Randomized Trial of Femoral Vein Hemostasis After Ablation for Atrial Fibrillation with manual pressure versus a Figure of 8 suture.

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Sponsor
NA

Site of Investigation
IFH

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ABSTRACT

Title: Randomized Trial of Femoral Vein Hemostasis After Ablation for Atrial Fibrillation with manual pressure versus a Figure of 8 suture.

Short Title: Femoral Vein Hemostasis.

Rationale: Patients who undergo ablation for atrial fibrillation typically have 2 sheaths placed in each groin, including a large sheath when the Cryo Balloon is used for pulmonary vein isolation. During the procedure, heparin is administered to maintain a target ACT > 300 seconds. At the conclusion of the procedure, the venous sheaths are removed and hemostasis is obtained. There are at least 2 ways of obtaining hemostasis after venous access. In the manual hemostasis approach, an ACT is checked and protamine is administered. The ACT is rechecked 20" later, and if < 220 msec, the sheaths are pulled and hemostasis is achieved with manual pressure (Manual Hemostasis Group). Another conventional approach is to place a Figure of 8 suture around the sheaths in each groin to achieve hemostasis as the sheaths are removed, and therefore obviate the need for assessment of the ACT, protamine administration, and manual pressure (Figure of 8 Group).

Objectives: The goal of this study is to compare the safety and efficacy of obtaining hemostasis after an ablation for atrial fibrillation with the Manual Hemostasis Technique versus with the Figure of 8 Technique.
Study Type: This is a non-blinded, prospective, randomized trial.

Study Design: Number and types of subjects to be enrolled, study location, study duration, inclusion/exclusion criteria.

100 (50 in each group) patients undergoing Cryo balloon ablation for ablation of atrial fibrillation will be randomized to the Manual Hemostasis Group or to the Figure of 8 Group for venous hemostasis. Clinical characteristics, medications, procedure duration, heparin dosage, and post procedure anticoagulation will be collected. Follow up will end when the patient is seen in the office one month after the ablation procedure.

The study location will be the EP Laboratories at IFH, and the EP MDs outpatient offices.

All patients undergoing ablation for atrial fibrillation with the Cryo Balloon will be eligible to participate. Any patient who is under age 18 years of age, pregnant, or with an untreated DVT(s) will be excluded from participation.

Study Methodology: Summarize study treatment/interventions as well as if there is a control group/randomization. Identify primary and secondary outcomes.

The primary short term study endpoints will be the time required to obtain hemostasis, and for the time required from the completion of the ablation portion of the procedure until the patient leaves

the EP Lab. Secondary end points include groin complications including bleeds, additional pressure required for hemostasis, hematoma, pseudoaneurysm, and transfusion.

Statistical Methodology: Continuous variables will be expressed as the mean +/- SD. Univariate comparisons will be performed on continuous variables with either paired T test, unpaired T test or analysis of variance, as appropriate. Categorical variables will be compared with Chi-square analysis. Statistical significance will be considered present with a p value ≤ 0.05.

1. INTRODUCTION

1.1. Specific Aims

The goal of this study is to compare the safety and efficacy of obtaining hemostasis after an ablation for atrial fibrillation (AF) with the Manual Hemostasis Technique versus with the Figure of 8 Technique.

Patients who undergo ablation for AF typically have 2 sheaths placed in each groin, including a large sheath when the Cryo Balloon is used for pulmonary vein isolation. During the procedure, heparin is administered to maintain a target ACT > 300 seconds. At the conclusion of the procedure, the venous sheaths are removed and hemostasis is obtained. There are at least 2 ways of obtaining hemostasis after venous access. In the manual hemostasis approach, an ACT is checked and protamine is administered. The ACT is rechecked 20" later, and if < 220 msec, the sheaths are pulled and hemostasis is achieved with manual pressure (Manual Hemostasis Group). Another approach is to place a Figure of 8 suture around the sheaths in each groin to achieve hemostasis as the sheaths are removed, and therefore obviate the need for assessment of the ACT, protamine administration, and manual pressure (Figure of 8 Group).

1.2. Hypothesis

The hypothesis of this study is that the Figure of 8 Technique to obtain hemostasis after Cryoballoon ablation for AF will take less time, and be associated with a lower frequency of groin complications.

1.3. Background and Significance

Ablation for AF is a common procedure and is considered first line therapy in many patients with symptomatic paroxysmal AF (1). The goal of AF ablation is to electrically isolate the pulmonary veins, which are attached to the left atrium. The procedure involves obtaining femoral vein access, usually with 2 access sites in each groin. The sheath sizes vary varies, depending on a variety of factors. However, when the cryoballoon is used, it requires a 12 Fr sheath. Three other smaller sheaths are also used. Usually, a 7 FR, 8 FR and 9Fr sheath are utilized. To access the left atrium, a transeptal puncture is required. To prevent thrombus formation and systemic emboli from occurring during the ablation procedure, heparin is administered to maintain the ACT > 300 seconds (1). Protamine is administered at the time the figure of 8 suture is placed to reverse the heparin after an ACT is obtained. The

protamine dosage is determined by the operator. After protamine is administered, the ACT is rechecked, and if < 220 msec, the sheaths are pulled. Hemostasis is often achieved with manual pressure (2). Alternatively, the use of a Figure of 8 suture can also be used to achieve hemostasis in anticoagulated patients, and obviates the need for reversing heparin with protamine. After catheters are removed, a silk suture is placed in a figure of 8 around each pair of sheaths. The sheaths are removed as the suture is cinched down, and tied firmly. The suture is removed at least 6 hours later.

Problems with venous access and hemostasis are the most common complications with Af ablation (1-2). There are no direct comparisons of manual compression versus the figure of 8 technique to achieve hemostasis after AF ablation. It is unknown if one or the other technique is better, associated with fewer complications, or requires less time to achieve hemostasis.

This study will randomize 100 (50 in each group) patients undergoing Cryo balloon for AF to manual (Manual Hemostasis Group) or figure of 8 (Figure of 8 Hemostasis Group) hemostasis. We will assess the time required for each technique, the time until the patient can leave the lab, and evaluate for groin complications that may occur during follow up.

There are few direct benefits or risks for patients who participate in this study. Both of the techniques that will be used in this study to achieve hemostasis are standard of care and are used. However, they have never been compared. If a patient happens to be randomized to the technique which is better, then the patient will have that benefit.

References.

1. Calkins H, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design. *J Interv Card Electrophysiol.* 2012. 33:171-257.
2. Packer, DL, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation. *J Am Coll Cardiol*. 2013;61(16):1713-1723.

1.4. Preliminary Studies

There are no preliminary studies that the Principal Investigator/Sub-Investigator (PI/SI) have performed to establish the experience and competence of the PI/SI to pursue this project. However, all of the PI/SI have clinical experience with both techniques to achieve hemostasis after an AF ablation.

2. STUDY DESIGN AND SUBJECT SELECTION

2.1. Study Type

This is a randomized, not blinded study of two standard of care techniques used to obtain hemostasis after an AF ablation procedure..

2.2. Setting/Location

This study will only be performed at the IFH EP Laboratories (330 Gallows Rd, Falls Church, Va 220042) The one month follow up visit will be performed at each investigators' office. 3020 Hamaker Ct, Suite 101, Fairfax, VA 22031; 422 Garrisonville Rd, suite 110, Stafford, VA 22554; 8100 Ashton Ave Suite 200, Manassas, VA 20109; 7617 Little River Tpke, Suite 710, Annandale, VA 22003.

2.3. Duration of Study

The study begins on the day of the AF ablation and ends at the 1 month outpatient follow up visit. Therefore, the subjects are required to continue in the study for 1 month. No biological specimens are collected for this study.

2.4. Number of Subjects

State the total number of subjects expected to participate. For multi-center protocols, this should include both the overall total and the number of subjects to be enrolled at each site.

This single center study is expected to include 100 patients.

2.5. Study Population

2.5.1. Gender of Subjects

Subjects of both genders will be able to participate.

2.5.2. Age of Subjects

Any subject 18 years or older, will be eligible to participate.

2.5.3. Racial and Ethnic Origin

Patients of any race and ethnicity will be eligible to participate.

2.5.4. Vulnerable Populations

Vulnerable populations are excluded. Specifically, patients who are pregnant, <18 years old, prisoners, and those who cannot provide informed consent in English will be excluded.

2.6. Recruitment

We will not advertise for subjects, there will be no recruiting materials—telephone or speech script, email or letter text, or advertisements or flyers. When patients are seen and they agree to undergo ablation of AF using the Cryoballoon, they will be asked if they wish to participate in this study.

2.7. Inclusion Criteria

Any patient who meets standard clinical criteria for an ablation of AF with Cryoballoon, and is to undergo the procedure, will be eligible to participate in this study; as long as they do not meet the exclusion criteria delineated below.

2.8. Exclusion Criteria

1. Pregnant patients.
2. Age <18 years.
3. Patients who cannot provide consent in English.
4. Prisoners.

3. STUDY METHODS AND PROCEDURES

3.1. Study Treatment/Intervention

See above. Besides the randomization, there will be no experimental procedures performed.

No drug or device that is investigational under FDA policy will be utilized. The figure of 8 technique to achieve venous hemostasis utilizes a silk suture that is FDA approved and is on the "shelf".

After the patient agrees to have an AF ablation with the cryoballoon, they will be asked to participate in this trial. If they agree, consent will be obtained. The ablation is usually performed 2 weeks to 3 months after being seen in the office. They will be seen by an investigator the morning after the ablation procedure, and again 1 month later.

3.2. Control Group

Is there a control group? The control group may be receiving no treatment or a standard treatment. Will randomization be required?

Patients will be randomized 1:1 to either the Manual Hemostasis Group (Control) or to the Figure of 8 Hemostasis Group.

3.3. Randomization

Patients will be numbered as they are randomized into the study. For instance, the first patient randomized, will be patient 001, and so on. The IHVI Research Center will serve as the randomization center. When the procedure is to begin, the randomization will be

provided. Randomization will be performed by a random number generator. Patients who receive an odd number, will be randomized to the control group, i.e., manual hemostasis.

3.4. Endpoints/Outcomes Measurements

3.4.1. Primary outcomes.

The primary short term study endpoints will be the time required for hemostasis, and the time required from the end of the ablation procedure until the patient leaves the EP Lab.

3.4.2. Secondary outcomes

Secondary end points include groin complications including bleeding, hematoma, pseudoaneurysm, and transfusion.

3.5. Consent/Assent

Written informed consent with an IRB approved consent form will be utilized. Consent will be obtained by the PI, SI, or IHVI research staff with training to obtain the consent. Consent will generally be obtained in the office, or prior to the procedure in IFH. Research personnel are likely to contact prospective participants by phone, when the PI/SI asks them to do so.

3.6. Monitoring Subjects and Criteria for Withdrawal of Subjects from the Study.

Beyond what is required for a standard cryoballon ablation for atrial fibrillation, there will be no additional tests, admissions, or outpatient visits. Participants will be seen the day after the ablation and one month later by an investigator, as is currently done. The study is not blinded, and a monitor will not be used. Participants can withdraw from study participation at any time. The study will stop when 100 patients have been randomized, and follow up completed.

4. STATISTICAL CONSIDERATIONS/DATA ANALYSIS

4.1. Sample Size

Provide justification of the sampling procedure and sample size. Delineate methods used to estimate the required number of subjects.

The estimated time +/- SD for the control and study groups is estimated at 30 +/- 15mins and 15+/-5 mins, respectively. Using a power calculation to identify an 90% power, then 10 patients in each group will be required. If however, the study group mean is 20 mins, and the sd is 16 mins, then 33 patients per group would be required. Therefore, to account for drop out, and/or a mistake in any of the above assumptions, the plan is to aim for 50 patients in each group.

4.2. Method of Data Analysis

Data collection will occur just prior to, and during the ablation procedure. Also, data will be collected at before hospital discharge after the procedure (usually the next day), and at the 1 month outpatient follow up visit. Data entry will be directly the statistical program, SAS. nto Continuous variables will be expressed as the mean +/- SD. Univariate comparisons will be performed on continuous variables with either paired or unpaired T test, or analysis of variance, as appropriate. Categorical variables will be compared with Chi-square analysis. Statistical significance will be considered present with a p value ≤ 0.05. Please see section 4.1 above for the power calculation.

4.3. Data Storage

4.3.1. Data Management

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Privacy and confidentiality of all enrolled patients enrolled will be maintained. Patients will be assigned a PIN chronologically, from when they sign the consent form. The PIN will start with 001. The PIN key will be linked to each patient's PHI, will be maintained separately from collected data, and the key will be secured in a locked cabinet in the IHVI research office. Data will not be stored outside of IHVI.

4.3.2. Records Retention

Data will be stored 3 years and then destroyed. The data will not be used for other studies. There will not be original audio or videotapes.

5. HUMAN SUBJECTS PROTECTION (RISKS, BENEFITS, AND ALTERNATIVES)

5.1. Risks

Potential loss of privacy. The risk will be minimized by shielding the participant by unlinking his or her identity from his or her personal health information.

Physical risk. Both techniques to obtain hemostasis are utilized clinically. Each technique to obtain hemostasis may be associated with minimal pain or discomfort (3/100), or associated with bleeding or vessel complications (5/100). These risks are intrinsic to an ablation procedure for AF, and participation in the study will not elevate or reduce these risks.

5.2. Benefits

Participation in this study is unlikely to have a significant benefit for participants, unless by chance they are randomized to a hemostasis group which is better than the alternate one.

Participation in the study is associated with benefits for future patients, and more generally may benefit science.

5.3. Alternatives

Usually, the alternative is not to participate in the research and should be stated. "The alternative is not to participate in the research." However, if the researcher is proposing a biomedical treatment or therapy, a disclosure of appropriate alternative courses or treatments that might be advantageous to the participant, if any, are required here.

The alternative to participation is to not to participate in the research. However, even if the patient does not participate, hemostasis will be obtained with one of the two techniques for hemostasis post AF ablation.

5.4. Confidentiality

Confidentiality will be maintained by using a unique PIN that is not related in any way to the patient's medical record number, social security number or other personal identifier. When the data is evaluated or used to create statistical measures, no patient identifiers will be present. The key to the unique PIN will be kept in a locked cabinet in the IHVI Clinical Research office, and all records will be destroyed 3 years after completion of the study.

6. SUBJECT COMPENSATION

6.1. Costs

There are no costs to participants or the insurance company for participation in this study.

6.2. Payment

There will be no payment for participation in this study.

7. ADVERSE EVENT REPORTING

An adverse event report will be provided to the IRB if a death, persistent disability, life threatening complication or breach of confidentiality occurs. Furthermore, a summary of adverse events will be provided to the IRB after 50 patients are enrolled, and after 100 patients are enrolled.

Potential reportable protocol deviations/violations include missed appointments, failure to perform all required study interventions at a designated encounter, inclusion of a patient who meets exclusion criteria, or who has a consent form which is incomplete, a wrong version, or missing signatures and dates.

8. FUNDING

There are no costs associated with this study, and it is unfunded.

9. CONFLICTS OF INTEREST

There are no financial or other conflicts of interest between the PI, or the SIs that are material to the research or the patient subjects.

10. FACILITIES AND EQUIPMENT

The EP lab staff performs the manual hemostasis. The figure of 8 suture for hemostasis is performed by the physician. All equipment and personnel required are routinely available in the EP lab for everyday use.

11. OUTSIDE CONSULTANTS/COLLABORATORS

NA.

12. CONTRACTURAL AGREEMENTS

NA.

13. REFERENCES

14. APPENDIX

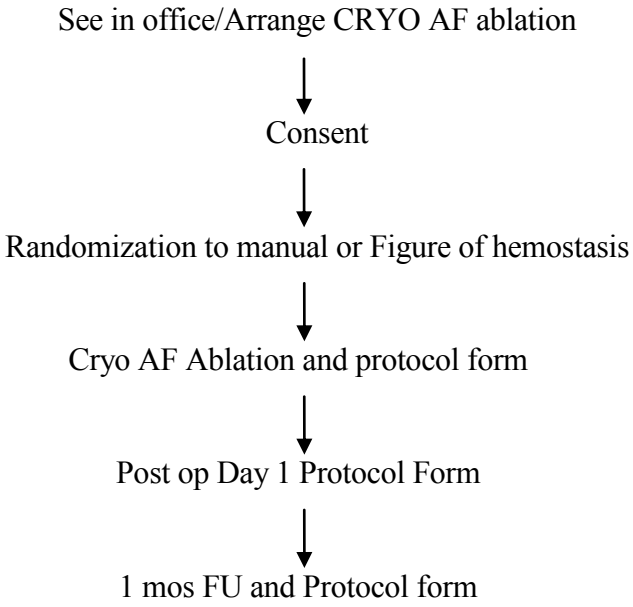
This section should contain all pertinent documents associated with the management of the study. The following list examples of potential attachments:

- Investigator Agreement (for any investigator, other than sponsor-investigator, who participates in the study)

Sample Consent Form The proposed consent document must be attached. It should be written in the second person, in language understandable to someone who has not completed high school.

- Study Procedures Flowchart/Table

Day 1	Day 2	Day 3	Day 30
Consent	Randomization	Groin ck	1 mos fu form
	ablation	Post op day form	
	Ablation form		


See in office/Arrange CRYO AF ablation
Consent
Randomization to manual or Figure of hemostasis
Cryo AF Ablation and protocol form
Post op Day 1 Protocol Form
1 mos FU and Protocol form

Sequence: We expect to enroll 3 patients per week, and have enrollment completed within approximately 35 weeks.