. 81%, p=0.46)[13]. Further single-center studies have reported on the efficacy of catheter ablation in patients with atrial fibrillation and LV dysfunction; however, the impact of structural heart disease on outcome has been limited by small numbers or excluding patients with KHD and inconsistent definitions[4, 5, 10, 14]. A meta-analysis of AF ablation outcomes in the heart failure population included 1838 patients from 26 studies and reported a reduction in AF recurrence in patients free of known heart disease[6]. The present multicenter study is consistent with the findings from the earlier meta-analysis in that patients with an idiopathic cardiomyopathy who underwent AF ablation had a significantly higher freedom from AF. However, the present study has some important differences. First, the study population included a greater proportion of persistent (78% vs 55%) and longstanding persistent AF patients (47% vs 5%) compared with the meta-analysis. Second, the meta-analysis reported studies with a conventional definition of AF recurrence (documented > 30 seconds of AF or atrial tachycardia) and found increased

recurrence in patients with KHD. The present study applied a definition of AF control defined as greater than 90% reduction in AF burden[15-17]. Last, significant improvements in heart failure symptoms and LV function were demonstrated compared with KHD group.

Functional Improvement

Functional improvement following AF ablation in the heart failure population is well established and proportional to the maintenance of sinus rhythm[4, 5, 7]. Although earlier studies have demonstrated improvements in NYHA functional class[4, 13] and quantitative functional capacity[4, 5] post AF ablation, the impact of LV dysfunction etiology has not been determined. Nedios et al reported an attenuated improvement in NYHA class post catheter ablation in 26 patients with coronary artery disease between those with and without regional wall motion abnormalities[15]. To our knowledge the present study is the first to report a significant difference in functional status improvement in patients with idiopathic CM compared with known KHD.

Improvement in Left Ventricular Ejection Fraction

Several studies have demonstrated significant improvements in LVEF following AF ablation, particularly in patients with no known cause of cardiomyopathy[4, 5, 18-21], although few have sought specifically to evaluate the population with KHD. Hsu et al found patients with 'concurrent structural heart disease' had significant improvements in LVEF post ablation although to a significantly lesser extent than those without (16±14% vs. 24±10%, p=0.007 for comparison)[13]. Nedios et al reported that the presence of structural heart disease was not a significant multivariate predictor of LVEF improvement post ablation, particularly in those with regional wall motion abnormalities[15]. The magnitude of improvement in LV function is

predominantly determined by the long-term maintenance of sinus rhythm, rather than other HF therapy[10, 13, 15]. The present study found no significant improvement in LVEF in patients post AF ablation with KHD.

The findings from the subgroup of patients who underwent CMR suggests that the presence of LGE may have a role in predicting LV recovery following catheter ablation in patients with IDCM, however the study was underpowered to draw meaningful conclusions.

Atrial and Ventricular Remodeling in Cardiomyopathy Post AF ablation

The physiological relationship between AF and HF is complex. Kalman and colleagues demonstrated that advanced atrial electrical and structural remodeling is present in patients with LV dysfunction[22]. In patients diagnosed with an idiopathic cardiomyopathy in which an arrhythmia mediated mechanism is in fact responsible for the LV dysfunction, improvement in LVEF following the restoration of sinus rhythm may be followed by reverse ventricular and atrial remodeling. KHD may be associated with progressive irreversible replacement fibrosis in the ventricular myocardium, irrespective of cardiac rhythm. Replacement fibrosis can be quantified by the extent of late gadolinium enhancement (LGE) on cardiac MRI and is associated with poor recovery of LV function[23], in addition to adverse cardiac events and prognosis. Similarly, fibrosis in the setting of other SHD such as hypertrophic cardiomyopathy[24] and severe valve disease[25] has been described and limits reverse remodeling. Persisting left ventricular dysfunction maintains elevated atrial pressure and chronic stretch likely explains the vulnerability to AF recurrence. A distinct pattern of mid wall replacement fibrosis is often present in IDCM and can predict LVEF recovery[26]. Ling et al have previously demonstrated that the absence of MRI detected fibrosis in patients with IDCM can predict LV remodeling post AF ablation[20].

Mortality

The finding of a significant difference in mortality between the groups should be interpreted with caution given small numbers and limited details regarding the nature of the deaths. The mortality demonstrated in the KHD group may reflect the attributable mortality in a HF population with significant co-morbidities whose LVEF remains essentially unaltered over several years[27]. Nonetheless, the anticipated mortality in the IDCM with AF of 10-30%[3] over the follow-up period was well above that demonstrated in this study (1.7%), in which 85% of patients had some improvement in LVEF, with nearly half of these normalizing LVEF over the period. The impact of AF ablation on long-term mortality in the heart failure population remains the focus of an ongoing international randomized controlled trial[28].

Limitations

This is a retrospective study with inherent limitations of this study design. We await with interest the outcome of large randomized controlled trials in this area such as CASTLE AF[28]. As with earlier studies there is a selection bias, as only patients referred for AF ablation were included. As such, this heart failure population may not be truly reflective of the wider heart failure population and, as such, the findings in this study may not be applicable to the broader heart failure population. The proportion of implantable devices capable of continuous atrial monitoring for the detection of atrial arrhythmia were significantly higher in the KHD group (42% vs 18%, p=0.018). However, there was no significant difference between the primary endpoint of AF control when comparing those with and without atrial monitoring (atrial monitor (n=54) vs no atrial monitor (n=47); 78% vs 70%, p=0.38), across the cohort. Given the

limited number of patients with AF control in the KHD group, no definitive conclusion can be made regarding the impact of AF ablation on LVEF improvement in this patient population.

Conclusion

The presence of KHD contributing to LV dysfunction is associated with a reduction in the maintenance of sinus rhythm post ablation, functional improvement and improvement in LVEF. Conversely, the absence of KHD identifies a HF population who receive greater benefit from catheter ablation for AF and should be strongly considered.

References

[1] Anter E, Jessup M, Callans DJ: Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. Circulation 2009; 119:2516-2525.

[2] Aleong RG, Sauer WH, Davis G, Bristow MR: New-onset atrial fibrillation predicts heart failure progression. The American journal of medicine 2014; 127:963-971.

[3] Talajic M, Khairy P, Levesque S, Connolly SJ, Dorian P, Dubuc M, Guerra PG, Hohnloser SH, Lee KL, Macle L, Nattel S, Pedersen OD, Stevenson LW, Thibault B, Waldo AL, Wyse DG, Roy D, Investigators A-C: Maintenance of sinus rhythm and survival in patients with heart failure and atrial fibrillation. Journal of the American College of Cardiology 2010; 55:1796-1802.

[4] Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, Goromonzi F, Sawhney V, Duncan E, Page SP, Ullah W, Unsworth B, Mayet J, Dhinoja M, Earley MJ, Sporton S, Schilling RJ: A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circulation Arrhythmia and electrophysiology 2014; 7:31-38.

[5] Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, McDonagh TA, Underwood SR, Markides V, Wong T: A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. Journal of the American College of Cardiology 2013; 61:1894-1903.

[6] Anselmino M, Matta M, D'Ascenzo F, Bunch TJ, Schilling RJ, Hunter RJ, Pappone C, Neumann T, Noelker G, Fiala M, Bertaglia E, Frontera A, Duncan E, Nalliah C, Jais P, Weerasooriya R, Kalman JM, Gaita F: Catheter ablation of atrial fibrillation in patients with left ventricular systolic dysfunction: a systematic review and meta-analysis. Circulation Arrhythmia and electrophysiology 2014; 7:1011-1018.

[7] Suman-Horduna I, Roy D, Frasure-Smith N, Talajic M, Lesperance F, Blondeau L, Dorian P, Khairy P, Investigators A-CT: Quality of life and functional capacity in patients with atrial fibrillation and congestive heart failure. Journal of the American College of Cardiology 2013; 61:455-460.

[8] Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW, American College of Cardiology Foundation/American Heart Association Task Force on Practice G: 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Journal of the American College of Cardiology 2011; 58:e212-260.

[9] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJV, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WHW, Tsai EJ, Wilkoff BL: 2013

ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013; 128:e240-e327.

[10] Gentlesk PJ, Sauer WH, Gerstenfeld EP, Lin D, Dixit S, Zado E, Callans D, Marchlinski FE: Reversal of left ventricular dysfunction following ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2007; 18:9-14.

[11] Jellis C, Martin J, Narula J, Marwick TH: Assessment of nonischemic myocardial fibrosis. J Am Coll Cardiol 2010; 56:89-97.

[12] A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation. New England Journal of Medicine 2002; 347:1825-1833.

[13] Hsu L-F, Jaïs P, Sanders P, Garrigue S, Hocini M, Sacher F, Takahashi Y, Rotter M, Pasquié J-L, Scavée C, Bordachar P, Clémenty J, Haïssaguerre M: Catheter Ablation for Atrial Fibrillation in Congestive Heart Failure. New England Journal of Medicine 2004; 351:2373-2383.

[14] Calvo N, Bisbal F, Guiu E, Ramos P, Nadal M, Tolosana JM, Arbelo E, Berruezo A, Sitges M, Brugada J, Mont L: Impact of atrial fibrillation-induced tachycardiomyopathy in patients undergoing pulmonary vein isolation. International journal of cardiology 2013; 168:4093-4097.

[15] Nedios S, Sommer P, Dagres N, Kosiuk J, Arya A, Richter S, Gaspar T, Kanagkinis N, Dinov B, Piorkowski C, Bollmann A, Hindricks G, Rolf S: Long-term follow-up after atrial fibrillation ablation in patients with impaired left ventricular systolic function: the importance of rhythm and rate control. Heart rhythm : the official journal of the Heart Rhythm Society 2014; 11:344-351.

[16] Steinberg JS, Palekar R, Sichrovsky T, Arshad A, Preminger M, Musat D, Shaw RE, Mittal S: Very long-term outcome after initially successful catheter ablation of atrial fibrillation. Heart rhythm : the official journal of the Heart Rhythm Society 2014; 11:771-776.

[17] Brooks AG, Stiles MK, Laborderie J, Lau DH, Kuklik P, Shipp NJ, Hsu LF, Sanders P: Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. Heart rhythm : the official journal of the Heart Rhythm Society 2010; 7:835-846.

[18] Bortone A, Pujadas-Berthault P, Karam N, Maupas E, Boulenc JM, Rioux P, Durrleman N, Ciobotaru V, Marijon E: Catheter ablation in selected patients with depressed left ventricular ejection fraction and persistent atrial fibrillation unresponsive to current cardioversion. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2013; 15:1574-1580.

[19] Zhu P, Zhang Y, Jiang P, Wang Z, Wang J, Yin X, Hou Y: Effects of radiofrequency catheter ablation on left ventricular structure and function in patients with atrial fibrillation: a meta-analysis. Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing 2014; 40:137-145.

[20] Ling LH, Taylor AJ, Ellims AH, Iles LM, McLellan AJ, Lee G, Kumar S, Lee G, Teh A, Medi C, Kaye DM, Kalman JM, Kistler PM: Sinus rhythm restores ventricular function in patients with cardiomyopathy and no late gadolinium enhancement on cardiac magnetic resonance imaging who undergo catheter ablation for atrial fibrillation. Heart rhythm : the official journal of the Heart Rhythm Society 2013; 10:1334-1339.

[21] MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, Denvir M, Bhagra S, Small S, Martin W, McMurray JJ, Petrie MC: Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. Heart 2011; 97:740-747.

[22] Sanders P, Morton JB, Davidson NC, Spence SJ, Vohra JK, Sparks PB, Kalman JM: Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. Circulation 2003; 108:1461-1468.

[23] Larose E, Rodes-Cabau J, Pibarot P, Rinfret S, Proulx G, Nguyen CM, Dery JP, Gleeton O, Roy L, Noel B, Barbeau G, Rouleau J, Boudreault JR, Amyot M, De Larochelliere R, Bertrand OF: Predicting late myocardial recovery and outcomes in the early hours of ST-segment elevation myocardial infarction traditional measures compared with microvascular obstruction, salvaged myocardium, and necrosis characteristics by cardiovascular magnetic resonance. Journal of the American College of Cardiology 2010; 55:2459-2469.

[24] Green JJ, Berger JS, Kramer CM, Salerno M: Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. JACC Cardiovascular imaging 2012; 5:370-377.

[25] Weidemann F, Herrmann S, Stork S, Niemann M, Frantz S, Lange V, Beer M, Gattenlohner S, Voelker W, Ertl G, Strotmann JM: Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. Circulation 2009; 120:577-584.

[26] Park S, Choi BW, Rim SJ, Shim CY, Ko YG, Kang SM, Ha JW, Jang Y, Chung N, Choe KO, Cho SY: Delayed hyperenhancement magnetic resonance imaging is useful in predicting functional recovery of nonischemic left ventricular systolic dysfunction. Journal of cardiac failure 2006; 12:93-99.

[27] Bart BA, Shaw LK, McCants Jr CB, Fortin DF, Lee KL, Califf RM, O'Connor CM: Clinical Determinants of Mortality in Patients With Angiographically Diagnosed Ischemic or Nonischemic Cardiomyopathy. Journal of the American College of Cardiology 1997; 30:1002-1008.

[28] Marrouche NF, Brachmann J: Catheter ablation versus standard conventional treatment in patients with left ventricular dysfunction and atrial fibrillation (CASTLE-AF) - study design. Pacing and clinical electrophysiology : PACE 2009; 32:987-994.

Tables and Figures

Table 1: Baseline Patient Characteristics

Variable	Idiopathic CM (n=77)	Known HD (n=24)	P value
Age	55 ± 11	61 ± 7	P=0.005
Gender (% male)	91% (70)	80% (19)	P=0.15
HTN	47% (36)	63% (15)	P=0.19
T2DM	10% (8)	21% (5)	P=0.19
Previous CVA (%)	1.3% (1)	8.3% (2)	P=0.08
Average LVEF (%)	36 ± 8	35 ± 8	P=0.59
Average NYHA class	2.3±0.7	2.5±0.3	P=0.30
Sleep apnea	5% (4)	4% (1)	P=0.83

BMI (kg/m^2)	30 ± 5	29 ± 5	P=0.38
LA diameter (mm)	46 ± 6	49 ± 8	P=0.06
LA area (mm^2)	31 ± 7	33 ± 9	P=0.38
Average CHADS2	1.6±0.7	2.0±0.8	P=0.016
Median CHADS2	2	2	P=NS
Amiodarone Rx	31% (24)	54% (13)	P=0.04
Duration of follow-up (months)	35 ± 22	33± 19	P=0.62
Sx to procedure (months)	41 ± 46	37 ± 23	P=0.69
Persistent AF	78% (60)	79% (19)	P=0.88
Longstanding PeAF	47% (36)	62.5% (15)	P=0.18
Duration of cont. AF pre-AF ablation (PeAF)	27 ± 44	32 ± 21	P=0.64
Average resting HR at time of LV assessment (bpm)	89 ± 20	83 ± 21	P=0.34
ICD implanted	9.1% (7)	38% (9)	p<0.001
Any implantable recording device	22% (17)	50% (12)	p=0.008
Implantable device with atrial monitoring (ILR or atrial lead)	18% (12)	42% (7)	p=0.018

AF & HF co-diagnosed	49% (38)	17% (4)	p=0.004

Table 2: Procedural Characteristics of the Study Population

Variable	Idiopathic CM (n=77)	Known HD group (n=24)	P value

No. of procedures	1.6 ± 0.75	1.8 ± 0.9	P=0.13
Right PV isolation	99% (76)	100% (24)	P=0.57
Left PV isolation	100% (77)	100% (24)	P=NS
Any substrate modification	77% (59)	83% (20)	P=0.49
Roof line	73% (56)	75% (18)	P=0.87
Inferior Line	58% (45)	50% (12)	P=0.33
Posterior wall isolation	56% (43)	50% (20)	P=0.59
Mitral line	23% (18)	21% (5)	P=0.70
CAFE ablation	35% (27)	46% (11)	P=0.07
CTI	52% (40)	46% (11)	P=0.77
Intra-procedure DCR	61% (47)	67% (16)	P=0.85
SR at case end	95% (73)	96% (23)	P=0.80

Table 3: Comparison of LVEF Outcomes in the IDCM Group – Stratified by Resting Baseline Heart Rate

Group	n	Average HR	NYHA class	Palpitations	Baseline (BL) LVEF	Follow-up (FU) LVEF	P value (BL vs FU)	Absolute % change
A. IDCM (HR ≥100bpm)	23	112 ± 14 bpm	2.5 ± 0.7	61%	33.3 ± 10.4%	49.4 ± 11.7%	P<0.001	16.1%
B. IDCM (HR <100bpm)	54	77.1 ± 11.1 bpm	2.2 ± 0.6	71%	37.4 ± 6.2%	50.9 ± 10.6%	P<0.001	13.5%
P value (A vs B)		P<0.001	P=0.10	P=0.25	P=0.05	P=0.64		

Figure 1: Patient Selection Flow Chart

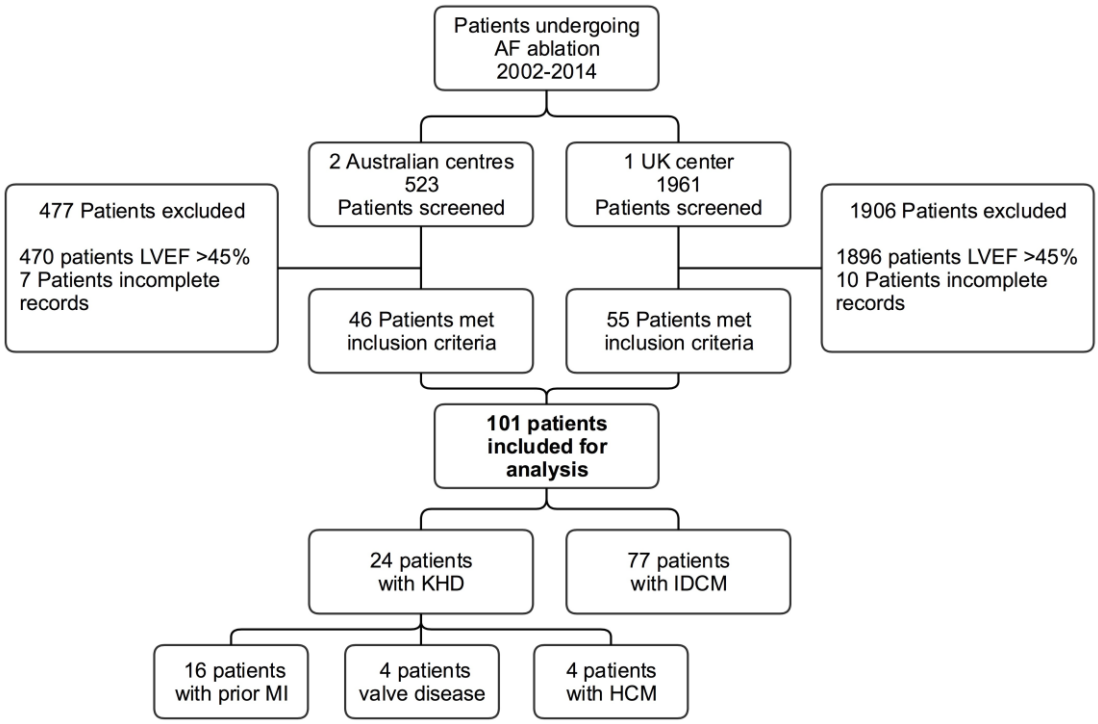


Figure 1: Consort diagram indicating the development of the study population. LVEF = left ventricular ejection fraction, UK = United Kingdom, KHD = known heart disease, IdCM = Idiopathic cardiomyopathy, MI = myocardial infarction, HCM = hypertrophic cardiomyopathy.

Figure 2: AF Control by Etiology

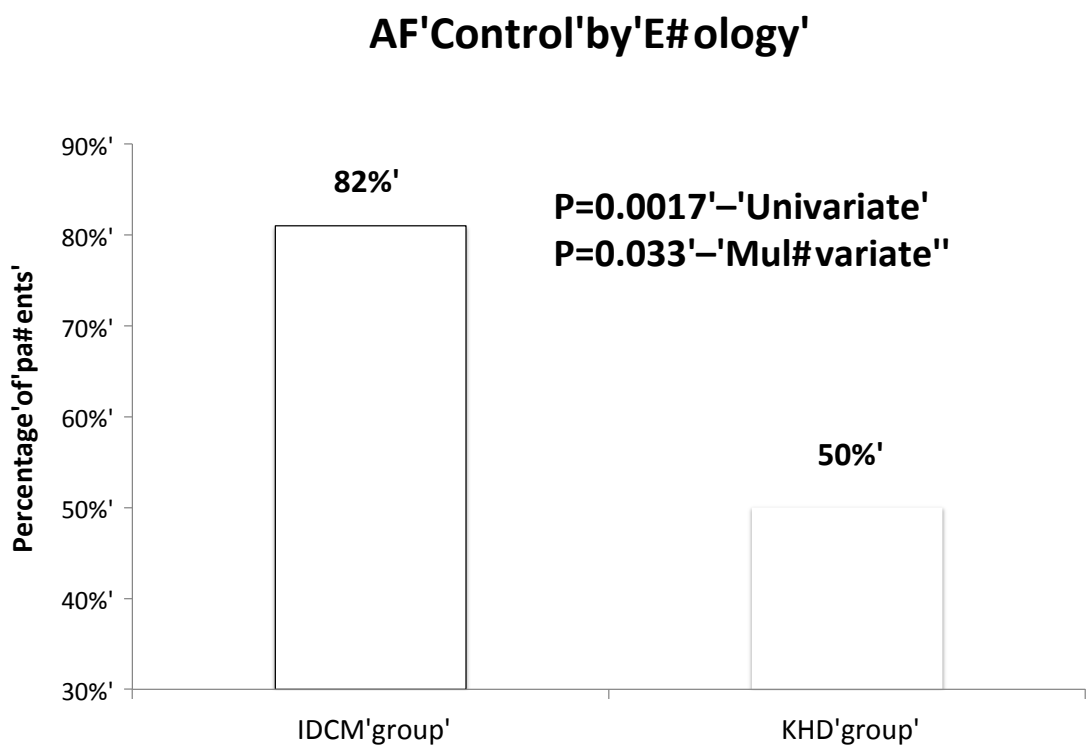
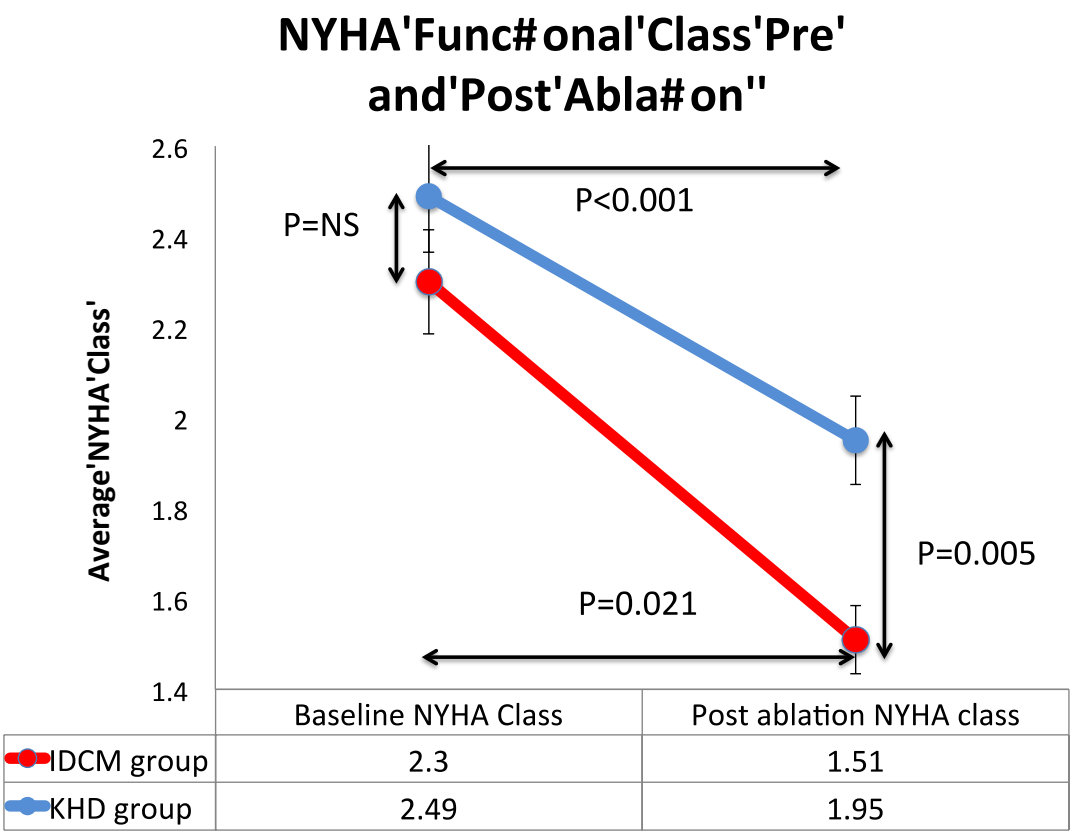


Figure 2: AF control by cardiomyopathy etiology. IDCM = idiopathic cardiomyopathy, KHD = known heart disease.

Figure 3: NYHA Functional Class Pre and Post Ablation



	Baseline NYHA Class	Post ablation NYHA class
IDCM group	2.3	1.51
KHD group	2.49	1.95

Figure 3: NYHA functional class before and after AF ablation. NHYA = New York Heart Association, IDCM = idiopathic cardiomyopathy, KHD = known heart disease.

Figure 4: Left Ventricular Ejection Fraction Pre and Post Ablation

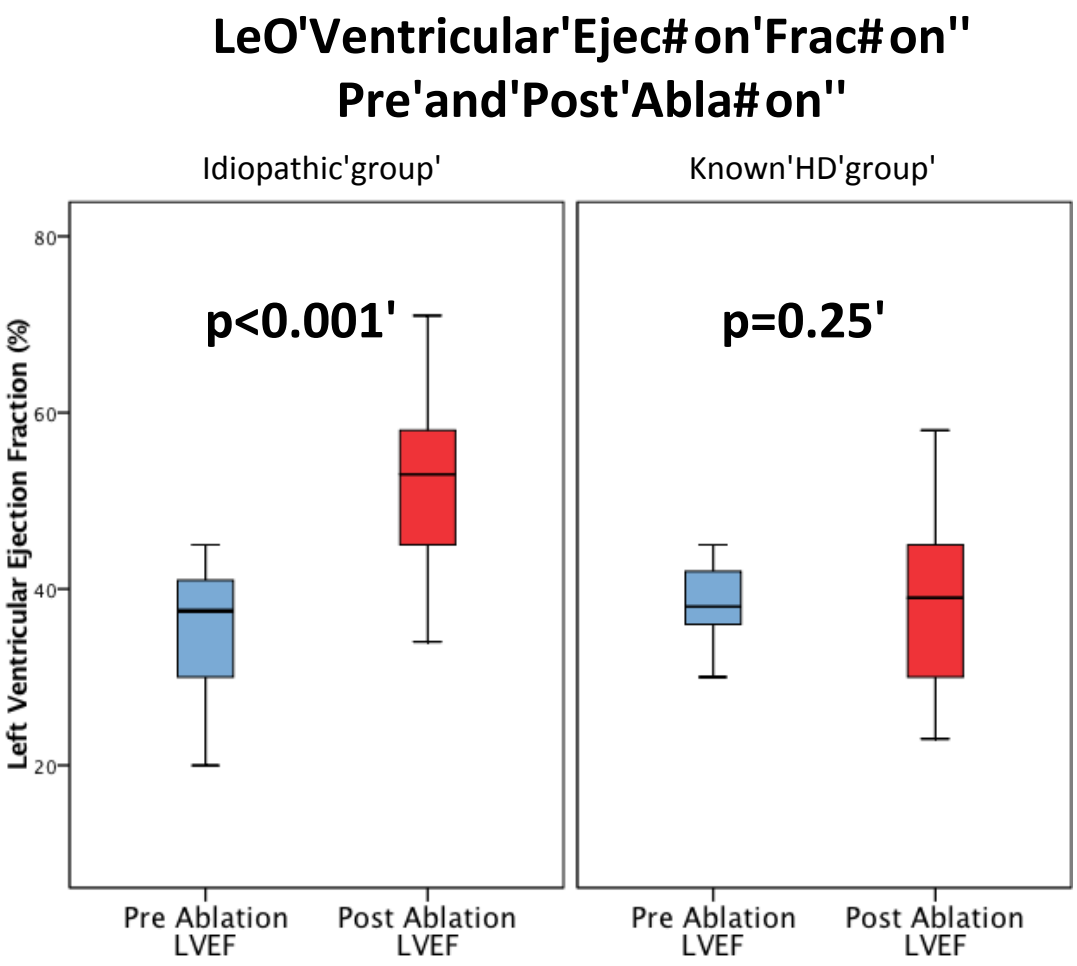


Figure 4: Average LVEF pre and post ablation for each etiology. LVEF = left ventricular ejection fraction, IDCM = idiopathic cardiomyopathy, KHD = known heart disease.

Figure 5A: Super responders and Non-super responders by eitiology

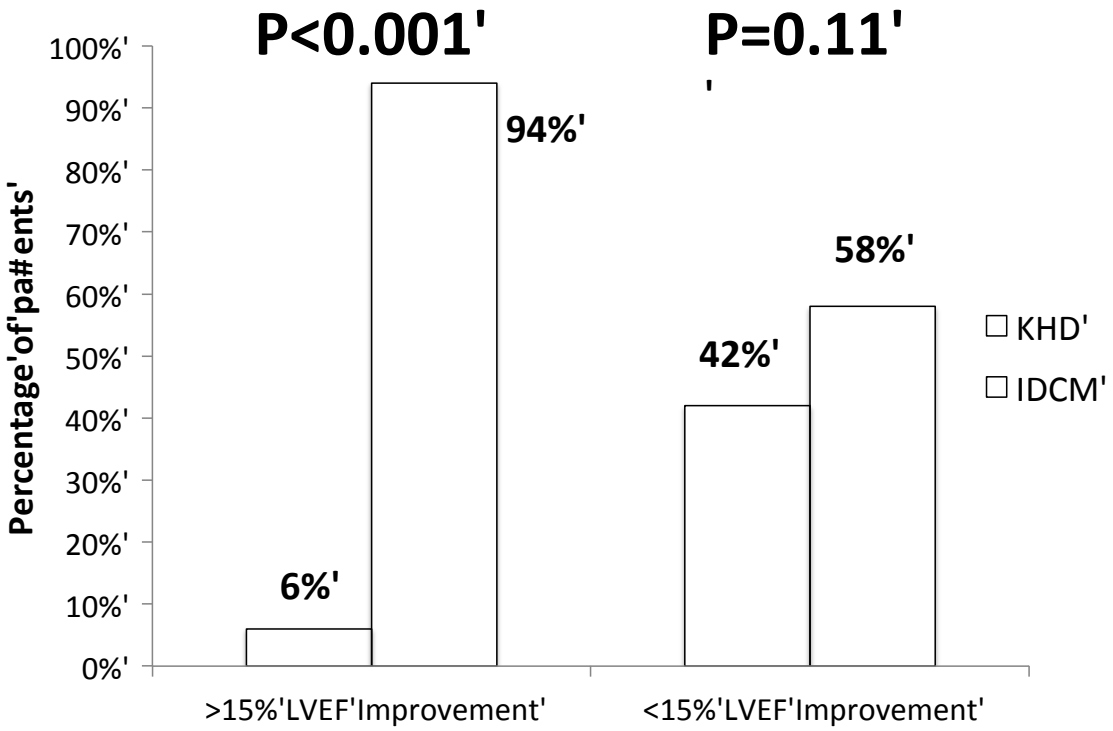


Figure 5A: The proportion of each etiology in super-responders (absolute LVEF improvement > 15%) and non-super responders. LVEF = left ventricular ejection fraction, IDCM = idiopathic cardiomyopathy, KHD = known heart disease.

Figure 5B: AF Control – Super responders vs Non-super responders

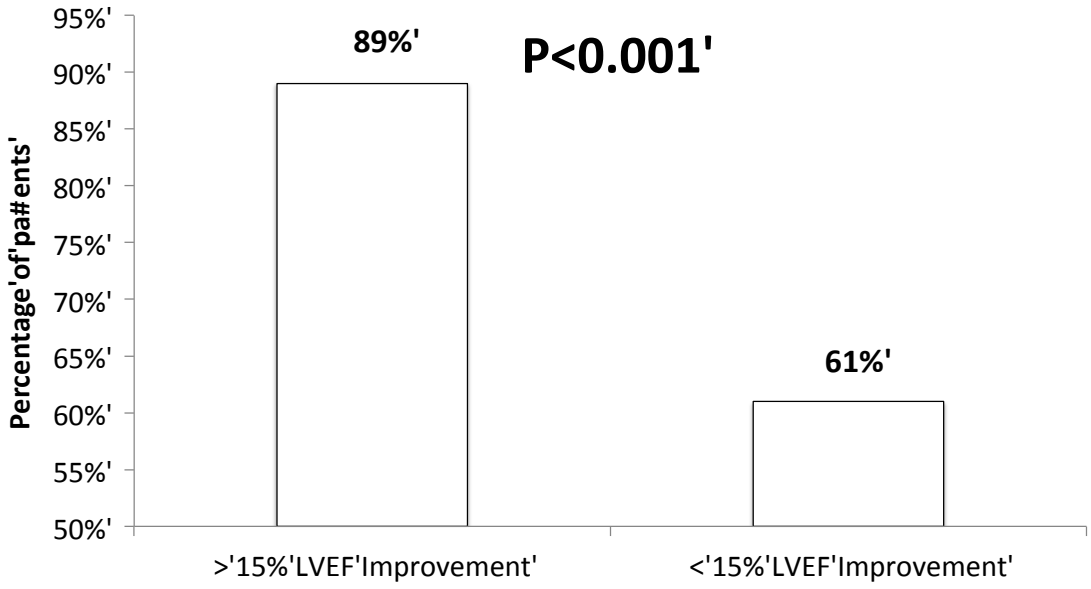


Figure 5B: A comparison of AF control at final follow-up in super responders and non-super responders