Principal Investigator

First Name: Chetan
Last Name: Naik
Degree: MD MS
Primary Affiliation: Baylor University Medical Center
E-mail: chetan.naik@bswhealth.org
Phone number: 8606342571
Address: 3410 Worth street
3410 Worth street
City: Dallas
State or Province: TX
Zip or Postal Code: 75246
Country: United States

General Information

Key Personnel (in addition to PI):
First Name: Chetan
Last name: Naik
Degree: MD, MS
Primary Affiliation: Baylor University Medical Center
SCOPUS ID: 16024964400

First Name: Ahmad
Last name: Abdelrehim
Degree: MD
Primary Affiliation: Baylor University Medical Center
SCOPUS ID:

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/coi_3.pdf
https://yoda.yale.edu/system/files/coi_form_aa_0.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT01106014 - AC-065A302 - A Multicenter, Double-blind, Placebo-controlled Phase 3 Study Assessing the Safety and Efficacy of Selexipag on Morbidity and Mortality in Patients With Pulmonary Arterial Hypertension

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all

supporting documentation

Research Proposal

Project Title

Predictive Value of QT Interval Dispersion in Patients with Pulmonary Arterial Hypertension (PAH)

Narrative Summary:

Analysis of EKGs of our PAH patients in our institutional database showed correlation between QT-dispersion and WHO functional class (WHO FC). WHO FC has been validated in clinical trials as a variable that correlates well with 1-year mortality in patients with WHO group 1 PAH. Monitoring of QT-dispersion may offer a way to monitor clinical condition of patients with WHO group 1 PAH in real time. We would like to confirm our observations regarding the clinical usefulness of monitoring QT-dispersion on a larger cohort of WHO group 1 PAH patients and expand our investigation to study correlation between QT-dispersion and other validated measures of prognostication in this population

Scientific Abstract:

Background: Electrocardiogram (EKG) records the electrical activity of the heart and provides insight into various heart diseases non-invasively. QT interval is a measure of the combination of cardiac depolarization and repolarization. QT interval differences within a 12?lead ECG may reflect regional differences in myocardial refractoriness and increased QT dispersion could reflect heterogeneity of myocardial repolarization. Prolongation of the QRS complex and QTc has been observed in severe PH however, there is an paucity of data regarding the significance of QT dispersion in PAH patients and its prognostic value. As pulmonary hypertension progresses, RV remodeling occurs as it becomes hypertrophic and dilated affecting QT dispersion at the spatial level. So, QT dispersion can theoretically help monitor RV remodeling and hence, PH severity.

Objective: Primary objective: To compare the QT dispersion between PAH 2015 ESC/ERS risk classes. Secondary objectives: To measure the association between QT dispersion to 2015 PAH ESC/ERS-risk-class variables. To assess predictors of patient outcomes using QT dispersion after controlling for other variables.

Study Design: This study is a cross section study.

Participants: Patients with WHO group 1 PAH from a large validated database (Griphon Trial/open label extension).

Primary and Secondary Outcome Measure(s); The patient's baseline EKGs will be reviewed and QT-dispersion will be measured. The QT-dispersion will then be correlated with validated prognostic markers of PAH namely, presence of clinical signs of right heart failure (JVP and LL edema), History of syncope, WHO functional class, 6-MWD, NT-pro-BNP plasma levels, RA area on echocardiogram.

Statistical Analysis. We will use R statistical software to conduct the descriptive and inferential statistics. For demographic, clinical, laboratory, imaging and RVC data, we will use frequency and percentages for qualitative data, and means ± standard deviations in normally distributed quantitative data. In skewed data, we will use median and quartiles. The Shapiro-Wilks test will be used to evaluate normality of continuous variables. Cohen’s Kappa statistic will be used to test interrater reliability. If interrater discordance <20 %, we will use the mean of QT dispersion of both raters. ANOVA test will be used to compare QT dispersion between the 3 groups of PAH patients for a difference overall. If significant, pairwise differences between groups will be assessed using two-sample t-tests with a Bonferroni adjustment for 3 multiple comparisons resulting in a significance level of 0.017 (0.05/3). In skewed data, we will use the Kruskal Wallis test for the overall comparison of groups, and Wilcoxon rank sum test for pairwise differences. For secondary objectives, Pearson correlation test will be used to assess for a linear correlation between QT dispersion and normally distributed quantitative variables, while Spearman rank test will be used for qualitative and non-normal quantitative variables. Univariable and multivariable ordinal regression analysis will be used to identify risk factors of WHO FC I-II, III and IV.

Brief Project Background and Statement of Project Significance:

Electrocardiogram (EKG) records the electrical activity of the heart and provides insight into various heart diseases non-invasively. QT interval is a measure of the combination of cardiac depolarization and repolarization [1]. There is some regional variation in the repolarization characteristics of the myocardium and that different ECG leads depict electrical signals of different myocardial regions [2-4]. QT interval differences within a 12?lead ECG may reflect regional differences in myocardial refractoriness and increased QT dispersion could reflect heterogeneity of myocardial repolarization [5, 6]. There is an association between the QT-dispersion and arrhythmias and death [7,8].
Prolongation of the QRS complex and QTc has been observed in severe PH [9, 10] however, there is an paucity of data regarding QT dispersion in PAH patients and its prognostic value in this population. As pulmonary hypertension progresses, RV remodeling occurs as it becomes hypertrophic and dilated[11]. This could alter regional cardiac repolarization and affect QT dispersion at the spatial level. So, QT dispersion can theoretically help monitor RV remodeling and hence, PH severity.

1. Postema, P.G. and A.A. Wilde, The measurement of the QT interval. Curr Cardiol Rev, 2014. 10(3): p. 287-94.
2. Higham, P., et al., QT dispersion does reflect regional variation in ventricular recovery. Circulation, 1992. 86(suppl I): p. 392.
3. Zabel, M., S. Portnoy, and M.R. Franz, Electrocardiographic indexes of dispersion of ventricular repolarization: an isolated heart validation study. J Am Coll Cardiol, 1995. 25(3): p. 746-52.
4. Zabel, M., et al., Comparison of ECG variables of dispersion of ventricular repolarization with direct myocardial repolarization measurements in the human heart. J Cardiovasc Electrophysiol, 1998. 9(12): p. 1279-84.
5. HAN, J. and G.K. MOE, Nonuniform Recovery of Excitability in Ventricular Muscle. Circulation Research, 1964. 14(1): p. 44-60.
6. Allessie, M.A., F.I. Bonke, and F.J. Schopman, Circus movement in rabbit atrial muscle as a mechanism of tachycardia. II. The role of nonuniform recovery of excitability in the occurrence of unidirectional block, as studied with multiple microelectrodes. Circ Res, 1976. 39(2): p. 168-77.
7. Kuo, C.S., et al., Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential durations. Circulation, 1983. 67(6): p. 1356-67.
8. Malik, M. and N. Batchvarov Velislav, Measurement, interpretation and clinical potential of QT dispersion. Journal of the American College of Cardiology, 2000. 36(6): p. 1749-1766.
9. Sun, P.Y., et al., Prolonged QRS duration: a new predictor of adverse outcome in idiopathic pulmonary arterial hypertension. Chest, 2012. 141(2): p. 374-380.
10. Rich, J.D., et al., QTc prolongation is associated with impaired right ventricular function and predicts mortality in pulmonary hypertension. Int J Cardiol, 2013. 167(3): p. 669-76.
11. Naeije, R. and A. Manes, The right ventricle in pulmonary arterial hypertension. European Respiratory Review, 2014. 23(134): p. 476-487.

Specific Aims of the Project:

Primary objective:
• To compare the QT dispersion between PAH 2015 ESC/ERS risk classes.

Secondary objectives:
• To measure the association between QT dispersion to 2015 PAH ESC/ERS-risk-class variables.
• To assess predictors of patient outcomes using QT dispersion after controlling for other variables.

Our hypothesis is that QT-dispersion is an easily measurable variable that can help monitor PAH severity and progression in real time and will correlate well with other known validated measures of PAH severity and PAH related mortality.

What is your Study Design?:

Other

What is the purpose of the analysis being proposed? Please select all that apply.

Preliminary research to be used as part of a grant proposal

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

A patient will be eligible for inclusion in this study if he or she meets all the following criteria:
• Patient >18 years,
• Patient's mean PA pressure >20 mm Hg,
• Patient's PAWP of ?15 mm Hg or lower,
• Patient's pulmonary vascular resistance of ?3 Wood units,
• WHO group 1 PAH patients
• Heart rate between 60 – 100 beats/minute.

Exclusion criteria
• Major electrolyte changes (K >5 or <3 mEq/l, Ca >11 or <8 mEq/l, Mg <1.3 or >2.1mEq/l),
• Voltage criteria of LV hypertrophy,
• Congenital heart diseases.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary objective:
• To compare the QT dispersion between PAH 2015 ESC/ERS risk classes.

Primary Objective: To compare the QT dispersion between PAH 2015 ESC/ERS risk classes.

Secondary objectives: To measure the association between QT dispersion to 2015 PAH ESC/ERS-risk-class variables (See below) in order to assess predictors of patient outcomes using QT dispersion after controlling for other variables.

ESC/ERS-risk-class variables:
1. WHO functional class
2. Clinical signs of right heart failure
3. Syncope
4. nT-Pro-BNP
5. 6-Minute walk distance
6. Echocardiograpic measures of right heart dysfunction - TAPSE/sPAP ratio, RA enlargement, pericardial effusion
7. Right heart Cath measures of right heart dysfunction - Cardiac index, RA pressure, PA sO2

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The efficacy of the study will be the value of the QT dispersion in predicting the following:
• Presence of clinical signs of right heart failure (JVP and LL edema),
• History of syncope,
• Patient WHO functional class,
• Patient 6-Minute walk distance,
• Patient NT-pro-BNP plasma levels,
• Patient RA area

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

NA

Statistical Analysis Plan:

We will use R statistical software to conduct the descriptive and inferential statistics.

Power calculations and sample size
Using a pilot sample, the group means ± standard deviations were 0.78 ± 0.3ms, 1.375 ± 0.4ms, and 1.875 ± 0.6ms for WHO FC groups I-II, III, and IV, respectively. Using these statistics, group sample sizes of 24 will allow to detect pairwise differences of 0.5 ms between groups with at least 80% power using a two-sided two-sample unequal variance t-test with a significance level of 0.017 that incorporates a Bonferroni adjustment for 3 comparisons to maintain the overall family wise error rate at 0.05. The total sample size needed is 72.

Descriptive statistics
For demographic, clinical, laboratory, imaging and RVC data, we will use frequency and percentages for qualitative data, and means ± standard deviations in normally distributed quantitative data. In skewed data, we will use median and quartiles. The Shapiro-Wilks test will be used to evaluate normality of continuous variables.

Primary objectives
Cohen's Kappa statistic will be used to test interrater reliability. If interrater discordance <20 %, we will use the mean of QT dispersion of both raters. If >20%, a third rater will assess QT dispersion and the mean from the two raters with the lowest disagreement will be used. ANOVA test will be used to compare QT dispersion between the 3 groups of PAH patients for a difference overall. If significant, pairwise differences between groups will be assessed using two-sample t-tests with a Bonferroni adjustment for 3 multiple comparisons resulting in a significance level of 0.017 (0.05/3). In skewed data, we will use the Kruskal Wallis test for the overall comparison of groups, and Wilcoxon rank sum test for pairwise differences.

Secondary objectives
Pearson correlation test will be used to assess for a linear correlation between QT dispersion and normally distributed quantitative variables, while Spearman rank test will be used for qualitative and non-normal quantitative variables. Univariable and multivariable ordinal regression analysis will be used to identify risk factors of WHO FC I-II, III and IV.
Software Used:
Open Office
Project Timeline:

Anticipated project start date: December 1, 2022
Analysis completion date March 31, 2023
Date manuscript drafted and first submitted for publication June 30th, 2023
Date results reported back to the YODA Project July 31, 2023

Dissemination Plan:

If QT-interval dispersion is validated in a large cohort of WHO group 1 PAH patients, it can be another tool used in risk stratification method used to prognosticate this disease.

Suitable journals: Journal of Heart & Lung Transplantation, American journal of Respiratory & Critical Care Medicine, Circulation, Pulmonary Circulation

Bibliography:

1. Postema, P.G. and A.A. Wilde, The measurement of the QT interval. Curr Cardiol Rev, 2014. 10(3): p. 287-94.
2. Higham, P., et al., QT dispersion does reflect regional variation in ventricular recovery. Circulation, 1992. 86(suppl I): p. 392.
3. Zabel, M., S. Portnoy, and M.R. Franz, Electrocardiographic indexes of dispersion of ventricular repolarization: an isolated heart validation study. J Am Coll Cardiol, 1995. 25(3): p. 746-52.
4. Zabel, M., et al., Comparison of ECG variables of dispersion of ventricular repolarization with direct myocardial repolarization measurements in the human heart. J Cardiovasc Electrophysiol, 1998. 9(12): p. 1279-84.
5. HAN, J. and G.K. MOE, Nonuniform Recovery of Excitability in Ventricular Muscle. Circulation Research, 1964. 14(1): p. 44-60.
6. Allessie, M.A., F.I. Bonke, and F.J. Schopman, Circus movement in rabbit atrial muscle as a mechanism of tachycardia. II. The role of nonuniform recovery of excitability in the occurrence of unidirectional block, as studied with multiple microelectrodes. Circ Res, 1976. 39(2): p. 168-77.
7. Kuo, C.S., et al., Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion

of action potential durations. Circulation, 1983. 67(6): p. 1356-67.
8. Malik, M. and N. Batchvarov Velislav, Measurement, interpretation and clinical potential of QT dispersion. Journal of the American College of Cardiology, 2000. 36(6): p. 1749-1766.
9. Sun, P.Y., et al., Prolonged QRS duration: a new predictor of adverse outcome in idiopathic pulmonary arterial hypertension. Chest, 2012. 141(2): p. 374-380.
10. Rich, J.D., et al., QTc prolongation is associated with impaired right ventricular function and predicts mortality in pulmonary hypertension. Int J Cardiol, 2013. 167(3): p. 669-76.
11. Naeije, R. and A. Manes, The right ventricle in pulmonary arterial hypertension. European Respiratory Review, 2014. 23(134): p. 476-487.

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }