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Research Article

Qtc Prolongation in Pulmonary Hypertension Cases Due to Lung Diseases

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Abstract

Background: Pulmonary hypertension (PH) due to lung diseases is one of serious complications. Echocardiography is useful but not enough suitable for screening of large number of the lung disease patients from the point of view of time and cost benefit. Therefore, another simple examination may be better for screening test. Although it is possible that corrected QT (QTc) interval prolongation reflects pulmonary hypertension, the involvement in lung diseases is still remained uncertain. To elucidate the relationship between QTc prolongation and PH in lung diseases, we compared QTc interval with echocardiography-calculated pulmonary artery systolic pressure (PASP).

Methods: The subjects were 972cases from January 1st 2011 to December 31th 2013. 634 cases 42 lung disease cases including 85 chronic obstructive pulmonary disease (COPD) cases and 492 non - lung disease cases) were entered into the analysis, and 341 cases (non - tricuspid regurgitation cases and/or arrhythmia cases) were excluded from the analysis. Electrocardiogram findings and echocardiography-calculated PASP were retrospectively compared. To compare the results of PASP in COPD patients as the marker of PH, we analyzed CT scan-measured pulmonary artery to aorta ratio (PA:A ratio) in lung diseases cases.

Results: In COPD subjects, PA:A ratio was correlated with echocardiography - calculated PASP ($r = 0.4338$, $p < 0.0001$) and also correlated with QTc interval ($r = 0.2481$, $p < 0.0022$). QTc interval was associated with PASP in lung diseases ($r = 0.3809$, $p < 0.0001$) and all subjects ($r = 0.3799$, $p < 0.0001$). Positive correlation between QTc interval and PASP prolongation is not specific event in only lung diseases but also in non-lung diseases.

Conclusions: These findings suggest QTc interval prolongation might be potential screening tool for detecting PH due to COPD and other lung diseases.

Keywords: *Pulmonary hypertension; Electrocardiogram; QTc interval*

Abbreviations: Alectrocardiogram-ECG; Corrected QT-QTc; Heart rate-HR; Tricuspid regurgitation-TR; Pulmonary artery systolic pressure-PASP; Right atrial-RA; Right atrial pressure-RAP; Inferior venacava-IVC; Right ventricular-RV; Standard deviation-SD; Receiver operating characteristic-ROC; Area under the curve-AUC; Chronic obstructive lung disease-COPD.

Introduction

Pulmonary hypertension (PH) due to lung diseases is one of the major and serious complications affecting their prognosis [1,2] and prognosis of chronic obstructive pulmonary disease (COPD) and interstitial pneumonia are highly concerned with PH. Since measuring cardiac catheter using pulmonary artery pressure (PAP) is invasive and is not appropriate for screening of these elderly lung disease patients, usually echocardiography-calculated peak velocity of tricuspid regurgitation (TR) is recommended for elderly as the screening [2]. But even transthoracic echocardiography is not also enough suitable for screening of whole the lung disease patients from the point of

view of time and cost benefit. And it is difficult to obtain clear echocardiography view in some COPD patients because of lung hyperinflation [3].

So far, electrocardiogram (ECG) has been thought to be insufficient as a screening tool for detecting PH [1]. Generally, demonstrating right ventricular (RV) hypertrophy, right axis deviation, and right atrial (RA) dilatation on ECG suggest possibility of PH. But the absence of these findings cannot exclude the presence of PH. Recently corrected QT (QTc) prolongation is recognized in PH patients [4,5]. Increased RV pressure affects electrical myocardial repolarization and QTc interval prolongation reflects prolonged total duration of ventricular myocardial repolarization [4,5]. We reported that elderly pneumonia patients showing prolonged QTc interval had a higher mortality than those with normal QTc interval [6]. The prognosis of elderly pneumonia is not satisfactory [7], and some patients showed QTc prolongation in our previous study [6]. We suspected the involvement of PH as one cause of QTc prolongation in that study. Furthermore involvement of QTc prolongation in COPD patients was also previously reported [8,9]. Taken together, we hypothesized that QTc interval prolongation could be useful as screening tool for detecting PH due to lung diseases. The purpose of the study is analyzing the correlation between pulmonary artery peak systolic pressure from peak TR gradient in echocardiography and electrocardiogram (ECG) finding in lung diseases including COPD.

Material and Methods

Study design

The study was conducted in Akiota Hospital (Hiroshima, Japan) which shared primary care-and critical care-medicine. As the clinical practice, both ECG and echocardiography were examined for 972cases (462 male; 510 females; 71.98 ± 7.57 years old) from January 1st 2011 to December 31th 2013. 634 cases (294 males, 340 females; 73.09 ± 11.15 years old) of them were entered into the analysis, including 142 lung diseases cases (95 males; 47 females; 76.75 ± 8.44 years old from 59 to 91years old) and 492 non-lung diseases (199 males; 293 females; 74.33 ± 10.61 years old, from 31 to 93years old). Lung disease cases included 85-COPD, 4-bronchial asthma, 8-pulmonary tuberculosis sequelae, 6-acute pneumonia, 10-bronchiectasis, 7-nontuberculosis mycobacterium and 22-pulmonary fibrosis. And non-lung diseases cases included 129-hypertension, 23-diabetes mellitus, 45-cerebral vascular disease, 43-acute heart failure, 85-chronic heart failure, 18-cancer, 24-anemia, 18-chronic kidney disease, 41-bone fracture, 42-digestive disease and 24-orthopediac disease. No QTc and/or pulmonary artery systolic pressure (PASP) from peak TR gradient measurement were obtained in the 338 cases (168 males, 170 females), and they were excluded from the analysis. 178were without TR cases (86 males, 92 females; 68.63 ± 15.23 years old) and 160 arrhythmia cases (82 males; 78 females; 74.98 ± 7.57 years old) were no adequate RR interval available. Heart rate (HR), PR interval, QRS interval, QTc interval, and PASP from peak TR gradient in echocardiography were retrospectively compared. The research team carried followed all cases via recording clinical and laboratory data and they were retrospectively compared for analysis. The study was approved by the institutional review board of Shimane University, School of Medicine (approval number: 602) and the local ethics committee of Akiota Hospital, and all subjects gave written informed consent for participation in the study.

Recording QT intervals

According to our previous report [6], QT interval was recorded. In lead II, QT intervals were measured on arresting ECG tracing. The QT interval was measured from the starting point of the QRS-complex to the terminal point of the down slope of the T-wave. QTc was calculated according to Bazett's formula [10]; $QTc = QT/ (RR)^{1/2}$.

Echocardiography

Transthoracic echocardiography and Doppler examinations were applied with commercially available equipment (HDExE; Philips Co., Ltd., Tokyo, Japan). PH was defined as PASP more than 25 mm Hg [1].The simplified Bernoulli equation describes the relationship of TR velocity and the peak pressure gradient of TR [11] as following; $4 \times (TRvelocity)^2$. RV systolic pressure is calculated as the sum of the peak pressure gradient of TR plus the estimated right atrial pressure (RAP).RAP can be estimated based on the diameter and respiratory variation of the inferior venacava (IVC) size according to the previous report [12] as following. RAP was estimated to be 5 mm Hg when the IVC diameter was less than20 mm and the collapsibility greater than 50%; 10 mm Hg when IVC diameter was less than 20 mm and collapsibility less than 50%; 15 mm Hg when IVC diameter was greater than 20 mm and collapsibility greater than 50%; and 20 mm Hg

when IVC diameter was greater than 20 mm and collapsibility less than 50%. We considered that PASP was equal to the RV systolic pressure except cases that RV outflow was obstructed.

CT measured pulmonary artery to aorta ratio (PA:A ratio)

To compare the results of PASP in COPD patients, we analyzed CT scan-measured PA:A ratio in lung diseases subjects (Light speed ultra; GE Healthcare Co., Ltd., Tokyo, Japan). CT measured-PA:A ratio is reported to be related with PA pressure in COPD patients [1]. According to the previous report [13], the PA diameter was measured at the level of PA bifurcation, and diameter of aorta was averaged from two perpendicular measurements taken from the same CT image.

Statistical analysis

Statistical analysis was performed using computer software (Excel Statistics 2012, SSRI Co., Ltd., Tokyo, Japan). All data was expressed as means ± standard deviation (SD) of the mean. Pearson correlation coefficient was used to analyze the relationship between the groups. One-way analysis of variance followed by Fisher's least significant difference test was used to detect differences among groups and a probability value of less than 0.05 was considered as statistically significant.

Results and Discussion

As the beginning, PA:A ratio as the indicator of PH was compared with PASP or ECG findings in COPD patients. PA:A ratio was measured in 136 lung disease patients (85 COPD patients and 51 non-COPD patients) from 142 of lung disease patients.6 patients had no data about CT scan. COPD subjects (65 males; 20 females; 77.48 ± 7.99 years old) (GOLD staging [4] was as following; stage I-24 cases, stage II-25 cases, stage III-28cases, stage IV-8cases) were compared to non-COPD subjects (24 males; 27 females; 76.45± 8.01 years old) (Table 1). PA:A ratio was correlated with PR interval, QTc interval, HR, and PASP in COPD patients. And PA:A ratio was also correlated with QTc interval and PASP in non-COPD patients.

	PA : A ratio		
	Lung Diseases		Total
	COPD	Non COPD	
	(n = 85)	(n = 51)	(n = 136)
PR interval (seconds)	0.2198	-0.2235	0.1263
	P = 0.0046	P = 0.1149	P = 0.1429
QRS interval (seconds)	0.0021	-0.1765	-0.0078
	P = 0.8444	P = 0.2155	P = 0.3637
QTc interval (seconds)	0.2481	0.2831	0.2775
	P = 0.0022	P = 0.0178	P = 0.0011
Heart rate (beat/minute)	0.2889	0.1695	0.2573
	P = 0.0073	P = 0.2344	P = 0.0025
PASP (mmHg)	0.4338	0.3738	0.3868
	P < 0.0001	P = 0.0075	P < 0.0001

Table 1: *Correlation between ECG findings and PA:A (ratio) of lung diseases. Pearson correlation coefficient was used to analyze the relationship between the groups. PASP: pulmonary artery systolic pressure. COPD: chronic obstructive lung disease. PA:A ratio: CT scan-measured pulmonary artery to aorta ratio.*

To analyze QTc interval in whole subjects in the study, then we compared ECG findings in patients with or without of lung diseases (Table 2). There was no significant difference about HR, PR interval, QRS interval, QTc interval, PASP, age and gender among the three groups.

	Lung diseases		Total	p value
	With (n = 142)	Without (n = 492)	(n = 634)	
PR interval (seconds)	0.182 ± 0.160	0.170 ± 0.026	0.155 ± 0.037	P = 0.4653
QRS interval (seconds)	0.103 ± 0.016	0.104 ± 0.051	0.121 ± 0.112	P = 0.9962
QTc interval (seconds)	0.432 ± 0.033	0.427 ± 0.030	0.428 ± 0.031	P = 0.2819
Heart rate (Beat/Min)	72.06 ± 13.32	68.82 ± 13.93	69.55 ± 13.85	P = 0.0587
PASP (mmHg)	23.73 ± 9.69	24.22 ± 9.99	24.11 ± 9.92	P = 0.9038
Age (years old)	76.75 ± 8.44	74.33 ± 10.61	74.87 ± 10.21	P = 0.0542
Male: female	95 : 47	199 : 293	294 : 340	P < 0.0001

Table 2: *Characteristics of subjects. All data was expressed as mean ± standard deviation. PASP: pulmonary artery systolic pressure.*

Next we compared the correlation between ECG findings and PASP in cases with or without of lung diseases (Table 3). PR interval and QRS interval did not showed significant correlation with PASP. QTc interval showed significant correlation with PASP ($p < 0.0001$) and r-value was 0.3809 in the lung diseases, 0.3827 in non-lung diseases, and 0.3799 in all subjects. HR in non-lung diseases and total subjects showed significant correlation with PASP ($p<0.0001$).But r-value was not enough high (0.1388 and 0.1398).

	PASP (mmHg)		
	Lung diseases		Total
	with	without	
	(n = 142)	(n = 492)	(n = 634)
PR interval (seconds)	0.0133	-0.0322	-0.0038
	P = 0.8756	P = 0.4619	P = 0.9242
QRS interval (seconds)	0.0791	0.0041	0.0278
	P = 0.3496	P = 0.9283	P = 0.4835
QTc interval (seconds)	0.3809	0.3827	0.3799
	P < 0.0001	P < 0.0001	P < 0.0001
Heart rate(beat/minute)	0.1522	0.1388	0.1398
	P = 0.0651	P = 0.0019	P = 0.0004

Table 3: *Correlation between ECG findings and pulmonary artery peak systolic pressure of each group. Pearson correlation coefficient was used to analyze the relationship between the groups. PASP: pulmonary artery systolic pressure.*

Then we figured receiver operating characteristic (ROC) curve, and sensitivity and specificity between PASP and QTc interval were evaluated. In figure 1, we showed ROC curve, and the cut-off value (PASP was more than 40 mmHg) was calculated. In lung diseases, the cut-off value was 0.440 seconds with QTc interval. Area under the curve (AUC) was 0.7369 (95% confidence interval (95% CI): 0.7039-0.7639) and the moderate accuracy was confirmed. The sensitivity was 70.8 % and the specificity was 72.2 % in lung diseases. AUC was 0.7481 (95% CI: 0.7211-0.7861) in non-lung diseases (sensitivity 68.4 %, specificity 83.3 %) and the cut off value was 0.443 seconds. AUC was 0.7477 (95% CI: 0.7197-0.7827) in total subjects (sensitivity 70.0 %, specificity 78.7 %) and the cut off value was 0.442 seconds.

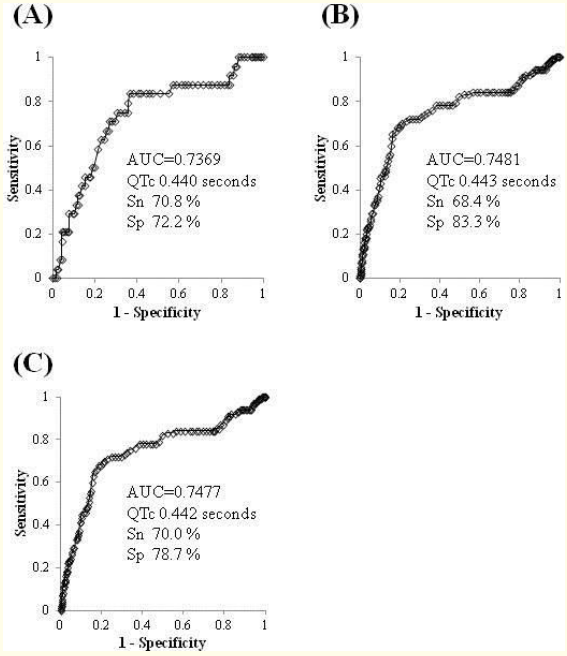

Figure 1: *Receiver operating characteristic (ROC) curve and pulmonary artery systolic pressure (PASP) among the groups: ROC curve was figured and the cut-off value (PASP was more than 40 mmHg) was calculated. Panel (A): lung diseases; Panel (B): non-lung diseases; Panel (C): total subjects.*

In the study, we showed the significant positive correlation between QTc interval and echocardiogram calculated PASP in lung diseases cases. When QTc interval was more than 0.440 seconds in lung disease patients, it might be possible that PASP was more than 40 mmHg. As far as we know, this is the first report analyzing about QTc interval and PH due to lung diseases. So far, previous reports [4,5] did not evaluated usefulness as screening test. Furthermore, there were no significant differences among three groups (lung diseases, non-lung diseases, and total cases) in the study. That means QTc prolongation is not specific event in only lung diseases but also in non-lung diseases.

Mechanism of QTc prolongation in PH is thought that QTc interval prolongation reflects prolonged total duration of ventricular myocardial repolarization. And increased RV pressure affects electrical myocardial Repolarization [15]. In animal models of RV hypertrophy, there is prolongation of the RV monophasic action potential duration and the QTc interval on the surface ECG [15].

Involvement of QTc prolongation in COPD was already reported in some papers [8,9,16-18]. They reported the association between hypoxia and QTc interval in COPD. But it is not uncommon to complicate hypoxia and PH in severe COPD. In this meaning, our data in the study did not contradict with these previous reports.

Mean age in the study was more than 70 years old, and our result did not show the data about younger age. The reason was simple that analysis was allowed to perform in only subjects complicated with TR. The whole entry subjects at the beginning included many younger subjects, but TR was uncommon in younger subjects. So far, there are no reports that elder people showed QTc prolongation by aging. Generally, major part of patients who having PH due to lung diseases is elderly and such like PH cases in younger is very rare. Therefore, there was no obvious disadvantage as the screening tool for PH due to lung diseases.

The advantage of measuring QTc interval as the screening of PH is that the cost is not expensive and easy to repeat examination even in the elderly. Clinical physicians could suspect the existence of PH in cases with QTc prolongation more than 0.440 seconds which are difficult to explain by serum calcium concentration disorder, medication, and the other reasons.

One limitation of doppler echocardiogram calculated PASP is that under or over estimations sometimes occurs because of difficulty of obtaining clear views in COPD patients [19, 20]. Since we had no data about the cardiac catheter measuring PAP of COPD cases in the study and could not rule out of the possibility of such bias in the study, we compared the PA:A ratio with echocardiogram calculated PASP and confirmed the correlation between them. Our sample size was enough large and the study included not only lung diseases subjects but also enough numbers of non-lung diseases subjects, and the statistical analysis was confirmed. Then we showed no obvious difference between lung diseases and non-lung diseases, therefore the results of our study might mimic such under- or over-estimation.

QTc prolongation is influenced by specific medications, including statin, clarithromycin and azithromycin [21], therefore it is necessary to consider background of each patient to realize the reason of prolongation of QTc interval.

Another limitation is that certain diseases complicate QTc prolongation. Recently QTc prolongation is reported in diabetes mellitus patients [22, 23]. Although the electrical and physiological mechanisms of QTc interval prolongation in diabetes mellitus are still uncertain, one possibility is that increased autonomic nervous system activity can be responsible for repolarization changes [23]. Acute and chronic cerebral vascular disease is also known as a cause of QTc prolongation [24]. Heart diseases such as ischemic heart disease and heart failure are associated with a higher rate of mortality and QTc interval prolongation [25-27].

Conclusions

In summary, QTc interval prolongation is associated with increased echocardiography-calculated PASP in both lung diseases and non-lung diseases. And QTc interval prolongation is also associated with PA:A ratio in COPD subjects. Although there are some limitations for interpretation, measuring QTc interval might utilize for simple screening tool of PH in elderly lung disease patients like COPD.

Author's contributions: YT, TI, AS and GT helped resolve statistical issues; YT, AT and GT helped to obtain the clinical data from all subjects; YT and TI conceived the study and participated in its design and contributed in critiquing the manuscript. All authors have read and approved the final manuscript.

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