

Published in final edited form as:

*Int J Cardiol.* 2013 August 10; 167(3): 669–676. doi:10.1016/j.ijcard.2012.03.071.

## QTc prolongation is associated with impaired right ventricular function and predicts mortality in pulmonary hypertension

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### Abstract

**Background**—In rodent models of pulmonary hypertension (PH) and right ventricular hypertrophy (RVH), the QTc interval is prolonged, reflecting downregulation of repolarizing Kv channels in RV myocytes. The significance of QTc prolongation in human PH is unknown. We hypothesized that QTc prolongation occurs in human PH, is associated with RVH and decreased RV function, and predicts adverse prognosis.

**Methods**—Patients receiving a PAH-specific therapy (a prostanoid, endothelin-receptor antagonist and/or a phosphodiesterase-5 inhibitor), who had a 12-lead electrocardiogram (ECG) (n=202) were compared to age- and sex-matched controls (n=100). The duration of QTc on ECG was correlated with invasive hemodynamics (n=156) and with the status of the RV, as measured by Brain Natriuretic Peptide (NT-proBNP, n=145) and magnetic resonance imaging (n=24). Survival of the entire PH cohort and a subgroup with WHO Group 1 and 4 PAH was prospectively determined from the Social Security Death Index.

**Results**—QTc intervals were longer in PH vs. controls (454.8±29 ms vs. 429.8±18 ms, p<0.001) and did not differ based on PAH-specific therapy. NT-proBNP increased proportionately with QTc and was higher for those in the upper quintile (QTc >480ms) vs. those with QTc <480ms (4004±6682 pg/mL vs. 1501±1822 pg/mL, p<0.001). The QTc interval also correlated directly with increasing RV end-diastolic volume (r=.67, p<0.001) and mass (r=.0.51, p<0.05), and inversely with RV ejection fraction (r=-.49, p<0.05). In the entire PH cohort and WHO Group 1 and 4 subgroup, QTc >480 ms and cardiac index were independent predictors of mortality.

**Conclusions**—QTc prolongation in PH patients reflects the status of the RV and is an independent predictor of mortality.

### Keywords

Biomarkers; brain natriuretic peptide; cardiac repolarization; pulmonary hypertension; right ventricular failure; right ventricular hypertrophy

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## Introduction

Pulmonary arterial hypertension (PAH) has an annual incident mortality rate of 15%, with most deaths occurring due to right ventricular (RV) failure[1–3]. It is increasingly recognized that prognosis in PAH is best predicted by RV function[4–5]. Simple screening tests for RV failure and hypertrophy include N-Terminal pro Brain Natriuretic Peptide (NT-proBNP) and echocardiography; however, early detection of RVH is difficult and patients with severe PAH and dyspnea have a mean delay to diagnosis of > 1 year[6]. Although the surface electrocardiogram (ECG) is specific for RVH, its sensitivity is quite low[7–8]. Recent studies of experimental PAH and RVH demonstrate that there are additional electrophysiologic changes in the RV that might offer insights into the status of the RV, notably prolongation of the duration of the QTc interval on the surface ECG[9].

In rodent models of RVH, whether accompanied by PAH (monocrotaline) or not (pulmonary artery banding), there is prolongation of the RV monophasic action potential duration and the QTc interval on the surface ECG[9]. Mechanistically, this reflects downregulation of repolarizing voltage-gated potassium channels in RV myocytes, including Kv1.5 and Kv4.2[9]. The QTc prolongation observed in these rodents with RVH was reversed with agents that regressed PAH and RVH, notably the pyruvate dehydrogenase kinase inhibitor, dichloroacetate, and these electrical changes were associated with improved RV function[9].

Few studies have examined whether humans with PAH manifest prolongation of the QTc interval or increased QRS duration and no studies have assessed whether QTc prolongation or increased QRS duration in patients with PAH are associated with indices of RV size and function or predict clinical outcomes[10–11].

We thus performed the current study to determine:

- a. whether PAH is associated with QTc prolongation or increased QRS duration.
- b. whether such ECG abnormalities correlate with established indices of RV dysfunction.
- c. whether such ECG abnormalities predict worse clinical outcomes.

## Methods

### Patient Selection

The institutional review board at the University of Chicago Medical Center approved the conduct of this study. We initially performed a retrospective chart review of patients diagnosed at the University of Chicago with pulmonary hypertension (PH) between January 2004 and February 2010. The following inclusion criteria were applied:

- a. Presence of PH, defined as a mean pulmonary artery pressure (PAP)  $\geq$  25 mmHg and an elevated pulmonary vascular resistance (PVR), measured during cardiac catheterization.
- b. An expert from the University of Chicago Pulmonary Hypertension Program confirmed the PH diagnosis and directed the management.
- c. The patient was prescribed at least one or more of the following FDA approved, PAH-specific therapies: a prostacyclin analogue (epoprostenol or treprostinil), a phosphodiesterase-5 inhibitor (sildenafil or tadalafil), and/or an endothelin receptor antagonist (bosentan or ambrisentan).
- d. A resting 12-lead ECG was performed at the time of the PH diagnosis.

After applying these criteria, we arrived at a final PH cohort consisting of 202 patients. The majority of these patients had WHO Group 1 PH (148/202). However, we also included patients from other WHO Groups only if they had pulmonary vascular disease of sufficient severity to warrant prescription of a PAH-specific drug by one of our PH specialists[1–2]. Regardless of the WHO PH Group, all patients in the study had not only elevated PA pressures but had significantly elevated PVR, reflective of pulmonary vascular disease. The severity of pulmonary vascular disease in those with non-Group 1 PH led the PH specialist to justify prescribing a PAH-specific medication for off label use. The rationale for this design reflects the fact that we intended to test the ability of the ECG to evaluate the status of the *right ventricle*, a key predictor of outcomes in all forms of PH.

The control group consisted of 100 consecutive, age- and sex-matched patients at the University of Chicago Medical Center with normal ECGs (defined as normal sinus rhythm without evidence of bundle branch block, ST-segment depression or elevation, left or right ventricular hypertrophy, or previous myocardial infarction). The clinical indication for the ECG in these controls was not determined; however the normalcy of their ECG was confirmed.

We recorded the following ECG variables: QT interval, QTc interval, QRS duration, presence of RVH, and presence of right axis deviation. All intervals were determined by commercial ECG software algorithm (Marquette™ 12SL™ ECG Analysis Program). The exact details of the algorithm can be found elsewhere[12]. Briefly, the onsets and offsets of all intervals are determined by an analysis of the simultaneous slopes in all 12 leads. Onsets are defined as the earliest deflection in any lead, and offsets are defined as the latest deflection in any lead. The QT interval is measured from the earliest depolarization in any lead to the latest detection of repolarization in any lead. The QTc interval was determined by the Fridericia formula (corrected QT interval =  $QT/RR^{1/3}$ ). In order to account for the possible impact of a RBBB on the QTc interval, we subtracted 40 ms from the measured QTc in the 14 patients from the PH cohort with a RBBB[13]. Right axis deviation was defined as a frontal plane QRS axis  $> 90$  degrees. The ECG criteria for RVH were achieved if there was right axis deviation and the R-wave in V1 was both greater than 0.5 mV and greater than the V1 S-wave[8].

Diuretic therapy is not uncommon in PH patients and can result in hypokalemia, which may prolong the QTc. Therefore, we recorded potassium values in all PH patients who had a measured level within 30 days of the index ECG (n=185).

### Right Heart Catheterization

Hemodynamic data from right heart catheterization were included if performed within six months of the index ECG (n=156). Hemodynamics recorded included: mean right atrial pressure, mean pulmonary artery pressure, PVR, pulmonary capillary wedge pressure, and cardiac index.

### Measures of Right Ventricular Status

NT-proBNP may predict clinical outcomes in PH, likely reflecting the status of the RV[14]. Thus, we recorded NT-proBNP levels in all PH patients who had a value within 30 days of their index ECG (n=145). We also identified 24 subjects among our PH cohort who underwent Cardiac Magnetic Resonance Imaging (CMR) within 6 months of the index ECG. All patients were imaged on a 1.5 Tesla scanner (Achieva, Philips, Best, Netherlands) using a phased-array surface coil with electrocardiographic gating. After scout imaging, retrospectively gated cine images were obtained in the short axis plane using a steady-state free precession (SSFP) sequence (TR 2.9ms, TE 1.5ms, flip angle  $60^\circ$ , and temporal

resolution ~40ms). Images were analyzed using commercial software (Philips ViewForum, Best, Netherlands). Short axis slices were used to calculate right ventricular end-diastolic volume (RVEDV), end-systolic volume (RVESV), ejection fraction (RVEF), and mass via the method of disks.

### Clinical Outcomes

>We prospectively followed subjects in the PH cohort to determine whether QTc prolongation or QRS duration predicted mortality during a subsequent follow-up period of one year. We also performed a subgroup analysis of clinical outcomes in patients restricted to Group 1 and 4 PH. Vital statistics were collected for all patients by searching the Social Security Death Index as previously described[15]. The vital status of patients who were not identified as deceased in the Social Security Death Index was determined and confirmed by chart review. Thus, no patients were lost to follow-up.

### Statistical Analyses

Continuous variables are expressed as mean  $\pm$  standard deviation and categorical variables as frequency and percentages. Continuous variables were compared using the unpaired Students t-test and multi-way ANOVA with Bonferroni's testing for post hoc analysis. Categorical variables were compared using the Chi-square test. Pearson's correlation coefficients were determined when comparing continuous variables. We compared survival in patients with a QTc interval  $\leq$  480 ms versus QTc interval  $>$  480 ms, which represented the highest quintile of QTc prolongation, using the Kaplan–Meier method and log-rank test. We used the multivariable Cox proportional hazard regression method to determine independent predictors of mortality. All baseline, clinical, and hemodynamic characteristics were included in our univariable analysis, including quintiles of QTc interval and QRS duration, which were entered as categorical predictors (Table 1). Covariates with a p-value  $<$ 0.06 from our univariable analysis were initially entered into our multivariate model; covariates with p-values  $>$ 0.10 were removed sequentially to arrive at a final multivariate model. All statistical analyses were performed using STATA11.1 (StataCorp LP, College Station, TX).

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology: Shewan LG and Coats AJ. Ethics in the authorship and publishing of scientific articles. *Int J Cardiol* 2010;144:1-2.

### Results

Patient demographic, electrocardiographic, clinical, laboratory, and invasive hemodynamic data can be seen in Table 1. There was no difference in age ( $54\pm 14$  years vs.  $52\pm 15$  years,  $p=0.48$ ) or sex (79% female vs. 74% female,  $p=0.31$ ) between PH subjects and controls, reflecting the effective case matching. However, subjects with PH had a significantly longer QTc interval ( $454.8\pm 29$  ms vs.  $429.8\pm 18$  ms,  $p<0.001$ ) and QRS duration ( $96.5\pm 16$  ms vs.  $84.4\pm 8$  ms,  $p<0.001$ ), as compared to controls (Figure 1AB).

Given that ECG changes in patients with PH likely reflects the status of the RV, it is not surprising that we found no difference in QTc interval or QRS duration based on WHO PH Group classification (Figure 2A–B), nor did the QTc or QRS vary according to the type of PAH-specific therapy. Among those with PH, both the QTc interval and QRS duration, respectively, were more prolonged in those with electrocardiographic evidence of RVH ( $458.8\pm 3$  ms vs.  $449.8\pm 3$  ms,  $p<0.05$ ) and ( $100.9\pm 2$  ms vs.  $90.9\pm 1$  ms,  $p<0.01$ ). A similar observation was seen in those with right axis deviation on the ECG ( $458.4\pm 2$  ms vs.  $446.1\pm 3$  ms,  $p<0.01$ ) and ( $99.2\pm 1$  ms vs.  $90.1\pm 2$  ms,  $p<0.01$ ). Interestingly, there was a poor correlation between the QTc interval and QRS duration in PH patients ( $r=0.21$ ,  $p<0.01$ ).

The mean serum potassium level in the 185 PH patients with available levels at the time of the index ECG was  $4.01 \pm 0.50$  mEq/L. Serum potassium was not different in those with a normal versus prolonged QTc ( $3.99 \pm .54$  mEq/L vs.  $4.08 \pm .43$  mEq/L,  $p=0.27$ ). There was also no difference in serum potassium levels in those with QTc prolongation in the upper quintile ( $> 480$  ms) compared to those with a QTc  $< 480$  ms ( $4.04 \pm 0.47$  mEq/L vs.  $3.89 \pm 0.62$  mEq/L,  $p=0.13$ ).

### Right Heart Catheterization

Hemodynamic status reflected a prevalence cohort with severe PH, as evidenced by a markedly elevated PVR (Table 1). The QTc interval and mean PA pressure were directly, but poorly correlated ( $r=0.18$ ,  $p<0.05$ ). However, there were no other statistically significant correlations between hemodynamics and the QTc interval and/or the QRS duration.

### Measures of Right Ventricular Status

The mean NT-proBNP level was elevated at  $1959 \pm 3401$  pg/mL (normal  $<125$  pg/mL) in the 145 PH patients with available tests. There was a significant but poor correlation between QTc and NT-proBNP levels ( $r=0.24$ ,  $p<0.01$ ). In addition, NT-proBNP levels were significantly higher in those with a QTc  $> 480$  ms compared to those with a QTc  $< 480$  ms ( $4004.0 \pm 6682.1$  pg/mL vs.  $1501.2 \pm 1822.3$  pg/mL,  $p<0.001$ ) (Figure 3). Mean RV size and mass were markedly enlarged and RV systolic function was reduced in the PH cohort (Table 2). In these patients, the QTc interval and QRS duration were both strongly correlated with all measured indices of RV size and function (Table 3 and Figures 4A–B).

### Survival Analysis

There were 23 deaths in the PH cohort during the 12 month prospective follow-up period. Compared to patients with QTc interval  $< 480$  ms, PH patients in the highest quintile (QTc  $> 480$  ms) had decreased survival (Figure 5A). The univariable and multivariable predictors of mortality are shown in Table 4. On multivariate analysis, those in the highest QTc quintile (QTc  $> 480$  ms) were at increased risk of death compared to those with shorter QTc (HR 3.09; 95% CI 1.14 – 8.38;  $p<0.05$ ). However, despite a trend, there was no statistically significant difference in absolute QTc interval ( $453.8 \pm 29$  ms vs.  $462.3 \pm 30$  ms,  $p=0.17$ ) or QRS duration ( $95.9 \pm 15$  ms vs.  $100.7 \pm 19$  ms,  $p=0.15$ ) in PH survivors compared to those who died. When we restricted our analyses to only those patients with WHO Group 1 and 4 PH ( $n=163$ ), a QTc  $> 480$  ms continued to be an independent predictor of mortality (HR 4.38; 95% CI 1.41 – 13.61;  $p<0.05$ ) (Figure 5B).

### Discussion

In the present study, we found that both the QTc interval and QRS duration are prolonged in patients with PH. Moreover, increasing QTc predicts increasing NT-pro BNP levels, suggesting a dose-effect of QTc on an important biomarker of RV function (Figure 3). Also, both prolonged QTc interval and increased QRS duration are associated with accepted indices of RV dysfunction in PH, including increased RV mass and depressed systolic function, as measured by CMR. Finally, a severely prolonged QTc interval ( $> 480$  ms) predicted mortality in the entire PH cohort ( $n=202$ ) as well as in the subgroup of patients with WHO Group 1 and 4 PH ( $n=163$ ). These findings are biologically plausible based on the observed prolongation of RV monophasic action potential duration and QTc interval observed in experimental RVH induced by monocrotaline or pulmonary artery banding[9].

Few studies have examined whether QTc prolongation or increased QRS duration occur in PH and none have examined the potential clinical implications of these changes. In 73 sickle cell patients, Akgul et al found QTc prolongation among the 26 with sickle-cell associated

PH (QTc=459ms) versus those with sickle disease without PH (QTc=436 ms) and both groups were longer than controls (QTc=402ms) [10]. Important limitations of their study included the small sample size and the use of Doppler to estimate PA pressure rather than right heart catheterization. The reliance on Doppler to diagnose PAH in a sickle cell disease cohort with mild PH (PA systolic pressure  $38\pm 5$  mmHg) is problematic because of the possibility of a high cardiac output state and the inability to quantify PVR [16]. Moreover, extrapolation to the broader PH population is quite limited by their exclusive use of a sickle cell disease population. More recently, Hong-Liang et al studied a cohort of PH patients and found the QTc was higher in those with severe PH versus controls ( $428.6\pm 32.8$  ms vs.  $411.1\pm 28.4$  ms,  $p=0.02$ ) [11]. However, the QTc in their PH cohort, though higher than controls, was within normal limits, unlike our study (where QTc was prolonged for the entire PH group). In addition, they used Bazett's formula for QTc correction, which over-corrects QTc at high heart rates and under-corrects at low heart rates. This is important because Bazett's formula systematically overestimates QTc relative to the other formulae (Fridericia, Hodges and Framingham) [17]. Indeed the upper limit of normal QTc, as defined as the upper 2% of values in 10,303 normal EKGs, is 483ms for Bazett's formula vs. 460ms for Fridericia and 457ms for Hodges and Framingham [17]. Thus, none of the QTc prolongations reported previously would fall outside the normal range and may simply reflect the sicker patients within their cohort (those with PH) having higher heart rate. Finally, and perhaps most importantly, they did not correlate QTc intervals with indices of RV function or determine the impact on survival.

Even less is known about QRS duration in adult PH. In a study that evaluated for the presence of intraventricular dyssynchrony in patients with PH, Kalogeropoulos et al found that PH patients had an increased mean QRS duration compared to controls, but associations with PH outcomes or QTc interval were not assessed [18]. To our knowledge, the present study represents the largest study to evaluate and confirm the presence of both QTc prolongation and increased QRS duration in a relatively sick cohort of patients with PH and the first study to determine the individual predictive values of each on survival.

The close correlation between QTc and QRS duration with NT-proBNP and measures of RV mass and function on CMR suggest these ECG abnormalities reflect the function of the RV and/or the severity of RVH. In this regard there are lessons to be learned from LVH. Both QRS duration and QTc interval are prolonged in patients with LVH [19–24]. LVH also results in increased arrhythmic vulnerability [25–26]. The impairment of depolarization and repolarization of cardiomyocytes in ventricular hypertrophy accounts for the ECG changes known as “electrical remodeling”. Similar ECG changes have been described in experimental RVH [9]. Impaired active depolarization-repolarization in hypertrophy reflects (in part) downregulation of repolarizing potassium channels, such as those which account for the transient outward current,  $I_{TO}$  (Kv4.2 and Kv4.3) or the ultra-rapid delayed rectifier  $K^+$  current ( $I_{Kur}$ ) (Kv1.5) [9]. In addition, ventricular conduction can be slowed by pathological processes that reduce cell-to-cell coupling, including impaired expression/function of gap junctions and myocardial fibrosis. In a double-transgenic, angiotensin II-induced rat model (overexpressing the human renin and angiotensinogen genes), Fisher et al showed that QTc prolongation and prolonged QRS duration accompanied LVH. This was due to a combination of factors: downregulation of cardiac Kv4.3, decreased expression of the gap junction protein Connexin 43 and myocardial fibrosis. The electrical remodeling led to arrhythmogenic early- and delayed after-depolarizations and reentry and inducible ventricular tachycardia [27]. In rodent RVH QTc prolongation results (in part) from downregulation of repolarizing Kv channels in RV myocytes (Kv1.5 and Kv4.2) and is reversed when RVH is experimentally regressed. This was associated with re-expression of repolarizing Kv channels [9]. The fact that rats with RVH induced by pulmonary artery banding (who have no PH) display the QTc prolongation indicates the effect is related to

RVH not PH. The reversibility of QTc prolongation in experimental RVH suggests this simple noninvasive marker could potentially be used to follow the progression/regression of RVH. However, it remains to be determined whether effective PH treatment in patients with PH would result in shortening of the QTc interval with a concomitant improvement in survival.

The consequence of long QTc in patients with PH has not previously been studied. In RVH it is not clear whether the consequence of QTc prolongation is arrhythmia, as in LVH, or impaired ventricular RV function. One of the more important aspects of this study is that the highest quintile of QTc prolongation was an independent predictor of mortality in patients with PH. The other two predictors of mortality in our PH cohort, NT-proBNP and cardiac index, respectively, both reflect the status of the RV in PH and both have been shown to be predictive of adverse outcomes in PH[3, 14, 28]. PH patients are not thought to be particularly susceptible to ventricular arrhythmias and are usually thought to die from RV failure and bradyarrhythmia[28]. However, many deaths are sudden and occur outside the hospital and this is an important area for future study[29].

Our study was not specifically designed to understand molecular mechanisms or investigate what initiates the QTc prolongation observed in patients with PH. However, emerging evidence supports the presence of chronic RV ischemia in many PH patients with RVH[30–31]. This ischemia may reflect microvascular rarefaction[32] and/or impaired right coronary artery perfusion pressure[31, 33]. Ischemia can prolong the QT interval by several mechanisms, including impaired function and expression of repolarizing Kv channels. Ischemia may also prolong QTc by increasing intracellular calcium during the cardiac action potential or through acidification of intracellular pH, both of which inhibit repolarizing potassium current[9]. Thus, chronic RV ischemia could be a potential mechanism responsible for QTc prolongation in PH patients and could possibly explain why those with the greatest QTc prolongation had the highest NT-proBNP levels (Figure 3) and were at the highest risk of death (Figure 5A). In addition, QTc interval duration is significantly affected by changes in the sympathetic nervous system and sympathetic tone[34]. PH patients with advanced RV failure are known to have neuroendocrine activation similar to that which is seen in LV failure and the QTc prolongation may be a marker of advanced disease with neurohormonal activation[35–36].

Another interesting finding in our study is that the QTc interval correlated better with measures of the status of the RV (NT-proBNP and RV mass and size) than with the PVR. This is consistent with our hypothesis that the QTc interval is primarily a reflection the status of the RV, rather than the pulmonary vasculature, and as in animal models, the CMR data show that the QTc does not prolong until there is severe RVH and a reduction in RV systolic function. Consistent with this, there appeared to be a threshold effect, with QTc only predicting survival at the highest quintile of QTc prolongation. This raises the question as to whether QTc prolongation might be useful to distinguish RVH that is “adaptive” (i.e. concentric RVH without chamber dilatation) versus “maladaptive” (i.e. eccentric RVH associated with reduced RV function and clinical RV failure). It has been reported, for example, that patients with the severest degree of pulmonary hypertension as measured by mean PA pressure and as described from post mortem analyses may not result in premature death if accompanied by concentric RVH[37]. Future studies that examine whether it is possible to discern the presence of concentric or adaptive RVH versus eccentric or maladaptive RVH on the basis of the QTc interval on the surface ECG would be important.

## Limitations

The present study is not without limitations. First, this was a retrospective cohort study and is thus subject to potential selection and information bias. However, we prospectively

followed the patients in our PH cohort for clinical outcomes which may minimize biases. Second, the PAH-specific treatments were not randomly or prospectively assigned but rather prescribed at the discretion of the PH specialist; thus, we cannot assess the effects (beneficial or deleterious) on the QTc interval. However, these specific treatments did not appear to have an effect on the QTc interval or QRS duration (Figure 2 C–D). Third, heart rate correction of the QT interval by the Fridericia formula (or any other corresponding formula) is appropriate under circumstances where there is a constant inverse relationship between heart rate and QT interval. In this study setting, it is conceivable that in PH patients there were factors present other than those related to the electrophysiology of the RV. Among potential extracardiac causes of QT prolongation, we corrected for electrolyte disturbances and PAH specific medications. However, there may be unknown confounders in PH that affect the QTc interval which are not accounted for by heart rate correction, including the direct effects of excessive neurohormonal stimulation. Nonetheless, it is noteworthy that in rodent models of RVH (where there are few confounders), QTc prolongation occurs in direct proportion to RVH severity and is reversible when an effective PH therapy is administered, as we have previously shown[9]. This is true both in pure RVH created by PA banding and in RVH associated with PAH-induced by monocrotaline. Finally, the inclusion of WHO Groups 2-5 patients might be considered a limitation but they were similar to the Group 1 patients with respect to the severity of the PH, as well as their QTc intervals. This is consistent with the interpretation that QTc prolongation reflects the status of the RV and is not specific for a particular WHO PH Group. Moreover, when we restricted our analyses to only those with Group 1 or Group 1 and 4 PH, a prolonged QTc continued to be an independent predictor of mortality.

## Conclusions

In conclusion, both QTc interval and QRS duration are prolonged in patients with PH and this reflects the status of the RV. We show for the first time that a QTc interval  $> 480$  ms is an independent predictor of worse clinical outcomes. If confirmed by others, the present work identifies an inexpensive and readily detectable abnormality on the surface ECG that can be potentially used to risk stratify PH patients. Whether effective treatment of the underlying PH would shorten the QTc interval and improve clinical outcomes remains to be determined.

## Acknowledgments

This work is supported by the National Institute of Health [NIH-RO1-HL071115, 1RC1HL099462-01, UL1RR024999]; the American Heart Association (AHA); and the Roche Foundation for Anemia Research.

## Abbreviation List

<b>CMR</b>	cardiac magnetic resonance imaging
<b>ECG</b>	electrocardiogram
<b>LVH</b>	left ventricular hypertrophy
<b>NT-proBNP</b>	N-Terminal pro Brain Natriuretic Peptide
<b>PAH</b>	pulmonary arterial hypertension
<b>PAP</b>	pulmonary artery pressure
<b>PVR</b>	pulmonary vascular resistance
<b>QTc</b>	QT interval corrected for heart rate



<b>RV</b>	right ventricle
<b>RVEDV</b>	right ventricular end-diastolic volume
<b>RVEF</b>	right ventricular ejection fraction
<b>RVESV</b>	right ventricular end-systolic volume
<b>WHO</b>	world health organization

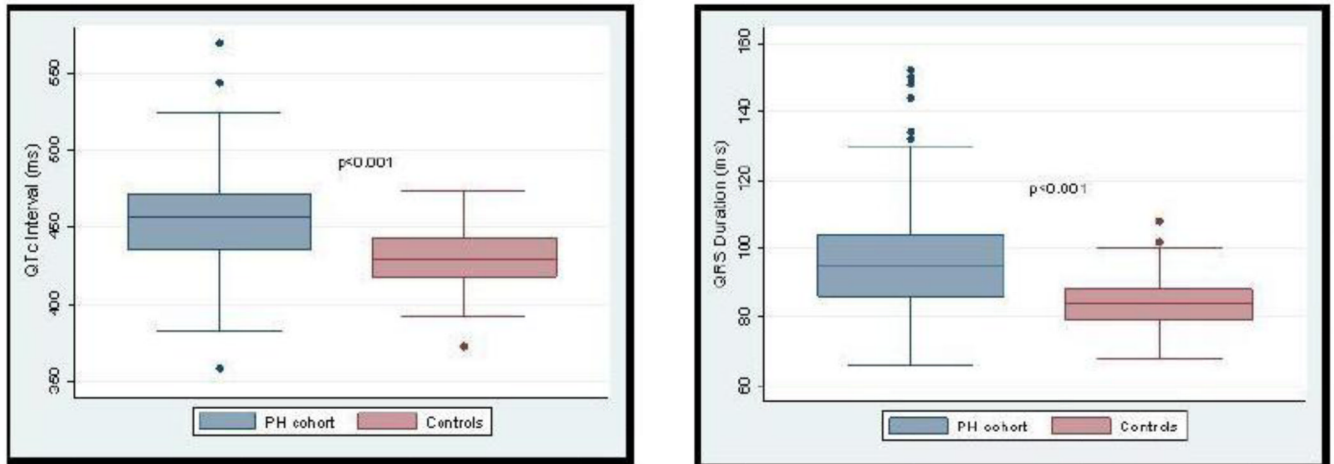
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# 1A and 1B

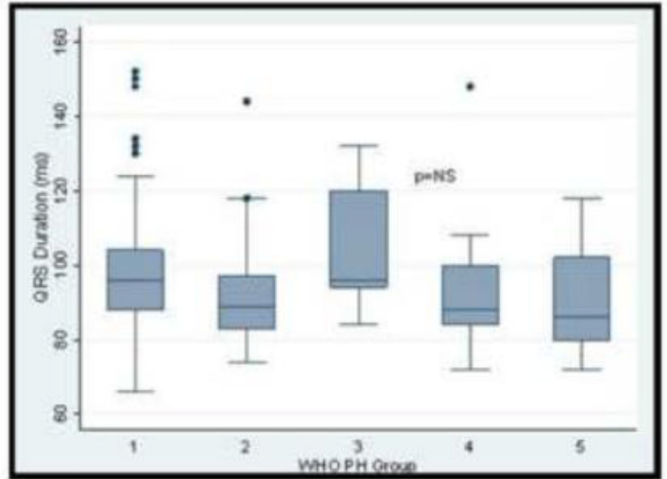
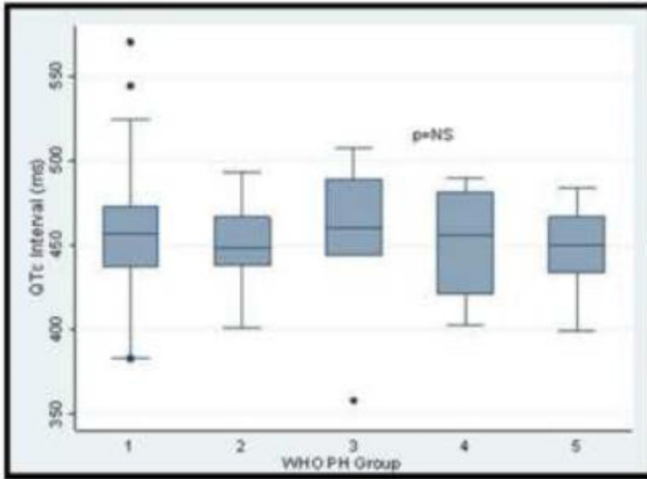


**Figure 1. Prolongation of QTc and QRS in PH Patients Versus Controls**

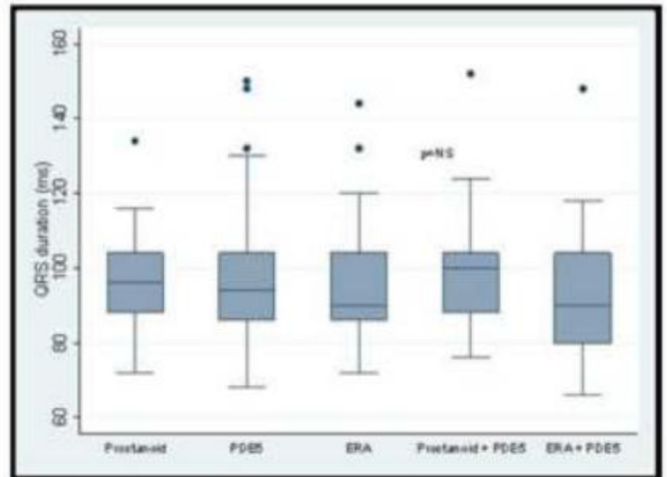
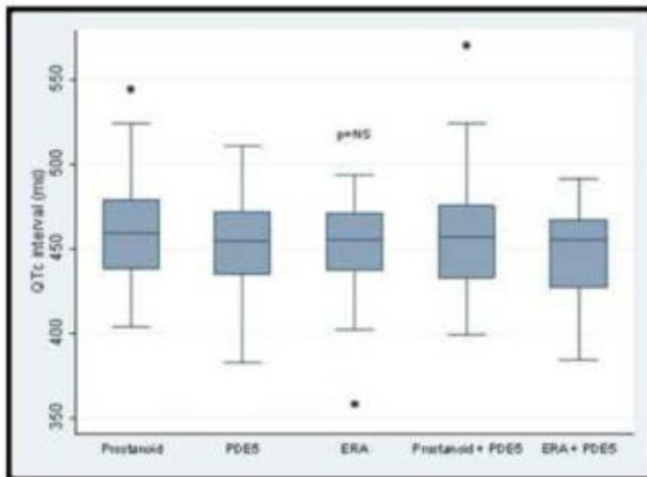
**A:** The QTc interval is significantly longer in PH compared to age and sex matched controls (454.8 ms vs. 429.8 ms,  $p < 0.001$ )

**B:** QRS duration is prolonged in PH compared to age and sex matched controls (96.5 ms vs. 84.4 ms,  $p < 0.001$ ).

# 2A-2B

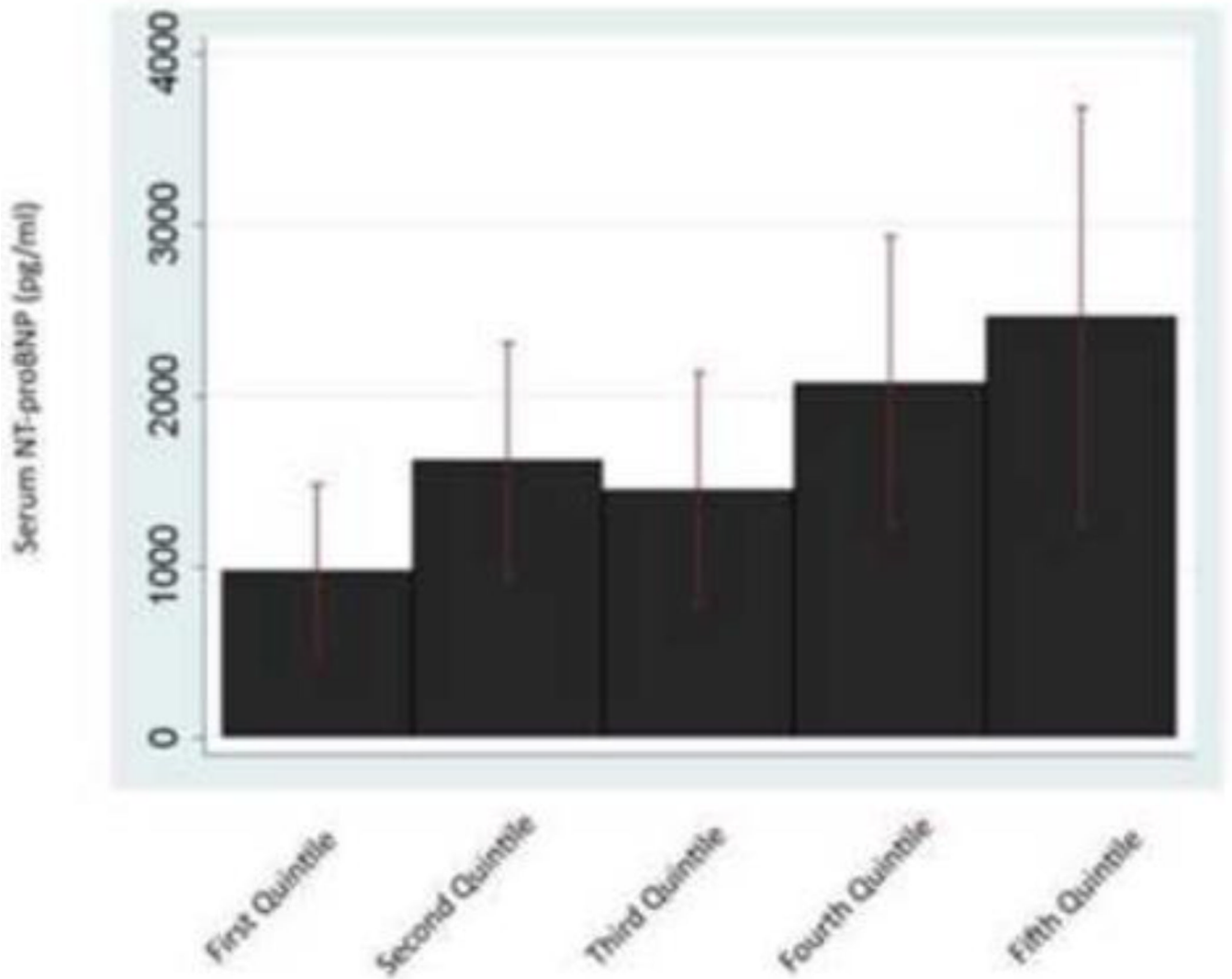


# 2C-D



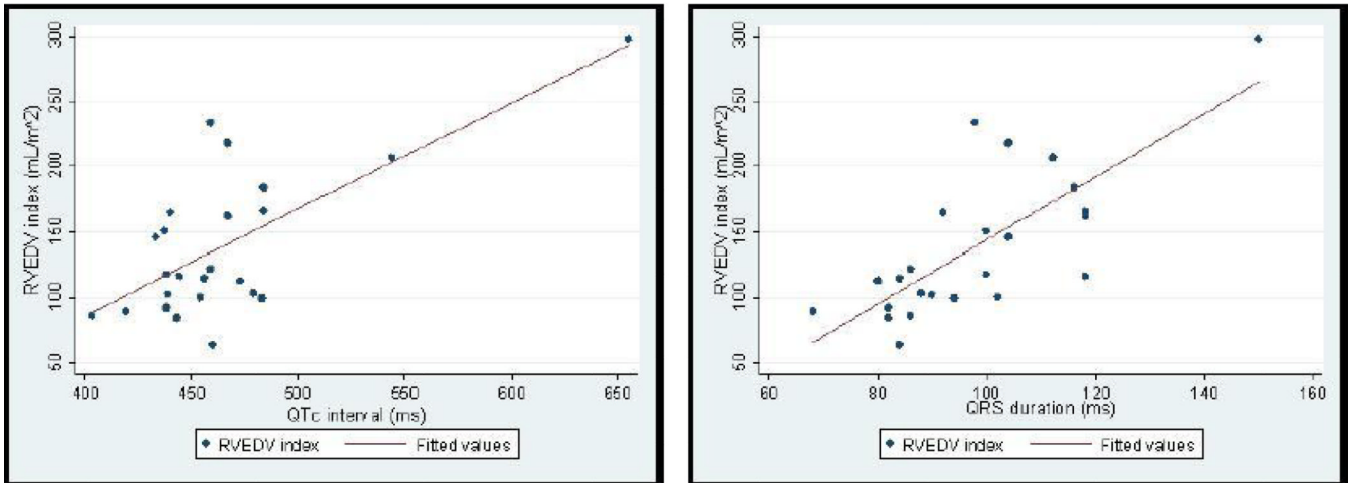
**Figure 2. No Difference in QTc and QRS According to WHO PH Diagnosis or PH-Specific Therapy**

There was no difference in **(A)** QTc interval or **(B)** QRS duration in subgroups based on WHO clinical classification of PH. Likewise, there was no difference in **(C)** QTc interval or **(D)** QRS duration in subgroups based on type of PAH-specific therapy receiving.



**Figure 3. Serum NT-proBNP levels stratified by quintiles of QTc interval in PH patients**  
Increasing serum NT-proBNP levels, reflecting severity of RV dysfunction, is associated with progressive increases in the QTc interval in PH patients.

## 4A-B



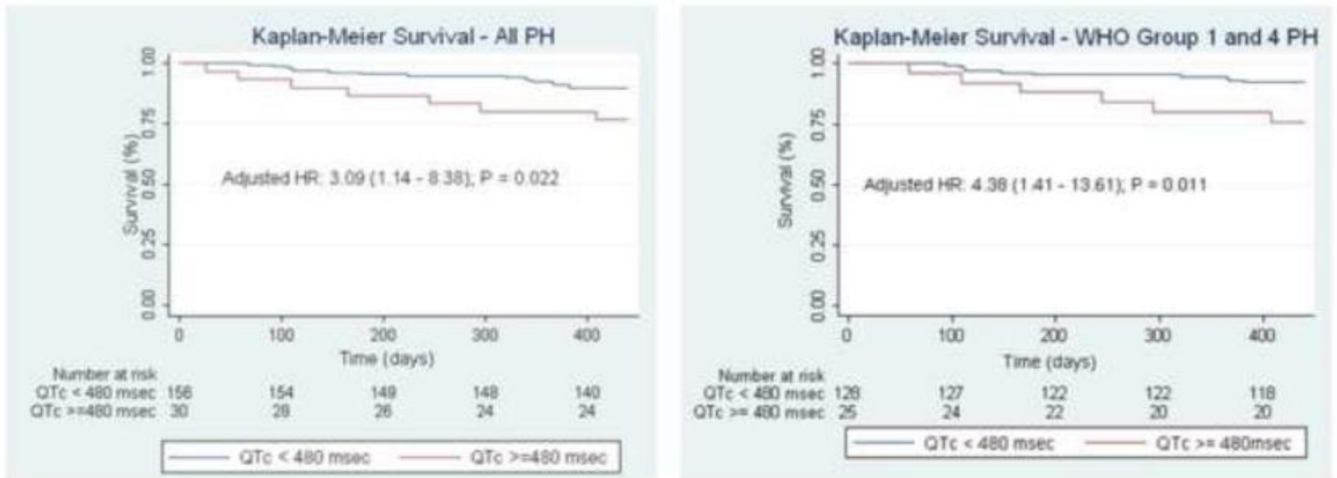
**Figure 4. Correlation between the QTc and QRS duration and RV Diastolic Dimension on CMR**

**A:** The QTc interval correlates strongly with indices of RV end diastolic dimension

**B:** QRS duration in PH correlates strongly with indices of RV end diastolic dimension.



## 5A-B



**Figure 5. Kaplan-Meier plots of QTc Interval and Risk of Death in PH**  
**A:** A QTc 480 ms Predicts Increased Mortality in the entire PH cohort  
**B:** A QTc 480 ms Predicts Increased Mortality in WHO Groups 1 and 4 PAH

**Table 1**

Baseline demographic and clinical characteristics of PH patients and controls

Variable	PH cohort (n=202)	Controls (n=100)	p-value
<b>Demographics</b>			
Age (yrs)	53.5±14	52.2±15	0.48
Female, n (%)	160 (79)	74 (74)	0.31
<b>ECG Findings</b>			
Heart rate	82.9±15	75.7±10	<0.001
QT interval (ms)	391.7±37	385.1±21	0.10
QTc interval (ms)	454.8±29	429.8±18	<0.001
QRS duration (ms)	96.5±16	84.4±8	<0.001
RVH	86 (42.6%)	0	N/A
Right axis deviation	129 (63.9%)	0	N/A
<b>WHO PH Etiology n (%)</b>			
Group 1	148 (73.3%)		
Group 2	16 (7.9%)		
Group 3	7 (3.5%)		
Group 4	15 (7.4%)		
Group 5	16 (7.9%)		
WHO Functional Class n (%)		N/A	
Functional Class I	4 (2%)		
Functional Class II	79 (39%)		
Functional Class III	104 (51%)		
Functional Class IV	15 (7%)		
<b>PAH Specific Therapy</b>			
Prostacyclin (IV/SQ)	42 (20.8%)		
PDE5 inhibitor	76 (37.6%)		
ERA	23 (11.4%)		
Prostacyclin + PDE5	35 (17.3%)		
PDE5 inhibitor + ERA	26 (12.9%)		
<b>Laboratory Tests</b>			
Serum Potassium mEq/L (n=185)	4.02±0.51	NR	
Serum NT-proBNP pg/mL (n=144)	1973.3±3379.5	NR	
<b>Invasive Hemodynamics (n=156)</b>			
Right atrial pressure, mm Hg	8.8±5.5		
Pulmonary artery systolic pressure, mm Hg	78.1±18.7		
Mean pulmonary artery pressure, mm Hg	47.4±11.4		
PVR, Wood units	9.2±5.2		
Pulmonary capillary wedge pressure, mm Hg	10.7±4.0		
Cardiac output, L/min	4.7±1.7		
Cardiac index, L/min/m <sup>2</sup>	2.6±0.9		

NR=not recorded; NA=not available; ECG=electrocardiogram; RVH=right ventricular hypertrophy; PH=pulmonary hypertension; PDE5=phosphodiesterase 5; ERA=endothelin receptor antagonist; NT-proBNP=n-terminal pro brain natriuretic peptide

**Table 2**

Clinical characteristics and indices of RV size and function among PH patients undergoing cardiac MRI

Variable	PH cohort (n=24)
<b>Demographics</b>	
Age, yrs	57±14
Female, n (%)	20 (83)
QTc Interval (ms)	464.9±49
QRS Duration (ms)	98.2±18
<b>PH diagnosis, n (%)</b>	
Group 1	17 (70.8)
Groups 2–5	7 (29.2)
<b>CMR variable</b>	
RVEDV (mL)	258.3±98
RVEDV index (mL/m <sup>2</sup> )	139.3±56
RVESV (mL)	180.6±93
RVESV index (mL/m <sup>2</sup> )	97.1±53
RV mass (g)	52.8±24
RV mass index (g/m <sup>2</sup> )	26.7±14
RVEF (%)	33.0±12

PH=pulmonary hypertension; CMR=cardiac magnetic resonance imaging; RVEDV=right ventricular end diastolic volume; RVESV=right ventricular end systolic volume; RVEF=right ventricular ejection fraction

**Table 3**

Correlation between QTc interval, QRS duration, and indices of RV size and function in PH

Variable	r-value	p-value
<b>QTc interval (ms)</b>		
RVEDV (mL)	0.67	<0.001
RVEDV index (mL/m <sup>2</sup> )	0.71	<0.001
RVESV (mL)	0.70	<0.001
RVESV index (mL/m <sup>2</sup> )	0.75	<0.001
RV mass (g)	0.51	<0.05
RV mass index (g/m <sup>2</sup> )	0.53	<0.01
RVEF (%)	-0.49	<0.05
<b>QRS duration (ms)</b>		
RVEDV (mL)	0.76	<0.001
RVEDV index (mL/m <sup>2</sup> )	0.76	<0.001
RVESV (mL)	0.74	<0.001
RVESV index (mL/m <sup>2</sup> )	0.75	<0.001
RV mass (g)	0.57	<0.01
RV mass index (g/m <sup>2</sup> )	0.59	<0.01
RVEF (%)	-0.46	<0.05

RVEDV=right ventricular end diastolic volume; RVESV=right ventricular end systolic volume; RVEF=right ventricular ejection fraction

**Table 4**

## Univariate and Multivariate Predictors of Mortality

Characteristics	Univariate Survival Analysis		Multivariate Survival Analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
QTc 480 ms	2.51 (1.61 – 14.23)	0.042	3.09 (1.14 – 8.38)	0.022
NT-proBNP (pg/mL)	1.0002 (1.0001 – 1.0003)	0.005		NS
Cardiac index (L/min/m <sup>2</sup> )	0.54 (0.29 – 0.99)	0.048	0.50 (0.26 – 0.94)	0.032
Right atrial pressure (mmHg)	0.97 (0.89 – 1.06)	0.530		NS
Pulmonary vascular resistance (Wood units)	1.06 (0.99 – 1.13)	0.072		NS