Elimination of Premature Ventricular Contractions in Heart Failure (EVAC-HF)

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Premature ventricular contractions (PVC) are the most common arrhythmia to be observed in the absence of structural heart disease, and 'frequent' PVCs are estimated to occur in 1–4% of the general population.[1] Idiopathic PVCs are usually associated with a benign course from the standpoint of arrhythmic death, but may result in a cardiomyopathy that is reversible with suppression of the PVCs.[2]

The concept that frequent PVCs might be responsible for the development of a cardiomyopathy was originally suggested following the observation that pharmacological suppression of frequent PVCs (>20,000/24 hour holter recording) in patients with dilated cardiomyopathy led to dramatic improvements in left ventricular (LV) systolic function and dimensions.[3] Since that time, a number of additional reports documented a reversal of LV dilatation and impairment by both chemical and radiofrequency ablation (RFA), supporting the hypothesis that frequent PVCs (as few as 5,000 ectopic beats) might have a causative role in the genesis of LV dysfunction.[4-8] A recent analysis of 174 patients found that a PVC burden of 24% best separated patients with >50% EF from <50% EF.[9]

It is well documented that RFA is a safe and effective procedure in patients with symptomatic frequent ventricular ectopic beats and PVC-induced cardiomyopathy. Successful PVC suppression ≥80% of RV and LV PVCs has been reported to be as high as ~80% using an ablation approach.[9]
Studies found improvements in LV dysfunction following ablation, and, notably, demonstrated a significant inverse correlation between EF and PVC burden before ablation, and a significant post procedural improvement in EF in 82% of patients who had abnormal systolic function before ablation.[8] Improvement of the overall LV EF ranged from 13%-23% after PVC ablation.[5,8,10] While the mechanism of PVC-induced cardiomyopathy is not clear, possible etiologies include asynchronous ventricular contraction generated by the PVCs, impaired calcium handling, or a decrease in calcium transient.[10]

Previous studies have been limited to case reports and non-randomized, observational studies with variable, non-consistent adjunctive heart failure treatment. As such, the efficacy of RFA ablation above optimized medical and possible device therapy for heart failure with reduced LV function and frequent PVCs is still uncertain.

Justification:
Frequent PVCs can be associated with cardiomyopathies and may be a target for therapy. To date, there have been no randomized, prospective trials to evaluate the efficacy of PVC suppression using RFA±antiarrhythmic therapy in improving left ventricular systolic function compared to optimal medical therapy.

Consequently no unified treatment approach for these patients exist. While some physicians prefer aggressive PVC suppression using ablation procedures, other opt for intensive pharmacological heart failure treatment first. If the treatment effects observed in the observational studies of improvement of EF of ~15% could be verified in a randomized trial this would open a uniquely effective, new treatment strategy in this patient population.

Study Objective:
EVAC-HF will be a prospective, multi-center, randomized study to assess if in patients with frequent PVCs (>20%) and non-ischemic cardiomyopathy (EF≤45%) PVC suppression of >80% using RFA and antiarrhythmic therapy results in an improvement of EF after 6 months compared to optimized medical therapy (OMT) alone. Patients and/or their physicians will be contacted for follow-up to assess symptoms, any hospitalizations, and obtain any study related procedure(s) documentation that may have occurred at 1 year and 2 years post enrollment.

Recruited patients will be randomized in a 1:1 fashion between continuation of stable optimal medical therapy alone (i.e. ACE-inhibitors/ARBS, beta-blockers, aldosterone antagonists, diuretics, and digoxin as indicated) and RFA ablation±antiarrhythmics plus OMT.

Study Population

Inclusion Criteria:

1. Patients with reduced ejection fraction (EF ≤45%) demonstrated by transthoracic echocardiogram and deemed to be non-ischemic by nuclear stress test or cardiac catheterization.
2. Patients with >20% PVCs on 24 hour holter-recording
3. Patient is 18 years of age or older
4. Optimized medical therapy on stable therapy for minimum 3 months with no changes in beta-blocker, ACE-I/ARB, digoxin doses (varying diuretic doses permitted).

Exclusion Criteria:

1. Patients who are under the age of 18 years of age
2. Patients with >2 dominant PVC morphologies
3. Patients with cardiac surgery in previous 3 months or scheduled for following 6 months
4. Patients who were implanted with a biventricular device during the last three months or single/dual chamber device (with ventricular pacing >10%) during the last three months
5. Significant symptoms associated with PVCs that would make favor immediate ablation
6. Intracardiac mural thrombus or myxoma

7. Pregnancy

Procedures

Enrollment

Patients will be recruited from cardiology or medicine clinics, inpatient services, cardiology consult service or referrals. Prior to enrollment patients should have been kept on stable doses of beta-blocker, afterload reducing agents and aldosterone antagonist for three months, while diuretics doses can have been adjusted. Beta blockers should be advanced to the highest tolerated dose with a target average heart rate of <70bpm. Patients on stable antiarrhythmic therapy but a residual PVC burden of ≥20% are eligible for the study. At chart review the results of a clinically performed TTE and Holter acquired after at least three months of stable therapy will be screened. If the PVC burden is ≥20% and the EF≤45% a copy of the anonymized TTE and Holter report will be send to the echo core lab/coordinating center at UMD. If both criteria are confirmed the patient will undergo the following research procedures:

- **Randomization** (1:1) to standard of care OMT or clinically indicated PVC ablation±antiarrhythmic therapy plus OMT. Assignment of randomization will be provided by the coordinating center; University of Maryland Medical Center.
- **Blood draws** at enrollment for biomarker studies performed at the UMD core lab.
- If available, a **copy of the anonymized cardiac MRI**, which is part of the standard clinical work-up of these patients in many centers, will be send to the radiological core lab at UMD.
- A **copy of the anonymized clinical TTE and Holter studies** obtained during screening/enrollment, will be send to the core lab at UMD
- The patient will undergo **a 6 minute walk** test at baseline.
- The patient will answer **heart failure questionnaires** (Kansas City cardiomyopathy as well as the Minnesota Living with Heart Failure Questionnaire and optionally SF12/36) at baseline.

All patients will remain on their stable, optimized heart failure regiment during the 6 month's study duration. A cross-over is planned after 6 months. If during these 6 months of standard clinical follow-up a clinical deterioration would lead to a documented decrease in the EF in an OMT patient a crossover to the PVC ablation group will be allowed prior to the 6 months follow-up.

Standard of Care Endocardial/Epicardial Ablation

Patients randomized to PVC suppression will undergo a clinically indicated, standard of care PVC ablation. The electrophysiology procedures will be performed according to the clinical standard of care in the respective institutions.

The following description is meant as a guideline, but will be modified according to the local expertise, best clinical care and outcome.
The ablation will be performed in the fasting state after informed consent is obtained. The PVC mapping will be performed using an endocardial and possibly epicardial ablation approach. Placement of the endocardial RV mapping catheters will be performed via femoral venous access. Mapping of the LV will be performed either via femoral arterial sheath and retrograde aortic access or via transseptal puncture. Epicardial access, if required, will be performed via a substernal, percutaneous puncture or a limited, surgically created epicardial access. Systemic heparinization to achieve an activated clotting time of 300s is performed for left- sided procedures. In the presence of frequent spontaneous ectopy, activation mapping might be performed with an open-irrigated catheter using a clinical three-dimensional mapping system. If the ectopy is infrequent, isoproterenol is administered. If PVCs remain infrequent, pace mapping can be performed at a pacing cycle length that matches the coupling interval of the spontaneous ventricular ectopy. RFA is performed at the site of earliest endocardial activation or best pace map. The energy is titrated to achieve an impedance drop of 10 ohms. The applications are continued for at least 30 s if adequate heating at the electrode-tissue interface is achieved. If the PVCs are abolished within 30 seconds, the energy application is continued for 60 secs and followed by another 60 sec application. If PVCs are still present after 30 secs, the energy application is terminated and mapping is continued after ablation of the PVCs, isoproterenol is administered at 2–10 mg/min as needed to shorten the sinus cycle length to 400 –500 ms to confirm that PVCs are not inducible by adrenergic stimulation. An effective procedure is defined as a reduction in PVC burden of 80%. In the event of pleomorphic PVCs, the dominant PVC morphologies will be targeted. VT induction is strongly encouraged (but not mandatory) during the PVC ablation. If patients with prosthetic valves are included the ablation approach will take this into account to minimize any possible negative effect on the valve function as determined by the local PI. Procedure success will be confirmed with a 24 hour Holter monitor during the first seven days after ablation therapy, which is standard of care after PVC ablations. If the goal of PVC reduction of ≥80% cannot be achieved with the initial procedure, then PVC suppression using either a repeat ablation procedure within 6 weeks of the initial procedure or a pharmacological approach with antiarrhythmics such as amiodarone, sotalol, dofetilide or dronedarone will be chosen for the duration of 6 months. If a PVC reduction of ≥80% cannot be achieved with a second ablation antiarrhythmic therapy will be chosen for the study duration of 6 months. Patients that had < 3 continuous sinus beats prior to the PVC-suppressive therapy will undergo a clinically indicated TTE after PVC suppression to obtain accurate echocardiographic measurements.

Follow-up

During regular clinic visits patients will be assessed for NYHA class and compliance with medications. Approximately six months after enrollment or the

last RF ablation a clinically indicated TTE and 24h Holter monitor will be performed.
All patients will undergo the following research interventions at the 6 months follow up:

- A **copy of anonymized clinical TTEs and Holter recordings** will be sent to the UMD echo core lab and UMD coordinating center.
- A second **blood draw** will be performed and sent to the UMD core lab.
- A second **6 MWT** will be performed.
- The patient will answer **heart failure questionnaires** (Kansas City cardiomyopathy as well as the Minnesota Living with Heart Failure Questionnaire and optionally SF12/36) after 6 months.
- If any additional clinical cardiac MRI has been performed an anonymized copy will be send to the radiological core center at UMD
- Patients and/or treating physicians may be contacted for **clinical follow-up at 1 year and 2 years** post enrollment to assess for symptoms, hospitalizations and clinical events. It will be attempted to obtain any records from medical procedures that were conducted during that time such as but not limited to echocardiograms, Holter monitors, CT, MRI or cardiac catheterizations.

Risks:

Ventricular tachycardia ablation procedures have a definite morbidity and mortality, with a major complication rate ranging from 2.5 to 6 %. This is to due to both patient-related and procedure-related factors. Patients typically suffer from congestive heart failure and other comorbidities and the procedures are long, requiring the patient to lie flat for up to eight hours at times.

In addition to the risks of sedation, standard risks of an endocardial procedure include bleeding and other vascular access complications, stroke, myocardial infarction and rarely myocardial rupture and pericardial tamponade, aortic valve avulsion, and entanglement of the catheter in the mitral valve apparatus requiring surgical intervention, and death. The safety data of PVC ablations is not as well established as for VT ablations. In general, significantly less ablation lesions have to be applied frequently reducing the procedure time and volume administered. Additionally, many PVC ablations can be performed from the RV resulting in less risk of thromboembolic events or groin complications than for left-sided ventricular tachycardia ablations.
Epicardial ablations will have to be performed in a subgroup of patients. This approach has been associated with complications such as RV perforation, coronary artery or phrenic nerve injury or abdominal bleeding.

There are no known significant risks associated with echocardiograms or Holter monitors. There is a slight possibility of skin redness or irritation due to the

placement of the ECG electrodes, which should disappear within several hours of removing the electrodes.

Blood drawing can cause pain, bruising, lightheadedness and, on rare occasion, infection.
There are risks of loss of confidentiality to patients that participate in this trial; however all necessary precautions will be taken to assure the patient's confidentiality is maintained. The information will be kept in secure locations. In any publication or presentation of research results, patient's identity will not be disclosed.

Pregnant females are excluded from participation in this trial because they are not eligible for catheter ablation due to radiation risks to the developing fetus. All females with child bearing potential that want to participate will need to do a pregnancy test the morning of the ablation procedure, and the test must be negative to have an ablation.

Specific data to be collected:

1- Patient demographics (not identified)
2- Peripheral blood samples will be collected and stored from the time of randomization and at 6 months. These samples will be send to core laboratory and assayed for relevant biomarkers including BNP, galectin-3, soluble ST2.
3- Blood samples will be collected at initial visit for genome analysis
4- Echocardiographic and electrocardiographic data
5- 24 hour Holter recordings with available HRV data
6- Procedural data such as 3-dimensional left ventricular mapping data including number and origin of PVCs and the successful ablation sites
7- Peri-procedural data collection including mode of sedation, inducibility, dose of sympathomimetic drugs, procedure duration and fluoroscopy time
8- The complications, if any, of the procedure
9- The acute and intermediate-term success rate of the procedure.
10- Procedure, medication and outpatient visit costs
11- 6 MWT at baseline and 6 months
12- Heart Failure Questionnaire at baseline and 6 months
13- Clinically performed high-resolution CMRI studies performed prior to the enrollment, during randomizatoin duration and after 6 months will be collected to assess anatomic, perfusion and delayed enhancement myocardial fibrosis.
14- Tissue samples that may become available during the study duration from clinically indicated procedures such as biopsy, LVAD placement or heart transplantation will be stored for further tissue analysis

15- Clinical data such as past medical history, medications, NYHA class, physical exam findings, hospitalizations will be assessed during the 2-years follow-up

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