Pilot Study for Treatment of Amiodarone-Induced Thyroiditis with Radiofrequency Ablation

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IRB Greater Than Minimal Risk Protocol

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Research Question and Aims

Hypothesis: Ablation of a portion of thyroid parenchyma with RFA technique will safely decrease thyroid hormone levels into the normal range with resolution of thyrotoxicosis.

Aims, purpose, or objectives:
We aim to study the changes in serum thyroid hormone levels in AIT patients after RFA therapy. This will address the hypothesis that ablation of a portion of thyroid parenchyma with RFA technique will safely decrease thyroid hormone levels into the normal range with resolution of thyrotoxicosis.

Background:
Background on Condition, Disease, or Other Primary Study Focus
Amiodarone induced thyrotoxicosis (AIT) is an entity developing in about 2-8 % of patients treated with amiodarone. It is considered to have a dual pathophysiology with increased thyroid hormone production in AIT type 1, and leakage of preformed thyroid hormone in a thyroiditis fashion in AIT type 2. The two types are in reality combined in many patients and combination therapy is required in such patients, which delays the therapeutic response. Furthermore even if combination therapy is used in some cases the response to therapy is suboptimal and the patients have complications related to hyperthyroidism and side-effects from the medications used[1,2]. We have shown an increase in frequency of hospitalizations, CHF, weight loss and arrhythmia in this group. Some patients require thyroidectomy for adequate control of their thyrotoxicosis [3], a procedure not without risks in this population with cardiac comorbidities.

Rationale:
RFA has been used for the management of thyroid nodules for more than a decade [4]. We have employed it here at Mayo Clinic for the past 4 years with good results [5]. While mainly used for non-toxic thyroid nodules there is encouraging data describing the response to RFA in the case of toxic thyroid adenomas. In total in the literature there are 47 cases of toxic nodules or toxic goiters that were treated with RFA (8-10) and in 50% of these cases the thyroid function normalized and in none of them did thyrotoxicosis worsened as a result of therapy. RFA has the capacity to lead to destruction of thyroid parenchyma and also to denaturation of stored thyroid hormone. Thus it seems to provide the perfect approach to target both mechanisms of AIT in an expeditious manner which is essential in these usually very sick individuals with coexistent cardiac co-morbidities. So far there is no reported data on the efficacy of RFA in AIT and this would be the first study on this therapy, hence our pilot study approach.

MAYO CLINIC

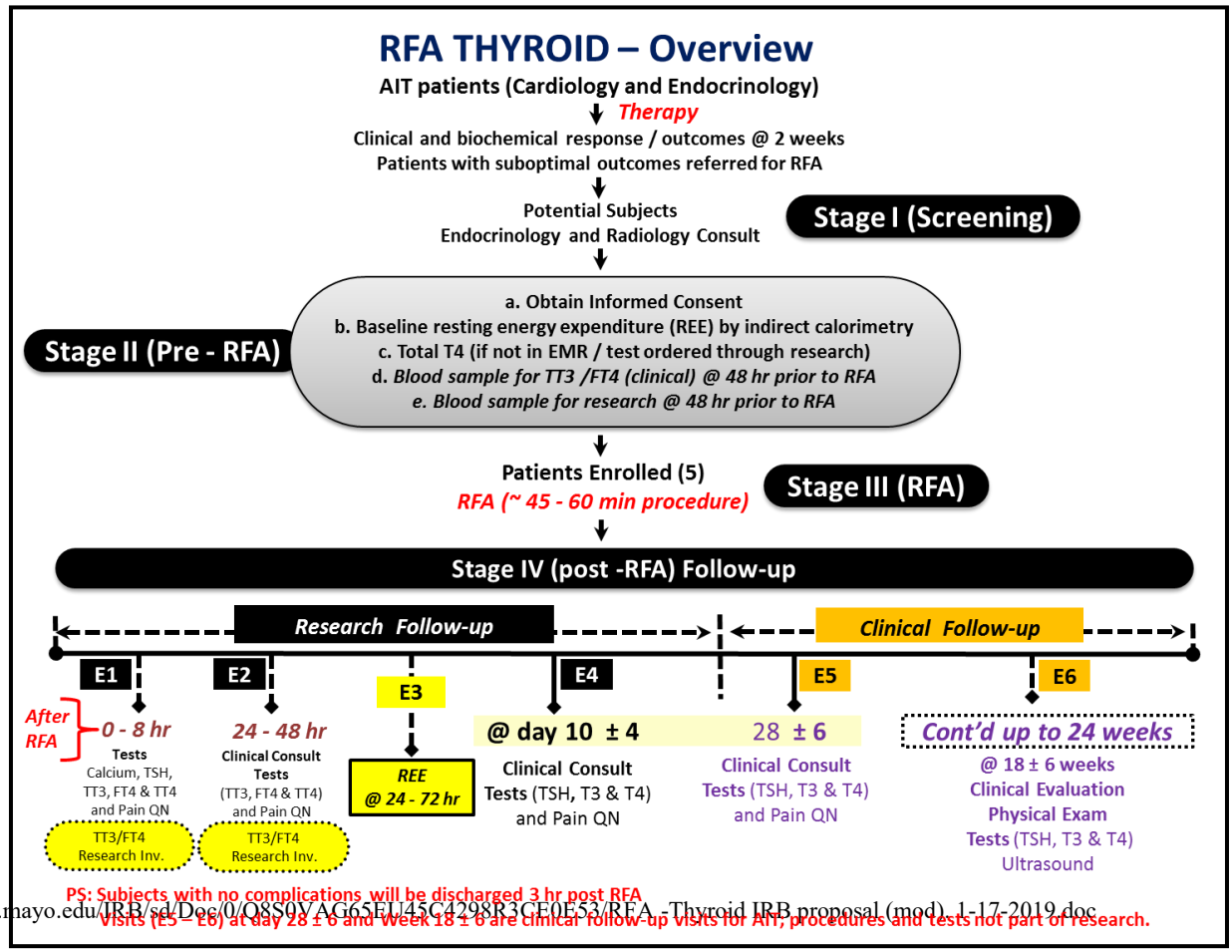
Study Design and Procedure

STUDY DESIGN

This will be an open-label clinical trial that will target AIT patients that fail to respond to medical therapy. We will treat them with RFA therapy and then asses the clinical and biochemical response (primary objective) in the coming 4 weeks and continue to monitor the clinical response for a minimum of 3 months or until the resolution of the AIT episode, whichever occurs later. We expect that an individual will be thus in the trial for a total of 4-6 months. The safety of the RFA procedure will be assessed as well (secondary objective) in the first month after the procedure. We plan to enroll 5 patients to undergo the procedure and use a historical control group for comparison of clinical and biochemical outcomes. The study will take place at Mayo Clinic in Rochester, MN and will recruit both from our out-patient as well as the in-patient population with AIT. We expect that we would be able to identify 10-15 cases/year that would qualify for this trial and given the potential acceptance to enrollment we expect that it would take 12-18 months for the trial completion.

PROCEDURE:

Each patient will undergo RFA in a single session using ultrasonographic guidance. Therapeutic



guidance and diagnostic ultrasound will be performed with a 6- to 15-MHz probe attached to the GE Logiq E9 ultrasound system. The thyroid volume will be calculated using the formula for an ellipse (height x width x depth x π/6) for each lobe and adding an additional volume of 1-2 cc for the isthmus, depending on its thickness. The percentage of volume reduction will be calculated as follows = [(initial volume - final volume) x 100%]/initial volume. All the patients will be sedated with general anesthesia during the procedure. General anesthesia will be used in light of the length of the procedure, the improved pain control, and the desire to avoid any motion interference that could compromise the accuracy of the technique. *A radiofrequency generator and an 18-gauge, 7-cm electrode with a 5mm, 7mm or 10mm active tip will be used. All radiofrequency procedures will be performed by 1 of 2 operators who are co-investigators in the trial and have extensive experience with this procedure. We will use an in-plane oblique approach for electrode placement as opposed to directly entering the thyroid parenchyma using the shortest pathway. The longer oblique pathway was chosen in order to lengthen the distance between the skin and the active tip of the RF electrode which reduces the chance of skin burns and allows a larger ablation diameter when needed by with the use of the pull-back technique. We will initially position the electrode in the deepest portion of the parenchyma, followed by more superficial placement. The approach is usually trans-isthmic, but to treat parenchyma in the upper portion of the thyroid, alternative oblique needle placements will be used to reach that area and to protect extrathyroidal structures from generated thermal energy.*

To minimize the risk of complications, the outer approximately 5 mm of the parenchyma will not be treated, and the active tip of the electrode will be kept at a safe distance to prevent a skin burn. These safety measures will be the paramount concepts that will dictate the final approach to RFA. The ablation will employ the moving-shot technique as described elsewhere.[6,7]. The number of ablation cycles (number of times the RF generator is turned off to reposition the electrode to a new location in the parenchyma), total energy delivered, and total ablation times will differ according to target size. The target for the RFA will be the central area of the thyroid parenchyma, to minimize exposure to the thyroid capsule and thus limit the risk of side-effects to the surrounding structures. Within this area special attention will be dedicated to the regions with higher vascularity, if present, based on Doppler signal (particularly in AIT type 1.

The volume of thyroid parenchyma to be ablated will be expressed as a percent of the solid (non-cystic) thyroid volume based on the assumption that there is a linear correlation between thyroid volume and free thyroxine (FT4) levels and a gradual increase will be tested in the first 3 cases to decide the best approach for the rest of the series. Thus for example if the FT4 value is 2.4 ng/dL and we aim to normalize this parameter to 1.6 ng/dL we would target about 33% of the total thyroid parenchyma in order to decrease FT4 by 1/3. This calculated volume will be increased by 25% in case 2 and by 50% in case 3. These results will serve as basis for deciding the approach for the rest of the series. If these calculations lead to a planned ablation volume that would infringe on the safety parameters described above those safety parameters will prevail. Overall the planned ablation volume is a relative estimation of the actual ablation volume. The final volume will be dictated by the safety measures already described as well as by the specific anatomy of the thyroid in that particular patient. The procedure will be performed in the Radiology intervention area. We expect the intervention to last approximatively 45-60 minutes. Patients will be intensively monitored during RFA and then they will be observed for approximately 3 hours after the procedure in the PACU area and released home thereafter, unless adverse effects developed. We will look specifically for signs and symptoms of adverse effects of the intervention (e.g. pain, swelling, hoarseness, hypocalcemia, skin injury). If any such effects occur we will treat patients as appropriate (analgesia, skin care, respiratory support etc.). Hospitalization will be initiated if the patients' clinical situation requires it and the signs and/or symptoms do not resolve in the 3 hours of observation.

In the first 48 hours post-procedure we will assess thyroid levels (TT3 and FT4) twice (once between 2 and 8 hours and again between 24 and 48 hours) and calcium level once between 24 and 48 hours. They will also have a brief clinical exam between 24-48h to assess procedure safety. In order to understand the bioactivity and the impact of thyroid hormone released during the procedure resting energy expenditure (REE) by indirect calorimetry will be assessed prior to RFA procedure and again 24 - 72h post RFA procedure; in addition, T3 and T4 research investigation will also be performed for that purpose; for this, separate blood draw for research will be done 48 hr prior to procedure and at E1 and E2 time points (see algorithm above) as well as measuring total T4 to have a better understanding if the measured hormone could be active hormone or a denatured chemical structure. The patients will then be monitored clinically at 2 and 4 weeks and biochemically at 1, 2 and 4 weeks, following thyroid levels and clinical signs and symptoms of thyrotoxicosis along with monitoring the procedure local area for signs and symptoms of adverse effects of the intervention (e.g. pain, swelling, hoarseness, hypocalcemia, skin injury). A final research evaluation will be performed at the time of the clinical follow-up between 3 and 6 months including thyroid values and a research thyroid ultrasound to assess parenchymal changes.

(Please refer to the overview of the study).

The volume of thyroid parenchyma to be ablated is based on our assumption about linear correlation between serum thyroid hormone levels and total parenchymal volume. We will test this hypothesis and use the first 3 cases to decide if an adjustment to this approach is needed. We will present this data to Data Safety Monitoring Committee and propose modification to the protocol if necessary.

Concomitant Interventions

Allowed Interventions
Medical therapy with steroids, antithyroid drugs or both will be ongoing peri-procedure with an increase in the ongoing anti-thyroid regimen the day of RFA and the day after the procedure after which pre-procedure doses will be resumed until thyroid levels are collected at the end of week 1 post-procedure. On a precautionary measure in the event of excess release of active T3 / T4 due to RFA, patients will be administered Lugols iodine solution (5 drops x 3 per day) starting after the procedure and continuing for the first 3 days post-RFA. Beta-blockers will be employed/increased starting 1 day before procedure and then adjusted in a manner analog with anti-thyroid regimen. These adjustments will be made in collaboration with cardiology, according to the cardiovascular status of the patient. If some of these changes are not clinically acceptable then bile-acid sequestrants will be used for their anti-thyroid effect [8], starting 2 days before procedure and continuing for 3 days after the procedure. If despite these interventions thyrotoxicosis will deteriorate post RFA both plasmapheresis and thyroidectomy will be discussed with the patient and pursued based on the clinical situation.
Of note – amiodarone can be continued during the study, at the discretion of the cardiologist consultant.

Required Interventions
Beta-blockers (if agreed by cardiology) and either steroid therapy, methimazole therapy or both will be required during the study.

Prohibited Interventions
There are no prohibited medications or interventions during this trial

Adherence Assessment
Adherence is defined as having had at least 80% of the intended volume of thyroid parenchyma ablated and taking at least 80% of the intended medical therapy tablets by the end of week 1 post RFA. Medication adherence will be tested through pill counts.

Resources: We have the commitment of the Division of Endocrinology and Department of Radiology of Mayo Clinic Rochester that they will support this study. These 2 areas have worked collaboratively in a similar project that has led to the adoption of our current RFA protocol for benign thyroid nodules. We have enlisted the collaboration of a company manufacturing RFA devices, StarMed, with some of the single use RFA instrumentation and partial financial support. Mayo Clinic is also providing support for the project through a Career Development Grant awarded to Dr. Marius Stan that will be utilized for covering cost of laboratory tests, partial financial support for travel expenses for the patients and PI and study coordinator dedicated time to the project.

Subject Information

Target accrual is 5 patients. To achieve this number of subjects, we will access medical records for about 100 patients.

Subject population: Adults (≥ 18 years of age) with AIT who undergo treatment at Mayo Clinic, Rochester and those referred to thyroid clinic for evaluation.

Inclusion Criteria:

We will enroll patients with AIT that meet all criteria 1 through 4 and then either criteria A or B as follows:

1. Are adults,
2. Have overt thyrotoxicosis (within 2 weeks prior to enrollment) with elevated Free and/or Total T4 and/or T3
3. Are receiving medical therapy for AIT
4. Are able to understand the study procedures and to comply with them for the entire length of the study

and:

A. have not normalized their thyroid levels after one month of standard therapy **or**
B. have persistent and clinically significant thyrotoxicosis (less than 25% decrease in T4 value or patients requiring hospitalization with CHF, tachyarrhythmias, hemodynamic instability or similar co-morbidities) after 2 weeks of standard therapy where additional medical therapy is deemed unlikely to be beneficial or with high risk of side-effects (e.g. hepatotoxicity of antithyroid medications, agranulocytosis of potassium perchlorate or ATD or fluid retention associated with steroids).

Exclusion Criteria:

All candidates meeting any of the following exclusion criteria at baseline will be excluded from study participation:

1. Pregnancy
2. Patients with prior neck surgery or neck radiation
3. Patients with neck anatomy that precludes easy access by RFA to the entirety of thyroid parenchyma
4. Patients on anticoagulation therapy
5. Patients with comorbidities deemed too high of a risk for general anesthesia
6. Treatment with another investigational drug or intervention (within 6 weeks of planned RFA).
7. Current drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.
8. Inability or unwillingness of individual or legal guardian/representative to give written informed consent.

Note: Pregnant women will not be allowed to enroll on this study. Please tell your study doctor if you are pregnant or think you might be pregnant.

There is a risk of claustrophobia (fear of closed space) while the patient is under the clear plastic dome during the indirect calorimetry (REE). Fresh air comes through the dome. If the patient is unable to tolerate the measurement, it will be discontinued.
If you are a female, you must have a negative pregnancy test in order to participate in this study unless you cannot become pregnant.

You are advised not to get pregnant owing to your current health condition (hyperthyroidism); however, from this study perspective there are no restrictions to pursue pregnancy post RFA procedure.

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. X **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the study design and procedure section)

2. X **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. X **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular

strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the study design and procedure section)

5. [X] **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. [ ] **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. [ ] **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

[ ] NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Blood samples will be obtained; Volume10 cc per clinical visit and 10 cc for research (3 time points)

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.

No blood samples will be obtained.

(3) Prospective collection of biological specimens other than blood: NONE

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range: All records through 8/3/2018
Check all that apply (data includes medical records, images, specimens).

☐ (5a) No data will be collected beyond the IRB submission date.

X (5b) The study involves data that exist at the time of IRB submission **and** data that will be collected after IRB submission. Include this activity in the study design section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.

External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	X	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data		
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. Note: Recording a year only is not a unique identifier.	X	
Social Security number		
Medical device identifiers and serial numbers	X	
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes	X	
Phone or fax numbers	X	
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	X None

Data Analysis

Power analyses and study endpoints are not required for minimal risk research, pilot or feasibility studies.

☐ No statistical information. *If checked, please explain*:

Data Analysis Plan:
Sample size has not been calculated as analysis will only include descriptive statistics. Results for continuous variables will be expressed as median and interquartile range, and for categorical variables as proportions.

References:

1. Stan MN, Sathananthan M, Warnes CA, Brennan MD, Thapa P, Bahn RS. Amiodarone-induced thyrotoxicosis in adults with congenital heart disease--clinical presentation and response to therapy. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2014;20:33-40.
2. Danzi S, Klein I. Amiodarone-induced thyroid dysfunction. J Intensive Care Med 2015;30:179-85.

3. Houghton SG, Farley DR, Brennan MD, van Heerden JA, Thompson GB, Grant CS. Surgical management of amiodarone-associated thyrotoxicosis: Mayo Clinic experience. World journal of surgery 2004;28:1083-7.
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5. Hamidi O, Callstrom MR, Lee RA, et al. Outcomes of Radiofrequency Ablation Therapy for Large Benign Thyroid Nodules: A Mayo Clinic Case Series. Mayo Clin Proc 2018;93:1018-25.
6. Baek JH, Jeong HJ, Kim YS, Kwak MS, Lee D. Radiofrequency ablation for an autonomously functioning thyroid nodule. Thyroid : official journal of the American Thyroid Association 2008;18:675-6.
7. Jeong WK, Baek JH, Rhim H, et al. Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. Eur Radiol 2008;18:1244-50.
8. Tsai WC, Pei D, Wang TF, et al. The effect of combination therapy with propylthiouracil and cholestyramine in the treatment of Graves' hyperthyroidism. Clinical endocrinology 2005;62:521-4.