# Protocol Title

Post-Acute Sequelae of COVID-19 (PASC) with DysPnEA on ExertIon And Associated TaChycardia TrEatment Study

**PEACE Study**

**Protocol Version**

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# Study Personnel

**PI:**

**David Landers, MD**

Department of Cardiology

Hackensack University Medical Center

**Sub-I(s):**

Taya Glotzer, MD

Sameer Jamal, MD

Joseph Parrillo, MD

Zoltan Turi, MD

Marian Vandycke-Acquah, MD

Department of Cardiology

**Data Manager/Coordinator/ Research Nurse:** Jana Tancredi, Research Nurse Coordinator, HUMC Heart and Vascular Hospital

**Statistical support:** Provided by the Office of Research Administration

**Sponsor**: Hackensack Meridian *Health*

# Abbreviations

| Abbreviation | Explanation |
|---|---|
| PASC | post-acute COVID 19 syndrome |
| DOE | dyspnea on exertion |
| HUTT | heads up tilt table |
| TTE | transthoracic echocardiogram |
| POTS | postural orthostatic tachycardia syndrome |
| Zva | valvulo-arterial impedance |
| Hgb | Hemoglobin |
| HCT | Hematocrit |
| TSH | Thyroid Stimulating Hormone |
| HR | Heart rate |
| BP | Blood pressure |
| SBP | Systolic blood pressure |
| DBP | Diastolic blood pressure |
| MLHF | Minnesota Living with Heart Failure |
| FOSQ | Functional Outcomes of Sleep Questionnaire |

# Summary


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| **Objectives** | Pilot study to assess the reduction of symptoms in patients with PASC dyspnea on exertion and associated tachycardia when treated with beta blockers. |
| **Hypothesis** | PASC symptoms of DOE and tachycardia result from excess sympathetic drive. Beta blocker modulation of sympathetic excess will improve DOE by reducing vascular resistance as measured by improvement in 6 minute walk test and reduction in Zva.<br>Secondary outcome will be subjective improvement in DOE, tachycardia and well being score as measured by the Minnesota Living with Heart Failure. |
| **Study Population** | Patients between age 18 to 50 with DOE and tachycardia for 3 to 12 months post acute COVID infection phase with POTS or POTS like abnormality as demonstrated in HUTT and a TTE Zva measurement > 3.5.<br>Patients between the ages of 18 - 50 with DOE and tachycardia for 3 to 12 months post acute COVID infection phase who do not meet inclusion criteria will be included in a prospective data collection cohort. |
| **Phase** | Pilot |
| **Number of Subjects** | 20 subjects will be enrolled in the single arm treatment with beta blockers cohort.<br>Up to 20 more patients will be enrolled to the data collection cohort. |
| **Study duration** | Patients will be part of the study for 10-12 weeks (±7 days).<br>The overall study is expected to last for 12-18 months |
| **Participant duration** | Initial 2 week period during which the patients will receive low dose 25 mg of metoprolol succinate. Those patients who are intolerant of beta blocker therapy will be removed from the study and will be replaced. Patients who demonstrate tolerance will then continue an 8 week dose escalating treatment period and a 2 week final visit. |
| **Inclusion Criteria** | 1. Subjects should be between the ages of 18 and 50 with DOE for 3 - 12 months with no prior evidence of diastolic heart failure.<br>2. Subjects are those patients who have either recovered from PCR positive, COVID-19 infection but then had recurrence of DOE and tachycardia or those whose symptoms have persisted beyond three months. |

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| | 3. Demonstration of tachycardia and/or dyspnea with minimal activity (subjectively different than pre-COVID 19 infection state)<br>4. Abnormal HUTT<br>5. Normal chest x-ray<br>6. Left ventricular ejection fraction (LVEF) >50% by transthoracic echocardiography<br>7. Zva > 3.5(mmHg mL^-1) m^2 as calculated from TTE.<br>8. Hemoglobin/Hematocrit within normal laboratory standards<br>9. Thyroid-stimulating hormone (TSH) within normal laboratory standards<br><br>For the data collection cohort:<br><br>1. Subjects meeting criteria 1 through 3 and 5, 6, 8 and 9<br><br>2. Not meeting criteria 4 and 7. |
| **Exclusion Criteria** | 1. Active pregnancy<br>2. Demonstrate a primary cause of appropriate DOE and sinus tachycardia<br>a. Fevers/infection<br>b. Hypovolemia<br>c. Anemia<br>d. Hyperthyroidism<br>e. Alcohol/drug/medication withdrawal<br>2. Currently taking beta blocker medications<br>3. Currently being treated for pre-existing neurally mediated hypotension/syncope or known dysautonomia.<br><br>4. Medical history of chronic lung disease or reactive airway syndrome. |
| **Study Design** | 1. Patients will undergo pre and post treatment ECHO with Zva measurement, 24 hour Holter monitor, 6 minute hall walk test, Minnesota Living with Heart Failure scale and Functional Outcomes of Sleep Questionnaire.<br>2. Metoprolol succinate escalating dose every 2 weeks starting dose of 25 mg po daily to a maximum dose of 400 mg po daily. With treatment goal of:<br>a. Heart goal of 50 to 60 beats per minute<br>b. Resolution of symptoms<br>c. Maximum tolerated dose of Metoprolol.<br>2. If the patient is not able to tolerate the low dose beta blocker at the end of the first 2 weeks, then they will exit from the study and be offered another treatment option by a treating physician.<br>3. Completion study visit to be performed after 8 weeks of beta blocker therapy.<br><br>For the data collection cohort, patients will receive the standard of care (SOC) treatment as per their treating physician's discretion. |

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| | They will complete the Minnesota Living Heart Failure scale and Functional Outcomes of Sleep Questionnaire at baseline and post treatment (between 8-10 weeks). There will be no other change in their SOC. |

# 1 – Introduction

Most patients with acute COVID-19 recover within weeks, however a significant number of individuals will develop the post-acute COVID 19 syndrome (PASC). As of July 2021, the post COVID syndrome qualifies as a disability under the Americans with Disabilities Act. The symptoms which comprise this condition are highly variable and often extraordinarily debilitating. They may be distinct from the initial presentation or may mimic those which defined the initial infection. The post COVID syndrome can be diagnosed when symptoms persist longer than 3 months and may extend to beyond one year. There are risks for permanent levels of disability. Patients who seemingly did not have active COVID-19 symptoms in the days following infectious exposure may also develop post Covid syndromes. These syndromes are considered to constitute a distinct clinical entity which has of yet no clearly defined pathogenic mechanism or validated treatment algorithms. International investigative efforts are now underway to determine who might develop the post COVID syndrome, it's long term consequences and how best to treat its many problematic symptoms.

# 2 - Background

Although the long Covid syndrome or PASC is a well recognized syndrome, its pathogenesis is poorly understood. Hypotheses have included persistent viral remnants with consequent provocation of the generalized symptoms characteristic of systemic inflammation. The virus may continue to infect heart, lung or neurologic tissue rendering various organs dysfunctional. Alternatively there could be persistently infected or damaged endothelial cells which line blood vessels and thereby create perturbations of blood flow. The altered blood flow might then explain the many reported symptoms. However the pathogenesis can be distinguished and studied independently from the physiological disturbance. Existing and accepted therapies for tachycardia and shortness of breath, although they might not reverse the virus caused injury, could be used to reduce the resultant physiologic abnormalities which in turn produce the symptoms of the long Covid syndrome. Beta blockers are standard therapies in sinus tachycardias, (1,2) and POTS (3,4) which are often characterized by high levels of sympathetic drive which beta blockers are designed to modulate.
Thus it is reasonable to hypothesize that that treatment with beta blockers may be an effective intervention as Covid-19 directly infects the nerve and vascular tissues which regulate sympathetic excess which in turn may produce the cardiovascular symptoms of PASC. Moreover it is important to specifically study beta blockers in PASC because they are currently actively in use for this indication. Yet the possibility remains that although the symptoms are similar to those in which beta blockers have been effective, the pathologic processes in PASC will not be responsive to beta

blocker therapy. If this were to be true, beta blockers would prove ineffective and might carry a risk of harm. Equally as important is to properly determine the effective dose as the therapeutic window for these agents is wide. Metoprolol which is a widely used agent in cardiovascular disease is approved in doses ranging from 25 to 400 mg per day.
The proposed study will compare 6 minute walk distances (pre and post the treatment), the echocardiographic measurement of the impact of sympathetic excess on the heart's ability to empty effectively and a quality of life survey. Each of these study elements will be measured before and after progressively increased doses of beta blocker.
Our study is thus designed to study two issues:
1: Whether beta blockers which have been utilized to treat tachycardias, POTS, and hypertension will have similar effectiveness in PASC

2: To determine appropriate dosing which may be different than those used on non PASC conditions.

# 3 – Rationale, Objectives and Hypothesis

### 3.1. Study Rationale/Problem Statement/Research question or Study significance

Beta blockers have been effective in treating tachycardia caused by other causes. With this study, we plan to investigate whether beta blockers could be an effective treatment for tachycardia caused by PASC.

### 3.2. Hypothesis

PASC symptoms of dyspnea on exertion (DOE) and tachycardia result from excess sympathetic drive. Beta blocker modulation of sympathetic excess will improve DOE by reducing vascular resistance as measured by improvement in 6 minute walk test and reduction in Zva.

### 3.3. Primary Objective

Pilot study to assess the reduction of symptoms in patients with PASC DOE and associated tachycardia when treated with beta blockers.

### 3.4. Primary Outcome Variable(s)

Primary outcome variables include :
- Change in the 6 minute walk test and
- Change in the Zva

### 3.5. Secondary Objective(s)

**Secondary objective 1** will be subjective improvement in DOE, tachycardia and well being score as measured by the Minnesota Living with Heart Failure.

**Secondary Objective 2** will be the comparison of the treatment cohort (treated with beta blockers) to the data collection cohort (treated as per SOC) for subjective improvement in DOE, tachycardia and well being score as measured by the Minnesota Living with Heart Failure.

**Exploratory objective** is to investigate the appropriate dosing which may be different from those used on non PASC conditions.

**Another exploratory objective** is to investigate the sleep patterns of PASC patients as measured by the Functional Outcomes of Sleep Questionnaire.

# 4 - Study Design

### 4.1 General Design

This is a prospective interventional pilot study looking at the use of beta blockers for tachycardia caused by post-COVID (PASC).
As PASC has been only recently characterized as a syndrome, there is no established standard of case (SOC) for its related symptoms. As per current practice, patients presenting with tachycardia that were infected by COVID are usually treated with beta blockers at a dose as per their physician's discretion. With this study, we want to conduct a pilot to establish the safety and efficacy of beta blockers starting with a dose of 25 mg of metoprolol succinate daily. If dose is effective and well tolerated based on treatment goals (see below), the beta blocker used (metoprolol succinate) will be escalated every two weeks for a duration of 8 weeks and to a maximum dose of 400 mg po daily.
Treatment goals include:

a. Heart goal of 50 to 60 beats per minute
b. Resolution of symptoms (DOE and tachycardia)
c. Maximum tolerated dose of metoprolol succinate

The patient's treating physician will present the study to potential participants and if participants express interest the research team will conduct the informed consent discussion and obtain informed consent.
Once consent is obtained, patients will be scheduled for their baseline tests that include Transthoracic ECHO with Zva measurement (TTE), Head up Tilt Test (HUTT), 24 hour Holter monitor, 6 minute hall walk test (6MWT), Minnesota Living with Heart Failure scale (MLHF) and The Functional Outcomes of Sleep Questionnaire (FOSQ) as well as a complete medical and medication history. (see schedule of events for details).
The beta blocker metoprolol succinate will be initiated at a starting low dose of 25 mg daily for two weeks and will be escalated if well tolerated every 2 weeks to a maximum dose of 400 mg po daily.
At the end of each 2-week period, the patient will have a visit (telehealth or in person) with the study physician to assess tolerability and efficacy of the low dose beta blocker by capturing vitals, symptoms and any adverse events. If the patient is not able to tolerate the low dose beta blocker at the end of the first 2 weeks, then they will be removed from the study and be offered another treatment option by a treating physician( who is also the study physician). Data collected from those patients will be maintained in the database and analyzed.
Patients will be encouraged to self-report any experienced new symptoms or side-effects to the study team for the whole duration of the project.
At the end of the 8 week-period, patients will be scheduled for an in-person visit and will have all the post-treatment tests done including the post-treatment TTE with Zva measurement, 24 hour Holter monitor, 6 MWT, MLHF and FOSQ.
If patients' symptoms are not completely resolved at the end of the study, patients will receive treatment at their physician's discretion and that treatment falls outside the scope of this study.

For the data collection cohort, patients will receive the standard of care (SOC) treatment at their physician's discretion. They will complete the Minnesota Living Heart Failure questionnaire and the Functional Outcomes of Sleep Questionnaire (FOSQ) at baseline and post treatment (between 8-10 weeks). There will be no other change in their SOC.

#### 4.1.1 Study Duration

Patients will be part of the study for 10-12 weeks (±7 days).
The overall study is expected to last for 12-18 months including recruitment, treatment, data analysis and publication of results.

#### 4.1.2 Number of Study Sites

This pilot study will take place at the Bergen Cardiology Associates (HMH Cardiovascular Partners), office of the PI and Hackensack University Medical Center

### 4.2 Study Population

In this pilot study, we will include patients presenting at Bergen Cardiology Associates or HMH Hackensack University Medical Center with post-COVID tachycardia and DOE.

#### 4.2.1. Number of Participants

Our target enrollment is 40 patients, i.e. 20 patients completing the treatment cohort and up to 20 patients completing the data collection cohort.
To achieve this goal, up to 50 patients will be enrolled to account for dropouts and patients that cannot tolerate beta blockers.

#### 4.2.2. Eligibility Criteria

**Inclusion Criteria**

1. Subjects should be between the ages of 18 and 50 with DOE for 3 - 12 months with no prior evidence of diastolic heart failure.
2. Subjects recovered from acute, PCR positive, COVID-19 infection, but then had recurrence of DOE and tachycardia or those whose symptoms have persisted beyond 3 months.
3. Demonstration of tachycardia and/or dyspnea with minimal activity (subjectively different than pre-COVID 19 infection state)
4. Abnormal HUTT
5. Normal chest x-ray
6. Left ventricular ejection fraction (LVEF) >50% by transthoracic echocardiography
7. Zva > 3.5 as calculated from TTE.
8. Hemoglobin/Hematocrit within normal laboratory standards
9. Thyroid-stimulating hormone (TSH) within normal laboratory standards

For the data collection cohort:

1. Subjects meeting criteria 1 through 3 and 5, 6, 8 and 9
2. Not meeting criteria 4 and 7.

**Exclusion Criteria**

1. Active pregnancy (negative pregnancy test is the SOC prior to HUTT)
2. Demonstrate a primary cause of appropriate DOE and sinus tachycardia
   a. Fevers/infection
   b. Hypovolemia
   c. Anemia

   d. Hyperthyroidism
   e. Alcohol/drug/medication withdrawal
3. Currently taking beta blocker medications
4. Currently being treated for pre-existing neurally mediated hypotension/syncope or known dysautonomia.
5. Medical history of chronic lung disease or reactive airway syndrome.

**4.2.3 Vulnerable populations**

No vulnerable populations are going to be included in this study. Vulnerable populations to be excluded include pregnant women and fetuses, minors, prisoners and persons with diminished mental capacity.

**4.2.4. Withdrawal criteria**

Patients can withdraw from the study at any point by notifying their treating physician and study nurse.

At the time of the withdrawal, patients will be asked whether the data already collected can remain in the study. If they do not agree, all data collected will be deleted and the patient will be replaced by another patient to equal a total of 40 completed study subjects.

**4.3.1. Study discontinuation**

If a patient does not complete all study visits, then they will be removed from the study. A new patient will be added for every patient discontinued, to equal a total of 20 completed study subjects in the treatment cohort.

If a patient is unable to tolerate the low dose medication, then they will be removed from the study and be offered an alternative treatment by the treating physician (who is also the study investigator). A new patient will be added for every patient withdrawn from the treatment cohort, to equal a total of 20 completed study subjects in the treatment cohort.

If a patient has symptom relief at a lower dose then the dose will not be escalated as outlined, but will remain in the study and complete all follow-up visits as required.

**4.3.12. Concomitant medication**

The concomitant use of another beta blocker is strongly discouraged, during study drug escalation. If a patient does not have symptom relief at the completion of all study visits, then another beta blocker may be utilized at the discretion of the treating physician.

**4.4. Risks and Benefits**

Patients are expected to experience symptom reduction by the use of beta blockers. PASC could in part be explained by uniquely high levels of circulating catecholamines. The syndrome may thus need treatment with high dose beta blockers to achieve reduction in tachycardia and DOE. Participants will benefit from measurements and testing that are not generally utilized in beta blocker titration.

The risk to the patients are those which are known to occur with beta blockers. These risks may be greater at higher doses of beta blocker than those commonly used, however the follow up and monitoring will be above usual standards. In general, beta blockers are one of the most common classes of drugs used in heart disease and serious adverse reactions are uncommon and we do not expect anything different in the PASC population.

### Serious Reactions

- CHF
- bradycardia, severe
- heart block
- cardiogenic shock (MI use)
- angina exacerbation if abrupt D/C
- MI if abrupt D/C
- ventricular arrhythmia if abrupt D/C
- Raynaud phenomenon
- gangrene
- bronchospasm
- hepatitis
- hypersensitivity
- photosensitivity
- lupus erythematosus
- agranulocytosis

### Common Reactions

- fatigue
- dizziness
- diarrhea
- pruritus
- rash
- depression
- dyspnea
- bradycardia

**More common**

- Blurred vision
- chest pain or discomfort
- confusion
- dizziness, faintness, or lightheadedness when getting up suddenly from a lying or sitting position
- slow or irregular heartbeat
- sweating
- unusual tiredness or weakness

**Less common**

- Bloating or swelling of the face, arms, hands, lower legs, or feet
- cough
- decreased urine output
- difficult or labored breathing
- difficulty with speaking
- dilated neck veins
- disturbed color perception
- double vision
- extreme tiredness or weakness

- fast, pounding, or racing heartbeat or pulse
- halos around lights
- headache
- inability to move the arms, legs, or facial muscles
- inability to speak
- irregular breathing
- loss of vision
- night blindness
- noisy breathing
- overbright appearance of lights
- pain, tension, and weakness upon walking that subsides during periods of rest
- paleness or cold feeling in the fingertips and toes
- rapid weight gain
- seeing, hearing, or feeling things that are not there
- short-term memory loss
- slow speech
- swelling of the face, fingers, feet, or lower legs
- tightness in the chest
- tingling of the hands or feet
- tingling or pain in the fingers or toes when exposed to cold temperatures
- troubled breathing
- tunnel vision
- unusual weight gain or loss

**Rare**

- Bluish color of the skin of the fingers or toes
- chills
- clay-colored stools
- continuing loss of appetite
- continuing or severe abdominal or stomach pain
- continuing or severe nausea and vomiting
- dark urine
- difficulty with moving
- fever
- general tiredness and weakness
- hoarseness
- increased frequency of urination
- itching skin
- light-colored stools
- lower back or side pain
- muscle pain or stiffness
- numbness of the fingers or toes
- pain, swelling, or redness in the joints
- rash
- sore throat
- decreased libidio
- decreased sexual performance
- may mask signs/symptoms of low blood sugar
- sores, ulcers, or white spots on the lips or in the mouth
- unpleasant breath odor

- unusual bleeding or bruising
- upper right abdominal or stomach pain
- vomiting of blood
- weakness
- yellow eyes and skin

There is a small but appreciable risk of data or confidentiality breach, but the investigators will work diligently to protect this personal information.

For the data collection cohort, the only foreseeable study related risk is related to confidentiality; as with the first group, the investigators will work diligently to protect their personal information.

# 5 – Methods

### 5.1. Screening

Prospective study patients will be selected from those actively being cared for in HUMC outpatient clinical sites.

Patients who are screened and do not meet the criteria regarding Zva and tilt test, will be included in the data collection cohort.

### 5.2. Recruitment, enrollment and retention

Patients will usually be recruited for this study at the time of initial visit to a study physician/cardiologist for PASC symptoms of DOE and tachycardia. Once a patient meets basic inclusion criteria, informed consent will be obtained from study staff. The subject will be scheduled for a HUTT to determine POTS. Once the HUTT demonstrates POTS or "POTS like" results then, the patient is considered enrolled in the study.

Those patients who do not demonstrate POTS or "POTS like" response to the HUTT will be included in the data collection cohort.

Once the patient meets all inclusion criteria, the patient will be scheduled for their baseline test that includes Zva calculation, 6 MWT, MLHF and FOSQ. If upon screening, they do not meet the above mentioned criteria, they will be included into the data collection cohort and they will only have to complete the MLHF questionnaire and FOSQ at baseline and post treatment.

### 5.3. Study intervention (including schedule of events and study visits)

See the schedule of events.

TTE, 24-hour Holter monitor, Chest X-ray, Hgb/HCT and TSH will be collected as standard of care testing at least 90 days prior to Day 1 visit. The results will be reviewed by the study team for inclusion criteria.

If any of the testing is not completed within 90 days prior to Day 1 visit, then the test will be repeated as necessary. (Chest X-ray must be post acute COVID period).

Once the patient meets all inclusion criteria, the patient will be scheduled for their baseline test that includes Zva calculation, 6 MWT, MLHF and FOSQ. Zva calculation is performed by a study physician (See appendix 4).

If the patient does not meet the inclusion criteria for the treatment cohort, but meets the inclusion criteria for the data collection cohort, then they will be enrolled to the data collection cohort by the study team.

Day 1: Subject will be seen by study physician to review completion of all study required data and prescribe metoprolol succinate 25 mg daily. The subject will be instructed to schedule either telehealth or office visit within 14 days to assess medication tolerance, symptom reduction.

Day 14: Symptom and medication assessment, current vital signs, including any self reported adverse events will be reviewed by a study physician either by telehealth or office visit. If a study physician deems clinically appropriate, then metoprolol will be escalated to: 50 mg daily.

Day 28: Symptom and medication assessment, current vital signs, including any self reported adverse events will be reviewed by a study physician either by telehealth or office visit. If a study physician deems clinically appropriate, then metoprolol will be escalated to: 100 mg daily.

Day 42: Symptom and medication assessment, current vital signs, including any self reported adverse events will be reviewed by a study physician either by telehealth or office visit. If a study physician deems clinically appropriate, then metoprolol will be escalated to: 200 mg daily.

Day 56: Symptom and medication assessment, current vital signs, including any self reported adverse events will be reviewed by a study physician either by telehealth or office visit. If a study physician deems clinically appropriate, then metoprolol will be escalated to 400 mg daily.

Final Visit: (Day 70 +/- 7 days) Subject will complete an office visit (in person) to completeTTE, 24 hour Holter monitor, 6 minute Hall walk test, Minnesota Living with Heart Failure survey and Functional Outcomes of Sleep Questionnaire. Symptoms and medication, vital signs and adverse assessment will be collected at the final visit. The evaluation of the patient will be considered completed.

Head Up Tilt Test (HUTT)
The subject will undergo a HUTT to determine POTS or POTS “like” response.
HUTT will be performed by a study physician to determine POTS or POT “like” response to either passive or active component.

The passive component will consist of 21 minutes with HR and BP collected every 3 minutes. If at the end of the passive component there is no response, then an additional 21 minute active component with sublingual nitroglycerine administration with HR and BP collected every 3 minutes. The total duration of the HUTT is 42 minutes.

POTS is determined if HR >30bpm and SBP decrease <20 mmHg or DBP decrease < 10 mmHg within the first 10 minutes of standing.
“POTS like” Pattern is determined if HR >30bpm and SBP decrease <20 mmHg or DBP decrease < 10 mmHg within the first 10 minutes of sublingual nitroglycerine administration.

24 Hour Holter monitor
The 24 hour Holter monitor will be used to measure average daily heart rate and peak heart rate and establish baseline rhythm. The 24 hour Holter monitor should be completed prior to first dose of metoprolol and at study completion.

Minnesota Living with Heart Failure Survey (MLHF)
Improvement in quality of life over baseline will be measured using the MLHF survey. Each Subject will complete the MLHF survey prior to the first dose of metoprolol and at study completion. The MLHF is a self-administered survey. Patients will be provided a quiet space and ample time to complete the survey. (See Appendix 2)

The Functional Outcomes of Sleep Questionnaire (FOSQ)
Improvement in functional status, a component of quality of life, will be measured using the FOSQ questionnaire prior to the first dose of metoprolol and at study completion. The FOSQ is a self-administered survey. Patients will be provided a quiet space and ample time to complete the questionnaire. To assess the impact of sleepiness on the ability to conduct daily activities. (See Appendix 7)

Six Minute Hall Walk Test
The 6 Minute Hall Walk Test should be administered prior to the first dose of Metoprolol and at the study completion visit. The test should be administered by staff who are trained on the standard test protocol. The test should not be performed during an acute illness. (See Appendix 3).

The following should be ensured at each evaluation:

1. Comfortable clothing and appropriate walking shoes should be worn.
2. Patients should use their usual walking aids during the test.
3. The patient's usual medical regimen should be continued.
4. Patients should not have exercised vigorously within 2 hour of beginning the test.
5. The patient should sit and rest near the starting place for approximately 10 minutes before the test starts.
6. Consistent phrases for encouragement should be used throughout.

TTE Zva
Each subject will undergo a transthoracic echocardiogram (TTE), with color flow Doppler, performed prior to Day 1 and at study completion visit. The TTE will be performed by will be performed by a study physician and the Zva will be calculated as follows:

1. The sum of systolic blood pressure (SBP) and mean transaortic pressure gradient divided by the stroke volume index (SVi).

For the data collection cohort, we will have patients complete the Minnesota Living with Heart Failure Survey and the Functional Outcomes of Sleep Questionnaire (FOSQ) at baseline and post treatment (at 8-10 weeks). Patients will receive the SOC treatment and we will only collect data of their treatment and outcomes.

**5.4. Data collection tools**
For this project we will use data tools developed by the team and hosted at HMH REDCap. (see Appendix 1)
In addition to the home-developed tools, we will also use the Minnesota Living with Heart Failure survey, a tool that has been validated to use in patients with heart failure symptoms. MLHF 2.0 "Copyright University of Minnesota 1986". The Functional Outcomes of Sleep Questionnaire, a tool that has been validated to use in patients to measure the impact of daytime sleepiness and activities of daily living. FOSQ "Copyright University of Illinois at Chicago 2019".

### 5.5. Data collection (data points, source and storage)

This project will utilize the REDCap platform for data collection and management. Project team members listed as Key Study Personnel with existing EPIC system access rights may also be granted use of REDCap Clinical Data Interoperability Services (CDIS) tools. These tools are designed to enable transfer of relevant study-related data from EPIC into REDCap.

The data points that will be transferred include the following:

Medical Record Number

Demographics: Name, gender, ethnicity, race, date of birth, age, phone number, email address

Medication list

Allergy list

Problem list

Labs and vital signs

See Appendix 1 for all data points to be collected.

For the data collection cohort, we will only collect data collected as per SOC in addition to the MLHF survey and FOSQ at baseline and post treatment. All data collection forms will be in REDCap.

### 5.6. Statistical Method

The study is a prospective interventional pilot study to determine effectiveness of beta-blocker treatment on alleviating symptoms of PASC as measured with ZVA, 6 minute hall walk test and MLHF score. Additionally, vital signs (HR and BP) and symptoms assessments will be compared at each 2-week interval to explore dose effects. Descriptive analysis will be performed as follows: continuous variables will be summarized by mean (standard deviation) or median (interquartile range) depending on whether the data are normally distributed. The assumption of normality will be assessed using the Shapiro-Wilk test of normality. Categorical variables will be summarized as frequencies (percentages). Unless specified otherwise, any p-value $< 0.05$ will be considered statistically significant.

Baseline and end-of-study continuous outcomes will be compared with a matched-pairs t-test or Wilcoxon signed-rank test, depending on normality. Baseline and end-of-study categorical outcomes in terms of proportions will be compared with a McNemar's test or Cochran-Mantel-Haenszel test, which extends to multiple categories. One-sided tests will be used because the researcher hypothesizes an improvement in outcomes, i.e., an alternative hypothesis is one-sided.

Effects of escalating doses of a beta-blocker at each intermediate time point will be compared with repeated-measures ANOVA or Friedman's test, depending on normality.

Note that this study is a pilot study, and as such is designed to help with hypothesis generation and to enable power calculation to justify sample size in future study.

# 6 - Trial Administration

### 6.1. Ethical Considerations - Institutional Review Board (IRB) Review

The study will be conducted according to the International Conference on Harmonization (ICH), Good Clinical Practice (GCP), the Declaration of Helsinki, Institutional Review Boards (IRB) and in accordance with the U.S. Code of Federal Regulations on Protection of Human Rights (21 CFR 50).

### 6.2. Institutional Review Board (IRB) Review

The final study protocol, ICF, survey and data collection tools will be approved by the Institutional Review Board (IRB) at HMH. Approval will be received in writing before study initiation.

Any changes to the study design will be formally documented in amendments and be approved by the IRB prior to implementation.

### 6.3. Data management (collection, storage etc.)

Data will be entered into REDCap in a fashion with discrete variables Subjects will be given an unique study ID number. The key linking the subject ID number to the medical record number will be kept separate from coded study data and will only be accessible by authorized study team members. The key will either be stored in a locked drawer or password protected spreadsheet.

#### 6.3.1. Safety and Adverse Events

A Data and Safety Monitoring Board (DSMB) will monitor the study and advise the PI and designated study team members. The DSMB will review the study protocol and provide recommendations including whether the protocol and patient recruitment can be initiated. Throughout the course of the trial, the DSMB will review recruitment, retention on a monthly basis or once the first 10 subjects have completed treatment and will provide recommendations to the PI and designated study team members.

The PI and designated study team members will monitor key aspects of protocol compliance and reports will be developed and disseminated to monitor the ongoing progress of the study. Protocol safety and compliance reports will include enrollment of ineligible patients, follow-up data collection outside of protocol defined windows, deviations from the protocol and adherence to established adverse event reporting. Reports will be provided to the DSMB for review.

Reported adverse events will be monitored for the incidence rates. Serious adverse events (SAE) that are related to the PEACE protocol and unanticipated problems and study outcomes will be evaluated by the DSMB on a monthly basis or once the first 10 subjects have completed treatment, whichever occurs first. If unexpected safety concerns arise from the trial data, safety data will be reported promptly to the IRB and DSMB.. The PI and designated study team members will work with the DSMB to make certain that the board

members have sufficient information to comprehensively monitor patient safety throughout the PEACE study.

**Adverse Events**

An adverse event is defined as an untoward or unfavorable medical occurrence in a human participant, including any abnormal sign, symptom, or disease whether or not related to the use of a beta blocker. Adverse events will be collected from time of enrollment through final follow-up visit. AE applies to an event with an onset after study enrollment or to any underlying or baseline disease severity that is exacerbated during the study. A serious adverse event (SAE) is defined as an adverse event that meet any of the following criteria:

- result in death;
- is life-threatening i.e. places a subject at immediate risk of death from the event as it occurred;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- require intervention to prevent permanent impairment.

An unanticipated problem is defined as any incident, experience or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity or frequency, taking protocol research procedures and population characteristics into consideration
- Related or possibly related to the person's participation in the research.
- Places participants or others at a greater risk of harm than was previously known or recognized.

**6.4. Confidentiality**

Patient charts, collected data, and analyses of the data will adhere to HIPAA & institutional patient confidentiality requirements. A unique identifier (study ID number) will be assigned to each patient. The study ID number will be included in the data collection tools and analysis software while the list with direct identifiers and ID numbers will be stored separately in a HMH password protected computer and/or locked office.

If results of the study are published, individual names or other identifying information will not be used.

**6.5. Informed consent**

Informed consent will be obtained from each participant prior to entering the study. The informed consent form provides information and explanations of the aims, methods, anticipated benefits, and potential risks of the study.

The acquisition of informed consent will be documented in the participant's record and the informed consent form will be signed and personally dated by the participant and by the person who conducted the informed consent discussion. The original signed form will be retained in the Investigator Site File and a copy of the original will be provided to the patient prior to participation in the study.

The participant will be informed that they may withdraw from the study at any time without prejudice and compilation of that person's data will cease as of the date of his/her written request for withdrawal.

Potential subjects will be approached by a study physician/cardiologist on initial visit for PASC symptoms of DOE and tachycardia. If a potential subject expresses interest in participation they will receive the consent form to read and review. The potential participant will be contacted by a study team member to discuss the study and answer all questions. The subject will be sent an email for participant signature of the consent form, then they will receive a fully signed consent form via email. (see Appendix 5)

For the data collection cohort, patients will be consented at the same time..

### 6.6. Study Records

Records will be retained in accordance with regulatory and organizational requirements, but for no less than six (6) years following the completion of the study. Disposal of records will be performed according to regulations.

### 6.7. Financing and Insurance

The study will be funded by the Heart and Vascular Hospital located at Hackensack University Medical Center.

### 6.8. Publication Plan

Results from this study will be presented internally and will also be published in peer-reviewed journals such as JAMA, Circulation, etc.

No individual names or other identifying information will be used in potential reports or publications.

References

1. Page RL et al. Guidelines for the Management of Adult Patients with SVT: A Report of the ACC/AHA Task Force on Clinical Practice Guidelines Circ.2016;133 (14); e506 Epub 2015 Sept 23
2. Brugada J et al. ESC Guidelines for the management of SVT. TheTask Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology Eur Heart J 2020; 41(5): 655
3. Deng X et al. Efficacy of Beta Blockers in Postural Orthostatic Tachycardia Syndrome in Children and Adolescents: A Systemic Review and Meta-Analysis. Front Pediatrics. 2019;7:460 Epub 2019 Nov7
4. Raj SR et al. Propranolol decreases tachycardia and improves symptoms in Postural Orthostatic Tachycardia: less is more. Circ 2009; 120(9): 725. Epub 2009 Aug 17

**Schedule of Events**

| Assessment | Screening Within 90 days Prior to Consent and Baseline/Treatment | Consent | Day 1 (Office visit) | Day 14 +/- 3 days | Day 28 +/- 3 days | Day 42 +/- 3 days | Day 56 +/-3 days | Final Visit (Office visit) +/-7 days |
|---|---|---|---|---|---|---|---|---|
| Review Demographics, medical and cardiac history, current medication and symptom assessment to determine eligibility | X | | X | | | | | |
| Current medications | | | X | X | X | X | X | X |
| Symptom assessment | | | X | X | X | X | X | X |
| Vital signs (HR and BP) | | | X | X | X | X | X | X |
| Informed consent form | | X | X | | | | | |
| Chest X-ray (+/- 3 months of ICF) | X | | X | | | | | |
| Hemoglobin/Hematocrit (+/- 90 days of ICF) | X | | X | | | | | |
| 24 hour Holter Monitor | X | | | | | | | X |
| TSH (+/- 00 days of ICF) | X | | X | | | | | |
| HUTT (90 days prior to first dose ) | | | X | | | | | |
| ECHO with Zva ( 90 days prior to first dose) (+/- 30 days final visit) | X | | X | | | | | X |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 6 minute hall walk test<br>(Prior to start of any treatment) | | | X | | | | | X |
| Minnesota living with HF<br>(Prior to start of any treatment) | | | X | | | | | X |
| Data Collection Cohort Only<br>Minnesota living with HF<br>(Prior to start of any treatment) | | | X | | | | | X |
| Functional outcomes of sleep questionnaire<br>(Prior to start of any treatment) | | | X | | | | | X |
| Data Collection Cohort Only<br>Functional outcomes of sleep questionnaire<br>(Prior to start of any treatment) | | | X | | | | | X |
| Metoprolol succinate 25 mg daily (low dose) | | | X | | | | | |
| Metoprolol succinate 50 mg daily | | | | X | | | | |
| Metoprolol succinate 100 mg daily | | | | | X | | | |
| Metoprolol succinate 200 mg daily | | | | | | X | | |
| Metoprolol succinate 400 mg daily | | | | | | | X | |
| Telehealth/in person MD assessment for escalating dosing | | | X | X | X | X | X | X |

# Appendices

| Appendix # | Name |
|---|---|
| 1 | Data Collection REDCap |
| 2 | Minnesota Living with Heart Failure |
| 3 | 6 Minute Hall Walk |
| 4 | Zva Calculation |
| 5 | Subject communication |
| 6 | Metoprolol succinate package insert |
| 7 | Functional Outcomes of Sleep Questionnaire |