Two-Dimensional Phased Array Color-Flow Doppler Intracardiac Echo (2D-ICE) in Combination with the 2nd Generation 28 mm Cryoablation Balloon and 20mm Achieve Circular Mapping System (Arctic Front Advance, Medtronic, USA) for Ablation of Atrial Fibrillation: The ICE^2 technique (ICE^{2}T): A Retrospective Review of a Community Based Single Center Atrial Fibrillation Ablation Program

Abstract

Introduction: One eighty five consecutive patients underwent large volume left atrial cryothermal AF ablation with the ICE2 technique (ICE2T). One forty two patients with a follow up of 12±6 months had outcome analysis, all 185 patients had procedural complications and fluoroscopic time analysis.

Methods: Cryoablation was performed by direct ICE visualization of antral PV contact, entrance and exit PV block confirmed using Achieve and esophageal temperature monitoring. Additional ablation included left atrial appendage micro reentrant tachycardia and cavotricuspid isthmus performed using focal cryoablation (Freezor Max, Medtronic, USA).

Results: The mean age was 62 years, 74.6% of the patients had long-term persistent atrial fibrillation with a mean duration of 4.49 years. Twenty seven patients had congestive heart failure with mean ejection fraction of 37%. Intraprocedural efficacy of PV isolation was 100%. The mean trough temperature was -51 degrees Celsius, lowest esophageal temperature was 9°C. Sinus rhythm was achieved in all patients intra-procedurally with mean heart rate increase of 15±3 bpm. Complications included 1 femoral pseudo aneurysm managed with outpatient thrombin injection and 1 esophageal erosion, spontaneously healed with PPIs (Outcomes).

Conclusion: CE2T eliminates contact force sensing erraticism and need for complex mapping techniques, reducing complications and attaining durable PVI. The increase in mean heart rate suggests concomitant ablation of antral ganglionated plexi in conjunction with PV disconnection contributing to increased efficacy. Extrapolated data from CHF patients strongly suggests mortality benefits of rhythm control.

Keywords: Atrial fibrillation; Cryoablation; Two-dimensional phased array intracardiac echocardiography; Pulmonary venous isolation

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Abbreviations: PVI: Pulmonary Venous Isolation; AF: Atrial Fibrillation; ICE: Intracardiac Echo, AADs: Antiarrhythmic Drugs

Background

Pulmonary venous isolation (PVI) remains the cornerstone of most atrial fibrillation (AF) ablation procedures. In ablation of persistent AF, PVI is usually the first step in a stepwise approach to AF ablation. Radio frequency energy and more recently cryothermal energy are currently used clinically for ablation. Though the results in randomized trials are promising, real world results leave much to be desired. We describe a series of 185 consecutive patients with atrial fibrillation who underwent large volume left atrial cryothermal AF ablation between May 2012 and December 2013 using an innovative and novel technique with two-dimensional phased array color-flow Doppler intracardiac echo (2D-ColorFlow ICE) in combination

with the 2nd generation cryoablation balloon system (Arctic Front, Medtronic, USA): the ICE^2 technique (ICE^{2}T).

Methods

Patients with symptomatic, medically refractory atrial fibrillation referred for ablation between May 2012 and December 2013 and who subsequently underwent atrial fibrillation ablation were included in this retrospective analysis. Atrial fibrillation was defined as per the 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation [1] as under (Table 1): Informed consent was obtained from all patients prior to the procedure. All antiarrhythmic agents, except amiodarone, were stopped at least 5 half-lives before the procedure. The most common antiarrhythmic agents used were amiodarone, sotalol, dronaderone and propafenone. All patients were therapeutically anticoagulated with warfarin through the procedure. Patients who were on newer anticoagulants including factor Xa inhibitor rivaroxaban or direct thrombin inhibitor dabigatran were transitioned to warfarin at least 6 weeks prior to the procedure with documented therapeutic INRs for 4 consecutive weeks prior to the scheduled ablation. The therapeutic INR range was 2-3.5. A transesophageal echocardiogram was performed to rule out a mural thrombus if the INR was sub therapeutic in the preceding 4 weeks. A 28 mm cryoablation balloon (Arctic Front, Medtronic, USA) with a 20 mm Achieve circular mapping catheter was used for mapping and ablation in more than 95% of the cases. A 23 mm balloon with a 15 mm circular mapping catheter was used only in instances where all the pulmonary venous ostia as measured through intracardiac echocardiogram (ICE) were less than 20 mm.

Table 1: Types and classification of atrial fibrillation**

Atrial Fibrillation Exposed	An atrial fibrillation episode is defined as that is documented by ECG monitoring and has a duration of at least 30 seconds, or if less than 30 seconds, is present continuously throughout the ECG monitoring Tracing. The presence of subsequent episodes of AF requires that sinus Rhythm be documented by ECG monitoring between AF episodes
Paroxysmal AF*	Paroxysmal AF is defined as (≥2 episodes) that terminates spontaneously within 7 days. Episodes of AF of ≤ 48 hours' duration that are terminated with Electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes
Persistent AF*	Persistent AF is defined as continuous AF sustained beyond seven days. Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after ≥ 48 hours of AF, but prior to 7 days Should also be classified as persistent AF episodes
Longstanding persistent AF	Longstanding persistent AF is defined as continuous AF of greater than 12 months, duration
Permanent AF	The term Permanent AF is not appropriate in the context of patients undergoing catheter or surgical ablation of AF, as it refers to a group of patients for which a decision has been made not to restore or maintain sinus rhythm by any means, including catheter or surgical ablation. If a patient previously classified as having permanent AF is to undergo catheter or surgical ablation, the AF should be reclassified

**It is recognized that patients may have both paroxysmal and persistent AF. A patient's AF type should be defined as the most frequent type of AF experienced within Six months of an ablation procedure.*

Continuous AF is AF that is documented to be present on all ECG monitoring performed during a defined period of time.

** The term "chronic AF" not be used in the context of patients undergoing ablation of AF as it is ambiguous, and there is no standardized definition of this term.

Venous access was obtained from the both the right and left femoral veins. A long 8 French Safe Sheath and a 6 French locking sheath were placed in the left femoral vein through which a 2-dimensional phased array intracardiac echocardiogram catheter (2D-ICE) and a steerable decapolar catheter were introduced into the cardiac chambers. The right femoral vein was accessed using Across trans-septal sheath system (St. Jude Medical, St. Paul, Minnesota, USA) which was used for trans-septal access into the left atrium. The left atrial multipurpose sheath was then exchanged for a 15 F deflectable sheath (Flexcath, Medtronic, Minneapolis, Minnesota, USA) for introduction of the cryoablation balloon and the Achieve circular mapping system into the left atrium. Antral cryoballoon positioning was performed under direct and constant visualization through 2D-ICE utilizing both two-dimensional and color-flow imaging with the posterior hemisphere of the balloon outside the PV antrum. Contrast pulmonary venography was performed only in selected cases by injection through the cryoablation balloon system after the balloon was positioned when 2D color flow Doppler could not confirm PV occlusion. The deflectable decapolar catheter introduced via the left femoral vein was used for coronary sinus pacing or pacing in the superior vena cava to capture the right phrenic nerve.

Cryothermal ablation applied to each PV consisted of two sequential applications each lasting 240 seconds after a good PV seal was achieved. No specific lowest (trough) temperature was targeted but cryoablation was monitored by direct visualization of antral PV contact through 2D and color flow Doppler ICE, PV potentials on the Achieve circular mapping catheter including time to effect of PV disconnection, nadir of the freezing temperature achieved and esophageal temperature monitored through a temperature probe in the esophagus. During cryoballoon applications to the right-sided PVs, the right phrenic nerve was captured by pacing (1200 ms CL, 20 mA output) in the superior vena cava. The operator monitored the strength of right hemi diaphragmatic contractions by palpation in the right hypochondrium, visualization of the contractions on 2D-ICE and fluoroscopy if required to quickly detect injury to the right phrenic nerve. Cryoballoon applications were immediately terminated when any attenuation of the strength of right hemi diaphragmatic contractions was observed. Application times were a reduced to 180 seconds if time to PV disconnection was less than 30 seconds from the onset of the freeze. During and after each PV antrum was treated with two cryoballoon applications, the PV ostia were assessed for both entrance and exit block by mapping and pacing through the Achieve circular mapping catheter. In persistent AF patients, additional lesions included ablation of left atrial appendage micro reentrant tachycardia if observed performed by focal cryoablation (Freezor Max, Medtronic, USA). Direct current cardioversion was performed to restore sinus rhythm as applicable. If typical atrial flutter had been previously documented during electrocardiographic monitoring, cavotricuspid isthmus ablation was performed using focal cryoablation (Freezor Max, Medtronic, USA) until bidirectional isthmus block was achieved.

Postoperative Care and Follow Up

After the procedure, oral anticoagulation with warfarin was continued for at least two weeks before transitioning back to the newer anticoagulants. Amiodarone was continued in patients with nonischemic cardiomyopathy and atrial fibrillation with the intention to continue for 3-6 months or until EF normalized which ever was earlier. No blanking period was applied such that any AF recurrence during post-operative period was considered as treatment failure which was treated with either antiarrhythmic drugs (AADs) or redo ablation. Follow-up was performed by clinic visits at 2, 10 and 20 weeks followed subsequently at 6 monthly intervals with repeat 48h holter monitoring and event recorders as applicable based on patient symptoms. All patients had at least 6 months follow-up. Recurrence was defined as any documented episode of AF (both symptomatic and asymptomatic) or atrial tachycardia lasting for more than 30 s.

Results

Patient Characteristics

In total, 185 consecutive patients who had an ablation performed for atrial fibrillation between May 2012 and December 2013 were studied. Of these 142 patients with a follow up of 12±6 months were studied for outcome analysis as described below. The mean age of the patients was 62 years, 74.6% of the patients had long-term persistent atrial fibrillation with a mean duration of 4.49 years and 25.3% of the patients had paroxysmal atrial fibrillation. Males comprised 69.7% the patients. All the patients had failed or could not tolerate at least 1 antiarrhythmic medication. The average ejection fraction of the population was 49.4% with 27 of patients suffering from congestive heart failure and moderate to severe nonischemic cardiomyopathy with a mean ejection fraction of 37%. The average CHA2DS2-VASc score of the patients was 2.3. All the 185 patients were analyzed with respect to rate of procedural complications and fluoroscopic times. The most common comorbidities included obstructive sleep apnea, diabetes mellitus, hypertension and obesity. All PVs were cannulated and isolated with an intraprocedural efficacy of PV isolation with the cryoballoon alone of 100%. Mean left atrial dwell time with the cryoballoon was 108±18 minutes and mean fluoroscopic time was 25.8±15.9 minutes. The mean trough temperature was -51 degrees Celsius. The lowest esophageal temperature noted was 9°C from a baseline of 35.8°C. Sinus rhythm was achieved in all patients intra-procedurally with an increase in mean heart rate of 15±3 beats per minute. Complications are defined as per the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation. No intraprocedural complications occurred. Post procedurally 1 patient had a femoral pseudo aneurysm that was managed with outpatient thrombin injection and 1 patient had superficial esophageal erosion on endoscopy that healed with proton pump inhibitors. This was noted in the patient whose esophageal temperature had dropped down to 9 degrees Celsius as described above. At a mean follow-up of one year 70.4% of the patients remained free from atrial fibrillation with a single ICE^{2}T. Eight patients had a redo ICE^{2}T procedure and 27.4% of patients required one antiarrhythmic medication to maintain sinus rhythm, all in the long-term persistent group leading to a composite success rate at 1 year of 97.8% (Table 2-4) (Figures 1-7).

Table 2: Baseline characteristics of the patients.

Paroxysmal AF	n=36	
Long-term Persistent AF	n=106	
Age (years) (n= 142)	Average age : 62.24 years	Median age: 64 years
Men (%) (n=142)	69.7	
Ejection Fraction (%) (n=142)	Average=49.4%	Median = 50%
Number years in Atrial Fibrillation (n=142)	Average = 4.49 years	Median = 3 years
Mean Number of Failed Antiarrhythmic Drugs (n=142)	1.19 ± 0.73	
CHA2DS2-VASc (n=142)	Mean 2.33	

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Table 3: All pulmonary veins.

Follow-up (n=142 patients)	12 ± 6 months
Left atrial dwell time (n=185 patients)	108 ±18 (min)
Mean fluoroscopic time (n=185 patients)	25.8 ± 15.9 (min)
Procedural complications (n=185 patients)	1.4% (minor)
Freedom from AF in PAF patients (n=36) with single ICE2T	100%
Freedom from AF in long term persistent AF patients (n=106) with single ICE2T	60.40%
Freedom from AF in long term persistent AF patients (n=106) with single ICE2T + 1 AAD	89.60%
Freedom from AF in long term persistent AF patients (n=106) with AAD + Redo ICE2T	97.20%
Mean EF pre-procedure (n=27, AF with non-ischemic cardiomyopathy and CHF)	37.18%
Mean EF at 6 months post-procedure (n=27, AF with non-ischemic cardiomyopathy and CHF)	52.59%

Table 4: Post-Procedural Outcomes.

	Pre Procedure	Post Procedure
AAD use (n=142)	90.20%	27.40%
Redo ICE2T	Paroxysmal AF=0 (0%)	Persistent AF=8 (1.06%)

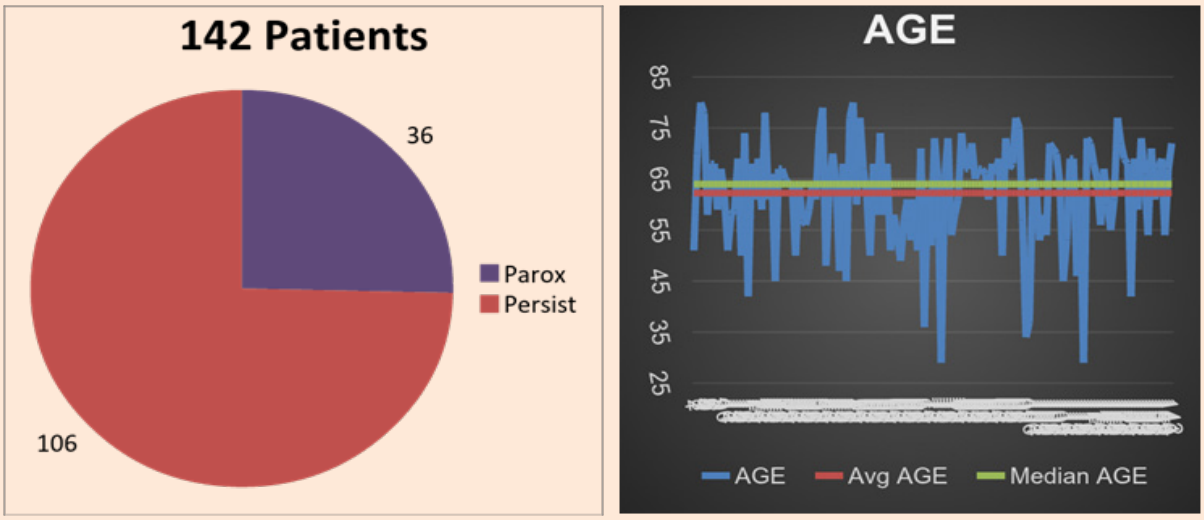

Figure 1: Age.

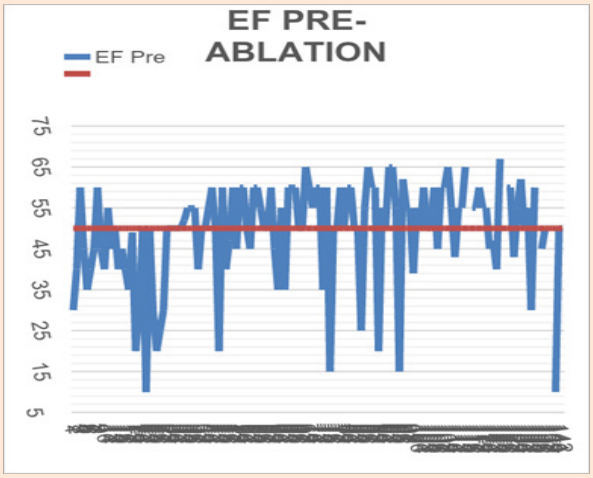

Figure 2: EF Pre-Ablation.

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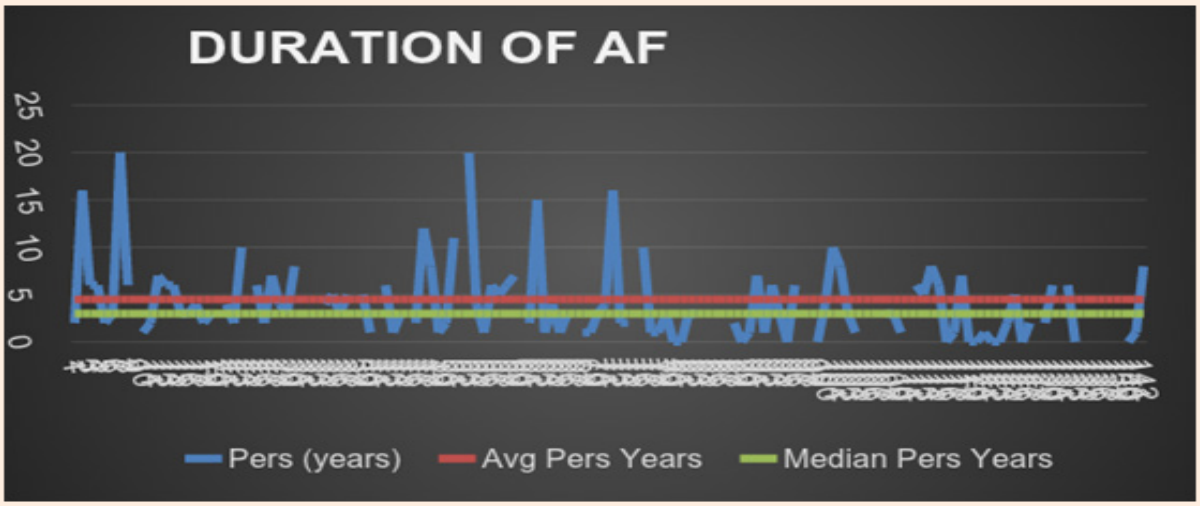

Figure 3: Duration of AP.

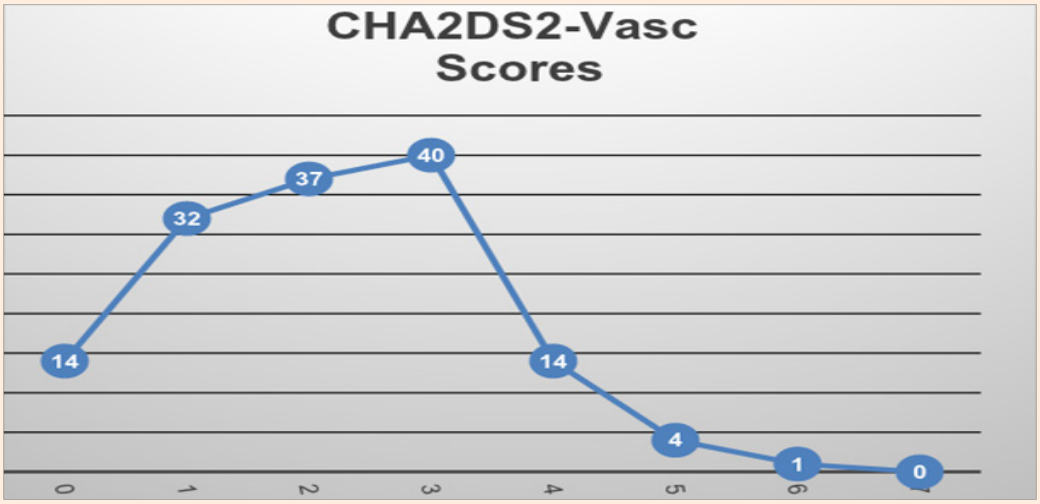

Figure 4: CHA2DS2-Vasc scores.

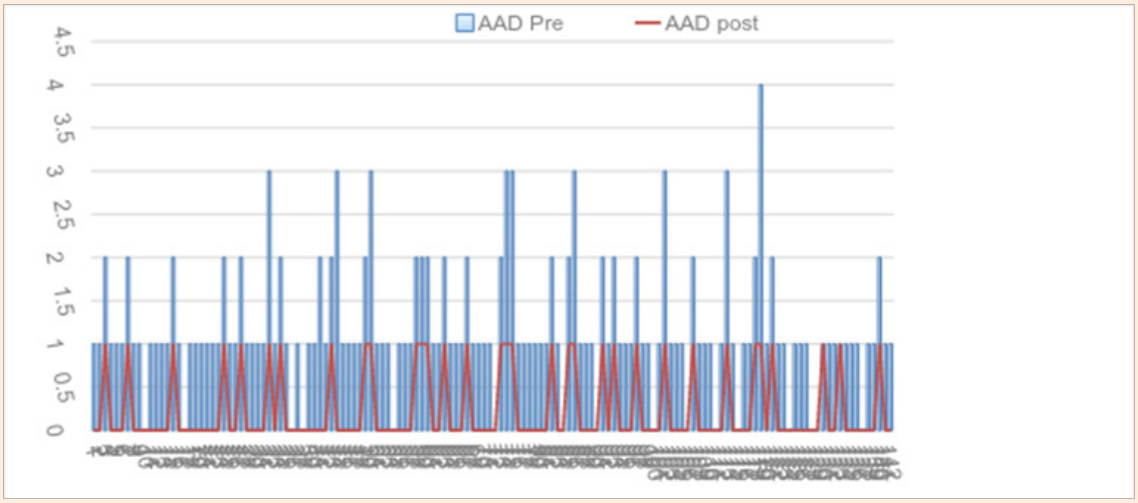

Figure 5: Fluoroscopy time.

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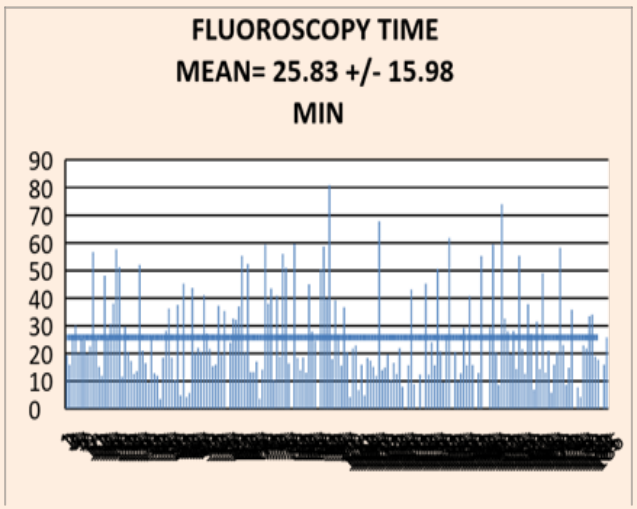

Figure 5: Fluoroscopy time.

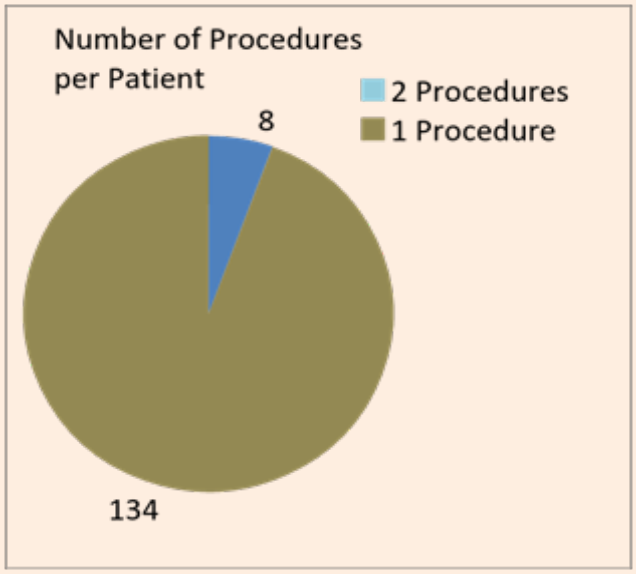

Figure 6: Number of procedures per patient.

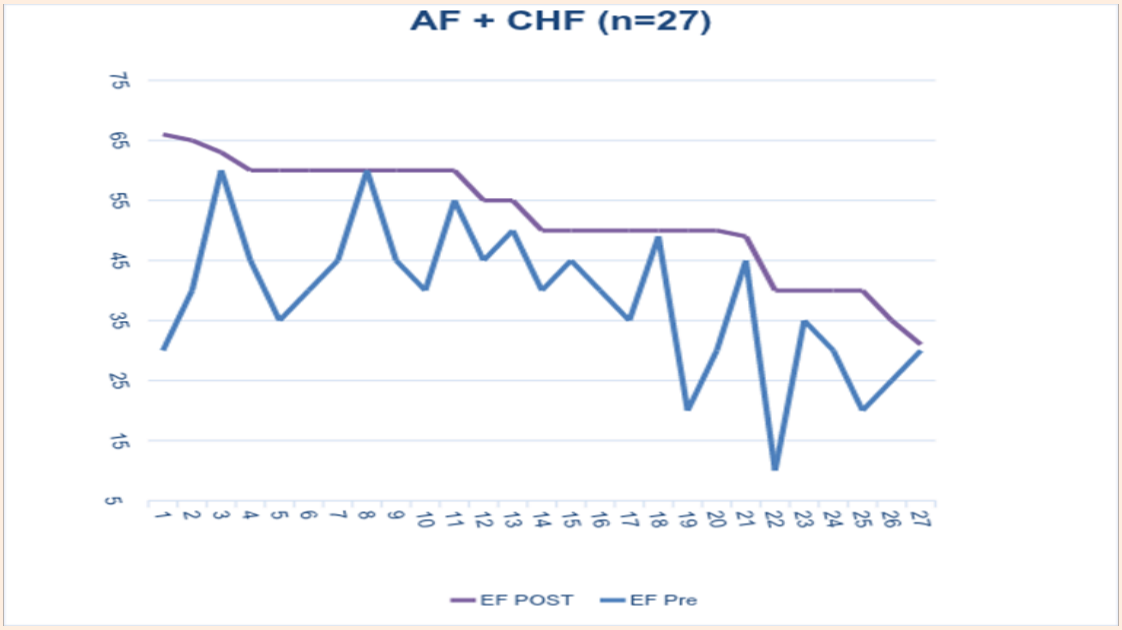

Figure 7: AF+CHF.

Discussion

Catheter ablation has rapidly gained acceptance as a mainstream therapy for paroxysmal atrial fibrillation. Eight prospective randomized clinical trials [1] that examined the outcomes of AF ablation with antiarrhythmic drug therapy reported an efficacy of AF ablation from 66-89% whereas antiarrhythmic drug therapy or rate control agents had a reported efficacy of 9-58%. Of these only two have been performed under the auspices of the FDA as part of an IDE approval process: Wilber et al. [2] (167 patients) and STOP-AF [3] (245 patients) which primarily enrolled middle-aged, white males with paroxysmal atrial fibrillation only with strict

exclusions for comorbidities. At 12 months of follow up efficacy of catheter ablation was 66% for radiofrequency ablation and 70% for cryoablation as compared to 16% and 7% respectively for antiarrhythmic drug therapy. The redo procedure rate was 19-34% and the use of antiarrhythmic drug therapy was 12-44%.

Outcomes of catheter ablation for AF in the real world however have been disappointing. A meta-analysis [4] of all reported randomized and non-randomized data of radiofrequency ablation reveals a single procedure success rate of ablation of paroxysmal atrial fibrillation of 57% and multiple procedure success rates of 71%. The multiple procedure success rates on antiarrhythmic medications was 77%. Contemporary substrate ablation techniques (including antral isolation alone, atrial isolation with lines, and antral isolation with CFAEs) for persistent or longstanding persistent AF are even more disheartening with a mean success rate of 47%. The incidence of major complications was 6%. The procedure is arduous and demanding takes on a grueling toll on the operator. A meta-analysis [1] of 1,221 patients who had cryoballoon ablation for paroxysmal AF and 87 for persistent AF revealed an average procedure time of 206 ± 72 minute and average fluoroscopy time of 46 ± 13 minutes. 73% of patients were free of recurrent AF.

This study is striking both in terms of its novel concept of integrating live two-dimensional intracardiac echo imaging with wide area contiguous antral pulmonary vein cryoablation with the second generation cryoballlon and the results so obtained.

The following points are noteworthy:

a) The success rate of paroxysmal AF ablation was 100%. When combined with the extremely low complication rates, this strategy could be considered as 1st line therapy for the treatment of symptomatic paroxysmal atrial fibrillation.

b) In long-term persistent AF, a single left atrial large volume cryoablation alone was effective in maintaining rhythm control in 89.6% of the patients in conjunction with an AAD (27%). With a second procedure, 97.8% of patients remained free from AF.

c) Patients with atrial fibrillation and non-ischemic cardiomyopathy and CHF derived significant benefit by maintaining sinus rhythm. Patients with severe cardiomyopathy had an average improvement in their ejection fraction by 41%. The extrapolated prognostic implication including impact on mortality for rhythm control appears to be immense and should be the subject of a randomized clinical trial.

d) The incidence of major complications with this technique was zero. The incidence of minor complications was 1.4%

e) Procedural and fluoroscopic times were significantly reduced as compared to contemporary cryoablation techniques.

f) Esophageal temperature monitoring although not currently recommended as a routine procedure with cryothermal ablations, should be considered with the newer generation of the cryoballoon.

g) AF ablation involves predominantly an anatomical approach. This procedure is simple, elegant and technically much less demanding on the operator. It entirely eliminates contact force sensing variability and the need for complex mapping techniques with their inherent inaccuracies.

The remarkable effectiveness of this technique could be attributed to the following:

a. Direct visualization and positioning of the cryoballoon across the PV antrum with utilization of color flow Doppler which is highly sensitive to detect any leak and hence ensure a complete antral seal.

b. The 2nd generation cryoballoon has a freezing surface encompassing the entire anterior hemisphere thereby ensuring large volume comprehensive contact with the left atrial endocardial surface eliminating incomplete lesion set due to inadequate contact of the left atrial endocardial surface with the ablation system.

c. The increase in mean heart rates observed in patients with paroxysmal atrial fibrillation after ablation suggests concomitant ablation of the left atrial antral ganglionated plexi In conjunction with PV disconnection, possibly contributing to the observed increased efficacy of the procedure.

Limitations

This report details clinical results of a novel cryoablation protocol for AF therapy. This was not a randomized comparison between RFA and cryoballoon by different experienced operators but a retrospective analysis. More episodes of AF may have been detected if long term recordings like an implanted monitor were used.

Conclusion

The present study is the first to show that a novel technique ICE^{2}T eliminates contact force sensing erraticism and need for complex mapping techniques, reducing complications and attaining durable PVI. The increase in mean heart rate suggests concomitant ablation of antral ganglionated plexi in conjunction with PV disconnection contributing to increased efficacy. Extrapolated data from CHF patients strongly suggests mortality benefits of rhythm control.

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