ISSN: 2573-9565

Case Report

Journal of Clinical Review & Case Reports

Clinical Significance of Tachycardia in Cystic Fibrosis Patients: A Case Report

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Submitted: 16 Jan 2018; **Accepted**: 23 Jan 2018; **Published**: 31 Jan 2018

Abstract

Background: *Post-bronchodilator evaluation of pulmonary function and collection of expectorated sputum samples are commonly used tests in cystic fibrosis (CF) clinical trials. β2 adrenergic receptor agonists, such as salbutamol, are used for this purpose.Supraventricular tachycardia is a known dose-related side effect of inhaled salbutamol. Under normal breathing conditions, CF patients have been found to be tachycardiac compared to healthy subjects. In addition, mutation in the cardiac CF transmembrane conductance regulatorgene may result in (subclinical) myocardial dysfunction and a deficiency in ischaemic preconditioning, resulting in an increased risk for ischemic heart disease in the CF patient. Nevertheless, the impact of β2agonists on the CF- associated tachycardia is often an ignored safety parameter in CF clinical trials.*

Case presentation*: A 21 year old CF female patient received an inhalation dose of 400ug salbutamol, in the context of a clinical trial, to perform post-bronchodilator pulmonary function tests and collect spontaneously expectorated sputum. The patient's cardiac electrical activities were monitored before and after salbutamol inhalation. The pre-bronchodilator (baseline) recording demonstrated large fluctuation in heart rate coupled with short episodes of sinus tachycardia. Post salbutamol administration, the tachycardia increased in rate and was associated with dynamic ST-T segment changes including flattening of the T wave and ST segment depression in at least 2 adjacent limb leads, ECG features suggestive of myocardial ischemia. Approximately 4 hours post salbutamol administration, heart rate and ST- T segment abnormalities returned to baseline morphology.*

Conclusion: *CF patients might have tachycardia as part of their disease natural history. The presence of continuous or fluctuating tachycardia should be verified in this group of patients. Administration of inhalation β2 agonists to tachycardiac CF patients should be considered with caution. This may entail individualized dose adjustment and telemetry monitoring of patients' cardiac electrical activity. This helps early detection and facilitates timely medical management of any emerged cardiovascular adverse effects such as myocardial ischemia in this medically fragile group of patients, particularly those with subclinical myocardial pathology.*

Introduction

Cystic fibrosis (CF) is a genetic multisystem disease caused by mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. *CFTR* gene encodes for a cell membrane protein called CFTR protein that functions as a chloride (Cl) channel and is expressed in the lungs, digestive system, hepatobiliary tract, pancreatic ducts, sweat glands and other organs including the heart [1-3]. Deletion of the phenylalanine residue at position 508 of the *CFTR* amino acid sequence (F508del-CFTR or CFTRΔF508) is the commonest mutation found in up to 90% of CF patients [4]. *CFTR* gene mutation leads to generation of misprocessed protein and therefore dysfunctional Cl channels. In this context, dysfunction in airway CFTR protein has received most of attention since pulmonary disease is a key cause of morbidity and mortality in the CF population. In the heart, CFTR channels can function as both inward and outward rectifying Cl channels. They become activated by stimulation of cAMP-protein kinase A (PKA), protein kinase C (PKC) or extracellular ATP [5].

Studies in experimental animals demonstrated an important role for CFTRCl channels in cardiac action potential and arrhythmias and in protection of the heart against ischemia [5-9]. A relationship between CFTR activation and action potential duration (APD) and therefore Q-T interval has been found. Disturbed CFTR Cl channels may prolong APD and consequently cause early after depolarizations resulting in repolarization disturbances and generation of serious tachyarrhythmia [5,6]. CFTR has also been reported to be involved in the cardioprotective effect of ischemic preconditioning (IPC)

and postconditioning (POC). IPC and POC are normal adaptive responses triggered by exposure to brief episodes of ischemia, proposed to protect the heart against ischemic myocardial injury and infarction upon exposure to subsequent prolonged ischemia. CFTR absence or dysfunction has been reported to negatively impact both IPC and POC mediated cardioprotection and therefore increase the risk of ischemic myocardial injury [6-9]. Regarding the functional state of the myocardium, Sellers et.al has studied left ventricular (LV) and aortic function in CFTRΔF508 mouse model using 2D transthoracic echocardiography and LV catheterization [10]. Aortic stiffness and altered diastolic flow, LV hypertrophy and dysfunction, and decreased cardiac reserve were found in CFTRΔF508 mice. Exposure of CFTRΔF508 mice hearts to β2 agonists, , dobutamine, increased cardiac contraction and relaxation. However, LV systolic and diastolic pressures were significantly diminished compared to baseline indicating decreased cardiac reserve [10].

In humans, a relationship between dysfunctional CFTR and cardiomyopathy, myocardial dysfunction and heart failure has been found. In this regard, the human failing heart demonstrated a 52% decrease in the expression of the mature CFTR channels compared to non-failing controls [6,7]. In clinical settings, Ionescu, et al. found subclinical right ventricular (RV) hypertrophy and dysfunction in young adults with cystic fibrosis and clinically stable disease. Both systolic contractility and diastolic filling were impaired [11]. The abnormalities were found to correlate with the lung disease severity. One year later, a similar finding, subclinical RV dysfunction, has been reported by Baño-Rodrigo et al [12]. Nevertheless, in the latter study, RV abnormalities did not correlate with clinical scores, pulmonary function tests, genotype, chronic bacterial colonization or pancreatic insufficiency.

LV dysfunction has also been found in CF patients during both early and late stages of pulmonary disease. On one hand, decreased left and right ventricular ejection fractions without other associated clinical signs or symptoms,in response to exercise testing has been found in 29% of CF patients with a wide range of clinical involvement, and in 51% of CF patients with severe lung disease [13,14]. On the other hand, Sellers et al used strain and strain rate echocardiographic imaging to assess left ventricular function in CF patients and found subclinical LV systolic dysfunction in 50% of male and 100% of female CF patients [15]. These findings were not detected by conventional echocardiography and were independent of lung function tests. Based on their results, the authors supported the assumption of a primary cardiomyopathy and ventricular dysfunction in CF patients.

In addition to the myocardial dysfunction reported in CF patients there are 2 other clinically relevant findings reported,in CF patients, by Szollosi et.al, and Florêncio et.al namely, mild tachycardia and predominance of sympathetic activity (compared to healthy subjects) [16,17]. These findings were present under normal resting spontaneous breathing conditions.

β2 receptors agonists (β2A) are commonly prescribed to CF patients to treat associated airway obstruction and hyper-responsiveness [18]. In the CF clinical trial settings, short-acting β2A might be used at screening and during the course of the trial to evaluate and monitor pulmonary function and to collect expectorated sputum samples. Significant increases in heart rate and cardiac output and dose-related supraventricular tachycardia are known pharmacological effects of inhaled short-acting β2A, and therefore increase cardiac oxygen (O2) demands. In this regard, a relationship between inhaled β2A and increased risk of myocardial ischemia and infarction through mismatch between cardiac O2 requirements and supply has also been reported [19-23]. Nevertheless, the impact of B2 agonists on potentially present tachycardia in CF patients is often an ignored safety parameter in CF clinical trials. Here we demonstrate a case of post- β2A clinically significant tachycardia associated with ECG features suggestive of myocardial ischemia in a CF patient.

Case report

A 21 year old non-smoking CF female patient (BMI18kg/m^2) has been included in a clinical trial evaluating a new medication for the treatment of CF. Aside from CF; the patient has no known past or current history for other organ diseases such as diabetes mellitus, cardiovascular or thyroid diseases; smoking; or drug or alcohol abuse. Serial spirometry obtained over the preceding year showed FEV1% predicted range between 75% and 85%, indicating stable non-progressive nature of the patient's pulmonary disease [24]. Screening physical examination including vital signs and laboratory investigations including serum CRP, thyroid function tests and, complete blood picture were all within normal limits. Screening ECG (Figure 1) showed normal sinus rhythm with regular heart rate (HR) of 78 bpm and rSr' QRS configuration in lead V1 (normal variant). Medication used by the patient included, Azithromycin 500 mg 3times a week, Symbicort 100/6ugq.i.d (budesonide 100 ug and formoterol fumarate 6 ug), Ventolin 100 ugp.r.n., Fexofenadine 120 mg q.d., Dornase alpha 2.5 mg q.d., Creon 300 mg before meals (for exocrine pancreatic insufficiency) and vitamins A and E.

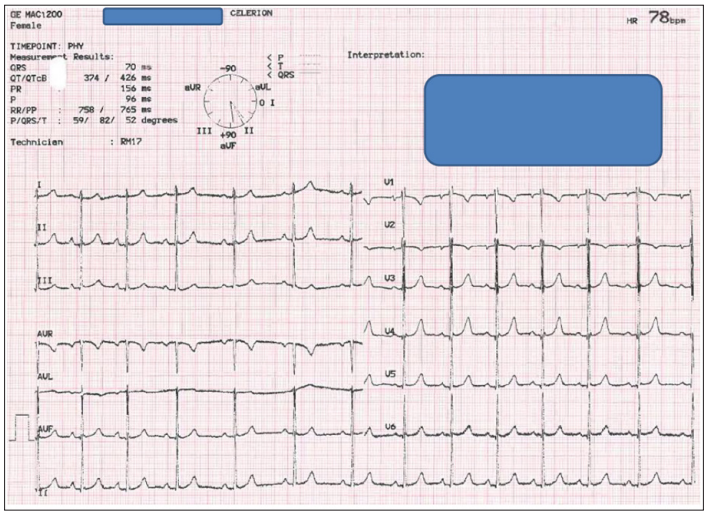


Figure 1: Electrocardiogram recordings (normal standardization, 10 mm = 1 mV) obtained at screening.This tracing depicts normal sinus rhythm and heart rate variability with respiration (sinus arrhythmia).

During an outpatient clinic visit, the patient received an inhalational dose of 400ug salbutamol in order to perform post bronchodilator pulmonary function tests and collect spontaneously expectorated sputum. The patient did not take any short-acting β2A within 12 hours prior to her visit. Before salbutamol administration, resting blood pressure (BP), pulse rate (PR) and blood oxygen saturation (SpO2 (%)) values were measured by an automated vital signs monitorin the sitting position,under normal tidal breathing condition andafter the patient had rested quietly for 5 minutes (baseline, BL, values). The values obtained were, 115/ 66 mmHg and 98% respectively for BP and SpO2. In terms of resting PR (RPR),

asymptomatic unprovoked rapidly fluctuating values with a nadir of 80 bpm and a zenith of 113 bpm over a very short period of time (during automated assessment of BP) had been observed. Given this, and in order to ensure patient's safety the patient remained in the same sitting position and breathing condition, and the following cardiovascular clinical safety parameters were then monitored: patient's cardiac electrical activity using telemetry (before and after salbutamol administration) and BP and SpO2 (assessed every 30 minutes for a period of 4.5 hours after salbutamol administration). Heart rate was obtained from continuous telemetry recording. Figure 2 demonstrates BP and SpO2 obtained values.

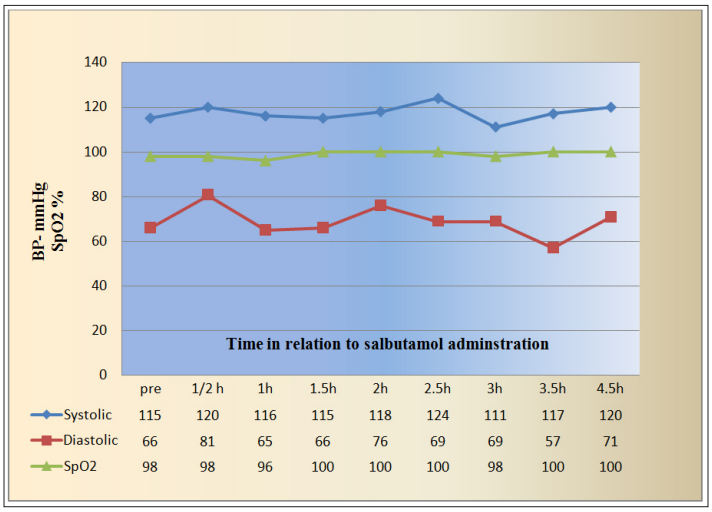


Figure 2: Pre- & post- salbutamol Bp & SpO2 profiles

The pre-bronchodilator (Pre-BD) telemetry recording showed episodes of asymptomatic sinus tachycardia with fluctuating resting heart rate between 79 to 117 bpm over a period of 5 minutes, without other clinically relevant ECG changes. Approximately 1 hour after salbutamol administration, the telemetric recordings showed changes in heart rate (HR) and ST segment- T wave morphology, compared to BL.The main changes were further increase in resting HRwith fluctuation between 97 to 141 bpm, associated with intermittent episodes of ECG findings suggestive of myocardial ischemia. The latter consisted of dynamic flattening of T waves coupled with upsloping ST segment depression in leads II, III and a VF. In this regard, T wave amplitude in the recording obtained before (BL) and1hour, 1.75 hours and 3.75 hoursafter β2A administration were respectively, 3mm, 1.5-2 mm and 2 mm (in leads II, III and a VF); ≤ 0.5 mm in all leads; flat imperceptible in all leads; and return to BL values in all leads. In terms of the ST segment depression, near horizontal or slow upsloping (<1 mV/ second) ST- segment depression in 3 contiguous limb leads, II, III and a VF has been observed (figures 3-6).

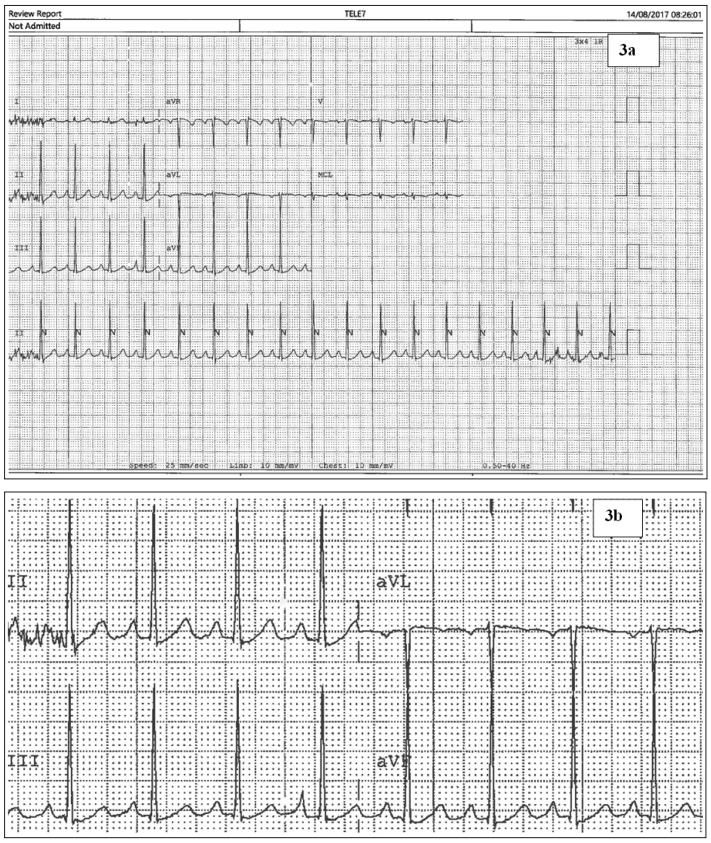
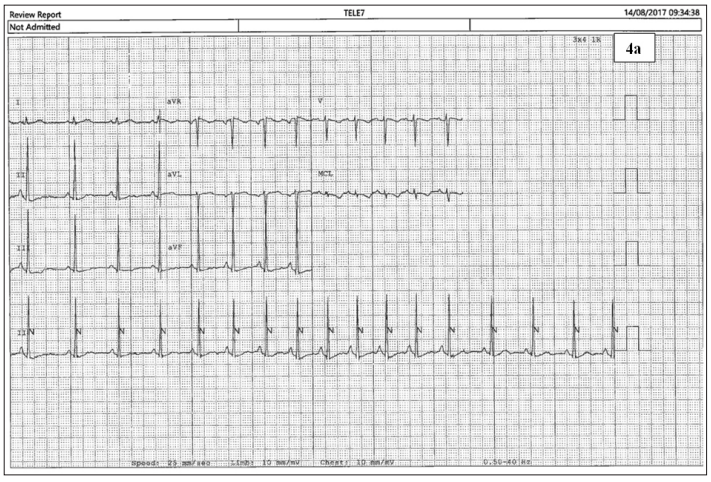


Figure 3, 3a: (100%, normal, magnification) and 3b (300% magnification). Telemetry recording obtained at normal standardization (10 mm = 1 mV) 4 minutes before salbutamol inhalation. The recording depicts mild sinus tachycardia (111 bpm) and small variation in the amplitude of QRS complexes. T wave amplitude in lead II = 0.3 mV, lead III= 0.15- 0.20 mV and lead aVF= 0.20 mV.



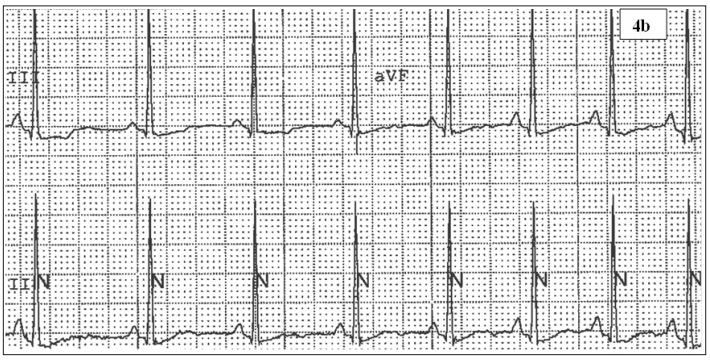
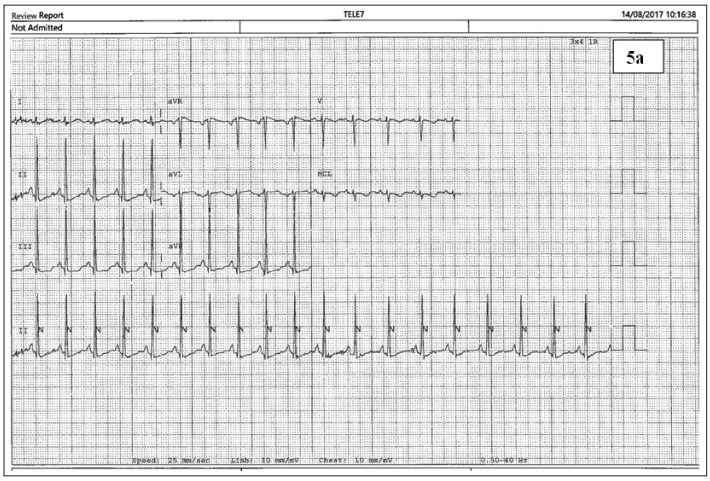


Figure 4, 4a: (100%, normal, magnification) and 4b (300% magnification). Telemetry recording obtained at normal standardization (10 mm = 1 mV) approximately 1 hourafter salbutamol inhalation. The recording depicts mild sinus tachycardia (102 bpm), small variation in the amplitude of QRS complexes with T wave flattening in leads, II, III and aVF (T wave amplitude ≤0.05 mV).



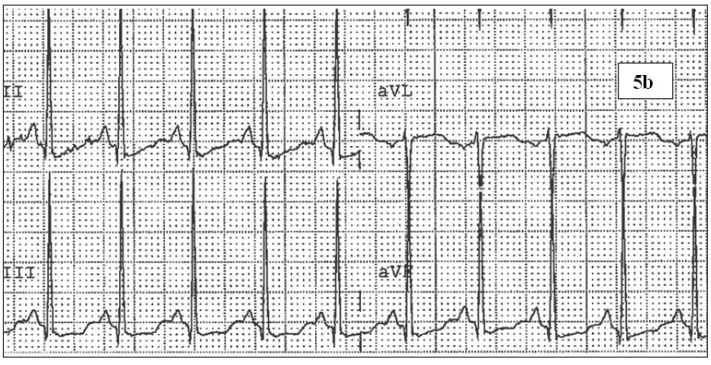
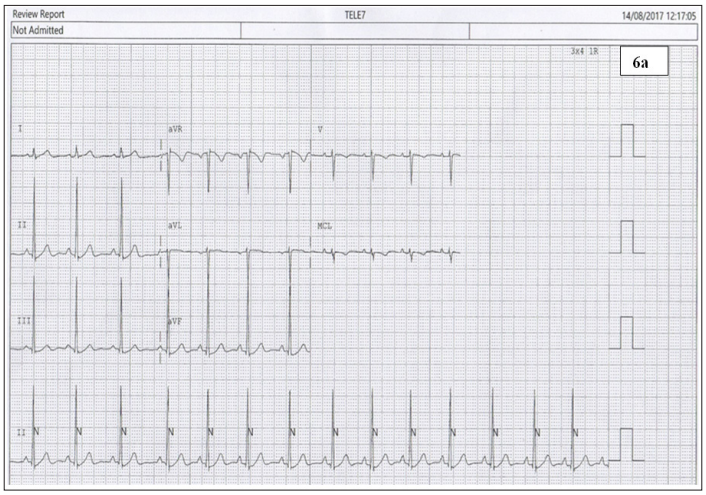


Figure 5, 5a: (100%, normal, magnification) and 5b (300% magnification). Telemetry recording obtained at normal standardization (10 mm = 1 mV) approximately 1.75 hour after salbutamol inhalation. The recording depicts mild sinus tachycardia (119 bpm); T wave flattening in II, III and aVF;and ≥1mm depression of the ST segment in 2 contagious limb leads (III and aVF) at 60-80 milliseconds after the J point with slow upsloping reaching < 1mV at 1 second (leadaVF and II) and horizontal ST- segment depression in III.There is also slight ST elevation in aVL (opposite of lead III) compared to BL trace (see fig. 3).



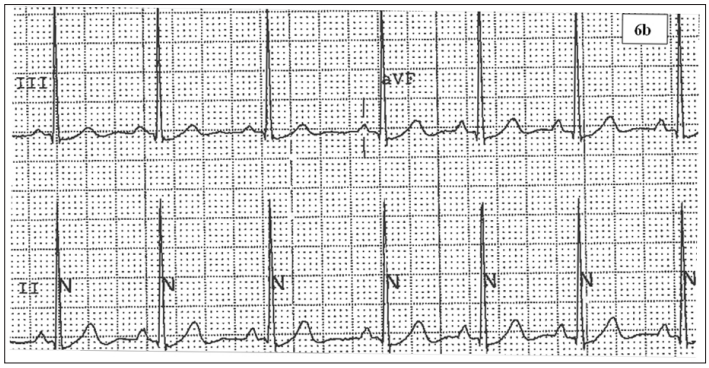


Figure 6, 6a: (100%, normal, magnification) and 6b (300% magnification). Telemetry recording obtained at normal standardization (10 mm = 1 mV) approximately 3.75 hour after salbutamol inhalation. The recording shows return of ST segment- T wave changes to BL morphology in leads II, III and aVF.

The duration of these episodes varied from 16 seconds to 310 seconds. It is noteworthy that the telemetry recordings obtained both before and after salbutamol administration showed variation in the QRS amplitude in different leads. There were no clinically relevant changes either in blood pressure or SpO2 levels. The ECG changes were not associated with anginal pain or any other subjective or objective β2A systemic manifestation such as palpitation and/ or tremor. The patient was therefore queried about her pain sensation and in this regard, she indicated a high threshold for painful stimuli in general including dental care. Approximately 3.75 hours post salbutamol the telemetry changes returned to BL, and the patient was discharged after ensuring her safety. In subsequent visits, a similar dose of salbutamol (400ug) had been re-administered under continuous cardiac monitoring. The obtained telemetry recordings confirmed the relationship between β2A inhalation and the findings (figures 7- 9).

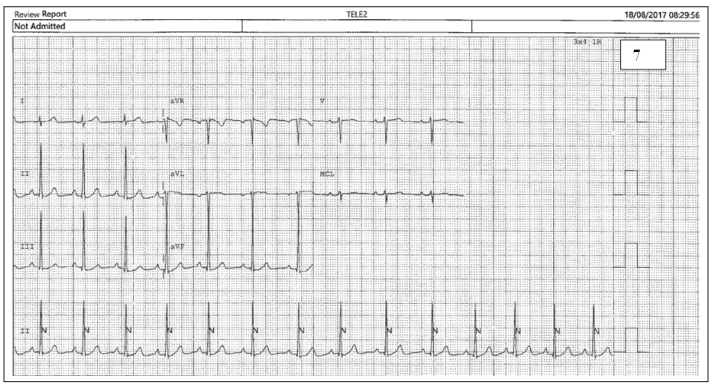
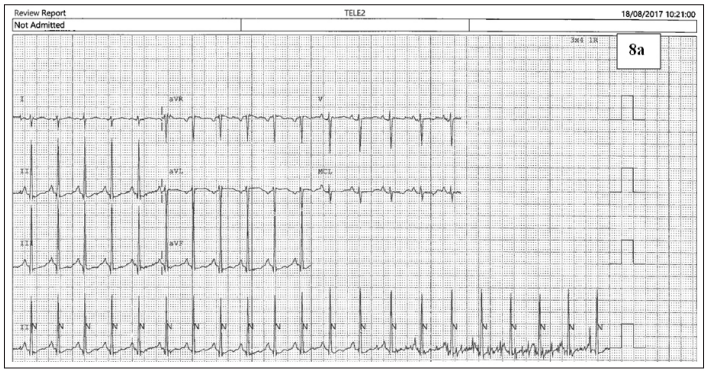


Figure 7: Salbutamol re-challenge telemetry recording obtained before salbutamol inhalation (normal standardization, 10 mm = 1 mV). The recording shows normal PQRST complexes with heart rate of 84 / minute.



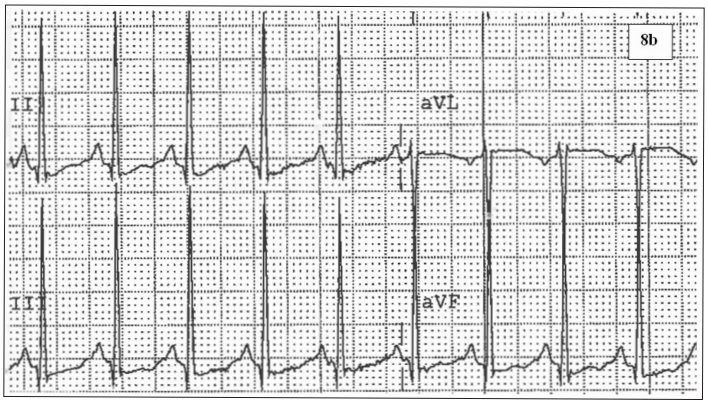
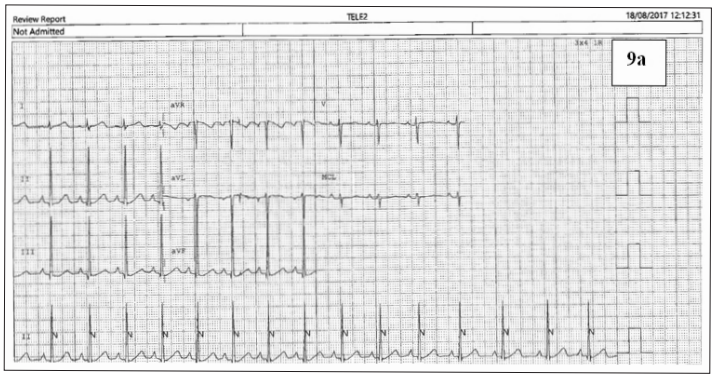


Figure 8, 8a: (100%, normal, magnification) and 8b (300% magnification).Salbutamol re-challenge; telemetry recording obtained at normal standardization, 10 mm = 1 mV, approximately 1.85 hours after salbutamol inhalation The recording shows sinus tachycardia (126 bpm), QRS amplitude variation and T wave flattening and depression of the ST segment in the 3 adjacent limb leads (II, III and aVF) with slow upsloping reaching < 1mV at 1 second.



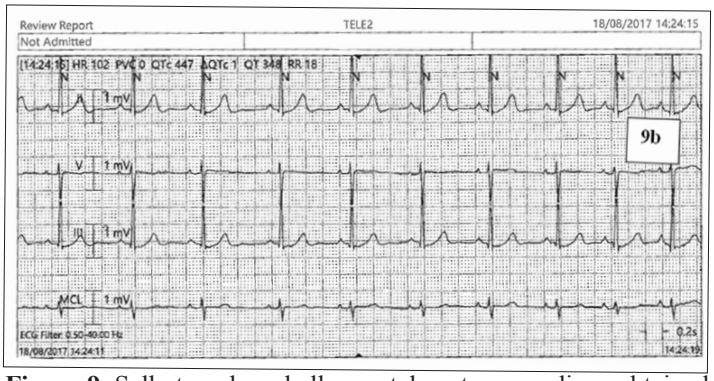


Figure 9: Salbutamol re-challenge; telemetry recordings obtained at normal standardization (10 mm = 1 mV) approximately 3.75 hours (9a, leads II, III and aVF) and 6 hours (9b, leads II and III) after salbutamol inhalation.The recordings show return of ST- T segment to BL morphology.

Discussion

This report describes 2 important telemetry findings observed in a young adult CF female patientwho received an inhalation dose of 400ug salbutamol in the context of a clinical trial. First, resting asymptomatic increase in heart rate with fluctuation between 79 and 117 bpm (fluctuation span of 38 bpm), coupled with episodes of sinus tachycardia, occurring over a period of few minutes before salbutamol administration. Second, an unprovoked post- salbutamol increase in basal HR associated with dynamic ST- T wave changes suggestive of myocardial ischemia. In this regard, the subject wasnot exposed to any physical or emotional stress, neither before nor after salbutamol administration. Increased HR in CF patients has been reported in earlier studies. Szollosi et.al observed a higher mean heart rate in cystic fibrosis patients age: 29.8 ± 9.1 years (mean± SD) compared to age matched control, 75.4 ± 11.2vs 60.2 ±9.0 bpm, a value similar to the recorded pre-salbutamol BL value in this patient (79 bpm). In this report, pre-salbutamol HR fluctuation span as large as 38 bpm has been observed [16]. The magnitude of increase in heart rate (48% above BL) and time period (over 5 minutes) is disproportionate to the amplitude of the nyctohemeral variations reported for heart rate in healthy subjects, 19.9% [25].

Mechanistically, tachycardia in CF patients might be caused by β2A administration, hypoxaemia or an inflammatory response [16]. The former is very unlikely a cause in this patient. This is reasoned by the fact that the patient had not used short-acting β2Aagonists 12 hours prior to her visit. In addition, the daily received formoterol fumarates dose (6ug q.i.d) is far below the dose that has been reported

not to induce tachycardia in human (up to 160ug) (26). Normal tidal breathing and SpO2 level as well as the normal values of laboratory test results (including blood picture and serum CRP) and body temperature exclude hypoxia or inflammation as a cause of this finding. At this stage, the exact underlying mechanism of this large fluctuation in HR and tachycardia episodes in this patient is unclear. A possible cause, however, might be disturbance/ disruption of the normal cardiac action potential, impulse formation and electrical conduction which in turn may predispose to cardiac morbidities including arrhythmias [27]. Interestingly, CFTR Cl channels in the heart have been demonstrated to be bidirectional Cl channels and have the unique ability to generate both inward and outward currents and cause both depolarization and repolarization during the action potential [5,6]. Accordingly, change in CFTR Cl channels activity has been suggested to significantly affect cardiac action potential characteristics and pacemaker activity [5,6]. In addition, F508 del mutation in cystic fibrosis has been found to destabilize full-length CFTR protein at the plasma membrane causing instability of CFTR chloride channels [4]. Meng et al demonstrated rundown of F508del-CFTR activity, described as reduced frequency of channels opening and change in Cl current flow, reaching 50% after 3 minutes and progressed to complete channel deactivation within 7 minutes [4]. This channel instability could in turn disturb cardiac action potential profile and duration i.e. CFTR depolarization- repolarization function in cardiac cell. Nevertheless, the relationship between the fast HR fluctuation, sinus tachycardia episodes and variation in QRS amplitude andthe F508del-CFTR function instability remains to be verified.

In this report, further increases in HR coupled with asymptomatic dynamic changes in ST- T segment have been observed approximately 1 hour after salbutamol administration. This observation has been confirmed by salbutamol re-challenge test performed under complete medical supervision. The observed salbutamol-related tachycardia episodes were in line with earlier reports [19-22]. Regarding ST-T segment changes, although the presence of static flattened T wave is a nonspecific finding, new dynamic T wave flattening in 2 or more contiguous leads may be an abnormal finding and may predict cardiovascular events not only in patients with coronary artery disease (CAD) but also in those *without* a known history of CAD [28]. Interestingly, ST-T segment changes had not been observed before salbutamol administration during the tachycardia episodes with a heart rate of 111 bpm (figure 3). However, after salbutamol administration, a heart rate of 102 bpm was associated with ST-T segment changes (figure 4). This indicates that although the ST-T segment changes observed in this patient might have been tachycardia-related they were not rate-related and therefore raise the possibility of other causes besides tachycardia for theobserved ST-T segment changes in this patient.

Clinical stress testing, whether via conventional exercise testing (treadmill ECG stress test) or its pharmacological surrogate (e.g. using beta adrenergic agonist) is a useful tool to assess the clinical and electrocardiographic condition of cardiac circulation and myocardial oxygen supply [10,29]. In this regard, tachycardia-related ST-segment depression during stress testing is the traditional electro cardio graphic sign of myocardial O2 deprivation due to imbalance between O2 demand and supply and might be considered a suggestive electrocardiographic sign of myocardial ischemia that requires confirmation by myocardial scintigraphy [29-31]. The shape and magnitude of ST segment depression are important clues in the diagnosis of myocardial ischemia where horizontal and down sloping ST segment depression have a diagnostic value, while upsloping one is an equivocal sign and might be encountered in normal healthy subjects [29].

However, these absolute criteria are not *Sine qua non* for myocardial ischemia and other factors should also be considered when evaluating ST segment changes. This might avoid underestimation of potential myocardial ischemia. Factors to be considered in this scenario include disease natural history, clinical context and other associated electrocardiographic signs. In terms of the latter, ST segment depression that is slowly upsloping (0.5- 1.0 mV/ second) may be considered abnormal especially if it occurs at low workload [32]. In this patient the magnitude of increase in HR that has been associated with ST- T wave changes represents a low cardiac workload. This is given the minimum and maximum target heart rate for the patient, based on her age in years, 119 and 169 bpm respectively. In addition, it has been reported that ST-segment depression or elevation (≥ 0.5 mm, using the usual standard of 1.0 mV = 10 mm) may be abnormal, particularly when the shape of the ST segment suggests ischemia, or when other ischemic signs such as T wave abnormalities, or reciprocal ST segment changes are concomitantly present [33]. This is reasoned by the fact that the extent and the magnitude of ST-segment depression correlate with the extent and the severity of ischemia rather than the presence or absence of ischemia [33]. Lastly, ST-segment depression has been reported to be consistent with ischemia if the *magnitude of ST-segment depression progresses or regresses on serial tracings* [33]. Such abnormalities have been shown in this report during the course of the event.

The Absence of symptoms during the course of myocardial ischemia has been reported to be the most common manifestation of myocardial ischemia (silent myocardial ischemia) accounting for 70% to 80% of transient ischemic episodes as assessed by electrocardiographic monitoring [34]. A possible mechanism for this is high threshold for painful stimuli which has been the case in this patient [34].

It is worth mentioning that slowing of cardiac oxygen uptake kinetics has been demonstrated in CF patients compared to healthy controls [35]. This might predispose to myocardial ischemia via increased oxygen deficit particularly in CF patients having exocrine pancreatic insufficiency with increased resting energy expenditure and more cardiac O2 uptake requirement [36,37]. Oxygen requirement may become more pronounced by the use of inhalation β2A that is reported to significantly increase HR and cardiac output and causes further increase in O2 needs [22].

Taken all together, a cautious approach is needed for CF patients in clinical (trial) settings when β2A is administered. This includes individualized β2A dose adjustment and close clinical supervision and monitoring of the patient. This avoids potential cardiovascular adverse effects such as myocardial ischemia and its unwanted sequelae in this fragile group of patients. This is particularly important in asymptomatic tachycardiac patients who have no symptoms to draw the attention of the treating/ clinical trialphysician.

Finally, 2 points related to this report are worth mentioning. First, the use of cardiac telemetry monitoring in patients with rapid HR fluctuation seems a better option than 12-leads ECG since the latter might not capture the tachycardia episodes at the time of recording. Compared to the 12-lead ECG tracing, telemetric recordings appear

technically a more time sparing procedure that facilitates continuous and detailed tracing of cardiac electrical activity. Second, this report is based on incidental observations. Accordingly, confirmation of myocardial ischemia with other investigational tests such as cardiac scintigraphy had not been scheduled and was not done. Further investigations to explore the clinical significance of the findings in this report are, therefore, still warranted.

Acknowledgment

The author would like to thank Dr Bruce Mortimore vice president scientific affair and Dr Robert Lester consultant cardiologist at Celerion Inc., USA for their review of this manuscript.

Abstracts containing some materials used in this paper have been presented at 3rd international conference on advanced clinical research and clinical trials, September 20-21, 2017 Dublin, Ireland and the Dutch Society of Clinical Pharmacology meeting held October 02- 03 2017 Ede the Netherlands.

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