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Electrocardiography at Diagnosis and Close to the Time of Death in Pulmonary Arterial Hypertension

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Abstract

Background—Scarce information exits on the electrocardiographic (ECG) characteristics of PAH patients close to their death and whether observed abnormalities progress from the time of PAH diagnosis.

Methods—We analyzed the characteristics of the ECG performed at initial diagnosis, during the course of the disease and close to the time of death on consecutive PAH patients followed at our institution between June 2008 and December 2010.

Results—We included 50 patients with PAH (76 % women) with mean (SD) age of 58 (14) years. Median heart rate (83 vs 89 bpm, p=0.001), PR interval (167 vs 176 ms, p=0.03), QRS duration (88 vs 90 ms, p=0.02), R/S ratio in lead V1 (1 vs 2, p=0.01) and QTc duration (431 vs 444 ms, p=0.02) significantly increased from the initial to the last ECG. In addition, the frontal QRS axis rotated to the right (97 vs 112 degrees, p=0.003) and we more commonly observed RBBB (5 vs 8 %, p=0.03) and negative T waves in inferior leads (31 vs 60 %, p=0.004). No patient had normal ECG at the time of death.

Conclusions—Significant changes progressively occur in a variety of ECG parameters between the time of the initial PAH diagnosis and close to death.

Keywords

Pulmonary hypertension; Electrocardiography; Outcome Assessment

Introduction

Pulmonary hypertension (PH) is a condition defined by a mean pulmonary artery pressure of ≥ 25 mm Hg that is caused by a variety of conditions [1,2]. In a substantial number of patients, PH still progresses to right heart failure and death, despite recent advances in the management [3,4]. Thus, there is a pressing need to identify non-invasive, easy to perform, and inexpensive diagnostic modalities that can help identify PH patients at increased risk of

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poor outcomes. Electrocardiography (ECG) is a widely available modality that fulfills these requirements; however it is criticized for its lack of sensitivity and specificity [5-12].

Several studies have evaluated the diagnostic and prognostic information provided by the ECG obtained at the time of diagnosis of PH, predominantly by assessing for the presence or absence of right ventricular hypertrophy [13-15]. Most of these studies were done in patients with various forms of PH, diagnosed by methods other than right heart catheterization making it difficult to compare their results.

More recently, a few studies have shown an increase in the sensitivity of electrocardiography in PH by using less conventional criteria such as negative T waves in right precordial leads, QRS duration, and QT prolongation [9,16,17]. However, controversy still exists regarding the utility and appropriate role of electrocardiography in PH. We conducted a study in patients with pulmonary arterial hypertension (PAH) to compare the ECG characteristics at the time of hemodynamic diagnosis, during the course of the disease and close to the time of death. We hypothesized that significant ECG changes would occur between PAH diagnosis and death, and that the identification of the parameters that change could provide the basis for future investigations that can validate electrocardiographic prognostic factors in PAH.

Methods

This study was approved by the Cleveland Clinic Institutional Review Board (protocol approval number: 11-021). Informed consent was waived as only deceased patients were included in the study. Consecutive deceased patients with a diagnosis of PAH confirmed by right heart catheterization (RHC) between June 2008 and December 2010 were included in the analysis. Patients who underwent lung transplantation were excluded. The diagnosis of PAH was established using standard criteria [18] and each patient underwent thorough investigations to identify the etiology of PH. These data were prospectively collected in our Pulmonary Vascular Registry (IRB number 8097).

On a weekly basis, the Cleveland Clinic Pulmonary Vascular Program Committee prospectively reviews the cause of death of all PH patients. At least two PH specialists had to agree on the most likely cause of death [19]. We routinely collect the age of the patient and date of expiration, date of PH diagnosis, PH specific diagnosis, treatment with PH-targeted therapy, cause of death, and the degree to which PH contributed to death. Clinical, echocardiographic and hemodynamic data were obtained from our Pulmonary Vascular Registry and the electronic medical records. Operators reviewing the echocardiograms were blinded to ECG results. Left ventricular ejection fraction, right ventricular function and dilation, and systolic right atrial and diastolic right ventricular area were obtained in the apical four chamber view. Right ventricular systolic pressure was estimated by the Bernoulli equation with the addition of right atrial pressure which was estimated by assessing the inferior vena cava size and inspiratory collapse [20]. Right heart catheterization was performed in all patients in the standard manner.

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ECG

Out of a total of 57 deceased PAH patients, 52 had ECG obtained during the last month before dying and were included in the study. Two subjects were excluded as they had atrial or ventricular paced rhythm. We reviewed ECGs obtained at the time of the right heart catheterization that confirmed the diagnosis of PAH, during the course of the disease (between the time of the right heart catheterization and death, i.e. “in-between ECG”) and before death.

Certified ECG technicians performed standard 12-lead ECG (10-second recording) in the supine position (Muse Network Series system; Marquette Electronics; Milwaukee, WI, USA). All ECG were acquired using a paper speed of 25 mm/s and a sensitivity of 1 mV = 10 mm. The ECG laboratory has standardized quality improvement protocols to minimize lead placement errors and motion artifact. Rulers and calipers were used for ECG measurements.

Two investigators blinded to the patient’s information reviewed all ECGs and recorded the date of ECG, heart rate, rhythm, P wave duration (lead II), amplitude (inferior leads and V1) and frontal axis, PR interval, QRS complex duration and frontal axis, R and S amplitude and ratio in lead I, aVR, V1, V5, and V6, intrinsicoid deflection in V1, and QT and QT corrected for heart rate by Bazett’s formula (QTc)[21]. Configuration of the QRS complex in V1 was determined and classified as Q, qR, R, qrS or rSR’. The rSR’ pattern was described as incomplete or complete right bundle branch block depending on a QRS duration < 0.12 or ≥ 0.12 s, respectively. Negative T waves and ST segment depressions in right precordial and inferior leads were identified.

The isoelectric point was defined at the PR interval, deflections below the isoelectric point were considered negative and ST depression was considered present if the deflection was ≥ 0.1 mV. The QRS transitional zone was defined as the site in the precordial leads in which the amplitudes of the positive and negative QRS deflections were of equal magnitude. The presence of RV hypertrophy was assessed by a variety of methods including Butler et al. [22], Heikkilä et al.[12,23], Lehtonen et al.[12], Louridas et al. [24] and WHO [25] criteria. We also used the criterion A + R – PL (A= maximal R or R’ in V1 or V2 + R= maximal S in lead I or V6 – minimal S in V1 or minimal R in lead I or V6) [22]. None of the patients had left bundle branch block. Fifteen patients were receiving either a beta-blocker (atenolol:3, metoprolol: 2, and other beta-blocker: 4 patients) and/or calcium channel blocker (diltiazem: 3, amlodipine 3, nifedipine 2 and felodipine: 1) at the time of the ECG before death. In all but 2 patients, we recorded the results of serum potassium, calcium and magnesium obtained on the day of the last ECG.

Statistical analysis

We used descriptive statistics. Data are presented as mean (± SD) or median (interquartile range (IQR)) when appropriate. Relationships between ECG and echocardiographic parameters are expressed as Pearson correlation coefficients. Paired continuous and categorical variables were compared using related samples Wilcoxon Signed Rank Test or McNemar’s test, respectively. Independent samples were compared using Mann-Whitney or

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Fisher exact test. Analysis of covariance (ANCOVA) was applied to obtain means adjusted for covariates. All *p* values reported are two-tailed. A *p* value of < 0.05 was considered significant. The statistical analyses were performed using the statistical package IBM SPSS, version 20 (IBM; Armonk, New York).

Results

Patient characteristics close of death

We included 50 patients with PAH (76 % females) with mean (SD) age of 58 (14) years. Causes of PAH were associated with connective tissue disease (n=22, 44 %), idiopathic / heritable (n=15, 30 %), congenital heart disease (n=6, 12 %), portopulmonary hypertension (n=4, 8 %), anorexigen-induced (n=2, 4 %), and pulmonary veno-occlusive disease (n=1, 2 %). At the time of the last ECG, patients were in NYHA class II (n=3, 6 %), III (n=13, 26 %) or IV (n=34, 68 %). PAH was the direct cause of death in 21 (42 %) patients. PAH was not directly related to death in 29 (58%) patients. The right heart catheterization, performed closest to the time of death, showed a mean (SD) right atrial pressure, mean pulmonary artery pressure, cardiac index and pulmonary vascular resistance of 13 (7) mm Hg, 51 (12) mm Hg, 2.8 (1.3) L/min/m^2 and 8.4 (5) Wood Units, respectively. All but two subjects were on PH-targeted therapies and 58% were receiving prostacyclin therapy at the time of the ECG close to death.

Characteristics of the ECG obtained close to the time of death

The ECG close to the time of death was performed a median (interquartile range (IQR)) of 0 (0-2) months before death. The rhythm was normal sinus (n=26, 52 %), sinus tachycardia (n=11, 22 %), junctional (n=1, 2 %), atrial flutter (n=6, 12 %), atrial fibrillation (n=5, 10 %) and supraventricular tachycardia (n=1, 2%). The most commonly observed ECG findings were a QRS axis deviated to the right (>90°) in 74 %, an R/S ratio ≥ 1 in 74 %, and negative T waves in right precordial (V1-V3) and inferior leads in 76 and 60 % of the patients, respectively. Other ECG parameters are shown in table 1. No significant ECG differences were observed in those taken calcium channel blocker and/or beta blockers at the time of the ECG close to death (data not shown).

Comparison of ECG at initial presentation and close to death

Electrocardiograms performed close to the time of death were compared to the ECG performed during the initial evaluation for symptoms of PH, before initiation of PH-specific therapies (Table 1). The median (IQR) time between initial and last ECG was 39 (10-77) months. Atrial fibrillation and flutter were not observed in the ECG at the time of presentation. When compared to the initial ECG, the one obtained close to the time of death showed higher HR and R/S ratio in lead V1 as well as longer PR interval, QRS duration and QTc duration. In addition, R wave amplitude in lead I decreased, the frontal QRS axis shifted to the right and right bundle branch block and negative T waves in inferior leads were more common (Table 1). No patient had normal ECG at the time of death. When adjusted for heart rate the PR interval (median (IQR) 178 (177-180) vs 170 (167-173), $p < 0.001$) and the QRS duration close to death (99 (98-99) vs 93 (92-93), $p < 0.001$) were significantly increased.

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Blood work obtained on the same day of the ECG close to death showed a serum potassium of 4.2 (3.7-4.7) mmol/L, calcium of 8.7 (8-9.1) mg/dL and magnesium of 2 (1.8-2.2) mg/dL. When adjusted for the electrolyte measurements QRS complex duration (97 (88-103), p=0.05), QTc interval (448 (439-462), p=0.03), QRS axis (103 (95-110), p=0.02) and R/S ratio in lead V1 (2.8 (2.5-3.2), p=0.01) remained significantly different when compared with the ECG at initial presentation.

Using the Butler et al.[22], Heikkilä et al. [12,23], Lehtonen et al.[12], Louridas et al.[24] and WHO [25] criteria, ECG evidence of right ventricular hypertrophy was present in the vast majority patients either at the time of PH diagnosis or close to the time of death (Table 2). All ECG performed close to the time of death showed right ventricular hypertrophy per Butler et al.[22] and Lehtonen et al.[12] criteria. The percentage of patients with right ventricular hypertrophy by Butler et al.[22] and Lehtonen et al.[12] criteria was statistically higher at the time of death than at diagnosis.

Characteristics of ECG performed between the time of PAH diagnosis and death

In 28 patients we also analyzed the ECG obtained amid PAH diagnosis and death. The initial and the “in-between” ECG were performed with a median (IQR) time difference of 27 (16-46) months. The median (IQR) time between the latter ECG and the one performed before death was 24.5 (14.3-41) months. We focused on the variables that were different between the initial ECG and the one performed before death. For the most part, the ECG determinations in the “in-between” ECG showed progression of the ECG findings from the first to the last ECG studied (table 3).

Comparison of ECG and echocardiographic parameters before death

Echocardiograms were performed within a month of the ECG obtained close to the time of death in 88 % of the patients. Right ventricular (RV) dysfunction was mild, moderate, moderately severe, or severe in 6 % (n=3), 14 % (n=7), 26 % (n=13), and 54 % (n=27) of the cases, respectively. The median (IQR) RA and RV area were 28.8 (24-34) and 31.7 (28-43) cm^2, respectively. RV diameter was 5.2 (4.6-5.8) cm.

PR interval was associated with RV area (r=0.35, p=0.03) and diameter (r=0.33, p=0.03). RV area was larger in patients with right bundle branch block (34 vs 43 cm^2, p=0.05) and R/S >1 in V1 (28 vs 38 cm^2, p=0.001). RV area was directly associated with QRS transition zone (r=0.3, p=0.03). RV dysfunction was associated with QRS and T wave axis (r=0.4, p=0.004 and r= -0.38, p=0.008, respectively). The percentage of patients with severe RV dysfunction (versus other degrees) was higher in those with negative T wave in V1-V3 (63 vs 25 %, p=0.048), negative T waves in the inferior leads (70 vs 30 %, p=0.01) and R/S > 1 in V1 (65% vs 23%, p=0.02).

ECG in patients who died of right heart failure versus other causes

The comparison of ECG in patients in whom PH was the direct cause of death (right heart failure or sudden death) (n=21) versus those that died of conditions not directly related to PH (i.e. pneumonia, cancer, sepsis, gastrointestinal bleeding, etc) (n=29) showed no significant differences except for more frequent right ventricular hypertrophy by Heikkilä et

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al.[12,23] and WHO [25] criteria and larger R waves in V2 (0.7 vs 0.3, p=0.03) in patients that directly died of PAH.

Discussion

This is the first study to characterize the ECG changes between PAH diagnosis and death and to relate these variations to PAH severity and cause of death. We found that although some individuals had normal ECGs at the time of diagnosis, all ECGs obtained close to the time of death were abnormal. These progressive abnormalities most commonly included right axis deviation, R/S ratio ≥ 1 in lead V1, negative T waves in right precordial (V1-V3) and/or inferior leads and RV hypertrophy. When compared with the ECG performed at the time of PAH diagnosis, the ECG close to patient's death revealed longer PR interval, QRS complex and QTc interval; more pronounced rotation of the frontal QRS axis to the right and higher R/S ratio in V1 as well as higher prevalence of RBBB and negative T waves in inferior leads. Furthermore, RV area and function on echocardiography were associated with several of these ECG abnormalities.

Electrocardiography has traditionally been considered a methodology with inadequate specificity and poor sensitivity for the diagnosis of PAH [5,10-12,15,26,27]. Furthermore a small percentage (9 – 13 %) of PAH patients (usually those with less severe disease) may have a normal ECG [15,26], casting doubt on the utility of ECG as a screening tool for PAH. The National Prospective study in patients with mostly severe idiopathic PAH showed that 79% of them had right axis deviation, 87% had RV hypertrophy, and 74% had right ventricular strain in the ECG [28]. The sensitivity of ECG in making the diagnosis of PH has been shown to increase with increasing PH severity[29]. In our study, all the ECGs performed before death had some degree of abnormality, meanwhile 8 % of the ECG were normal at the time of PH diagnosis, a similar percentage described by others [15,26]. The novel aspect of our study is the identification of the ECG characteristics at the time of death in PH subjects and parameters that change from the time of PH diagnosis to death. This approach could help determine the best ECG predictors of disease progression, especially given that the correlation between different ECG parameters and severity of disease has not been ideal [26]. In fact, only a few studies have reported an association between ECG parameters and the severity of hemodynamic impairment in PH [13,14,26,30].

In support of the findings of our study, investigators showed that a higher resting heart rate is one of the variables associated with prognosis in PAH [3,31]. Other studies observed a prolonged PR interval in PH patients [30] and they also reported that a QRS duration > 120 ms is observed in 16.5% (right bundle branch block in 9.9 % and nonspecific intraventricular conduction delay in 6.6%) of idiopathic PAH patients[16]; a feature associated with worse WHO functional class, lower six-minute walk distance and worse survival when compared with subject with a QRS duration < 120 ms [32]. Similarly, the QTc interval was longer in patients with PH than controls [17,33] and it was associated with worse RV function and survival [17]. The R wave amplitude in V1, R/S ratio in V1 and frontal QRS axis were also associated with RV enlargement and hemodynamic impairment in PH [14,26,34]. Furthermore, ECG parameters suggestive of right ventricular hypertrophy were associated with higher pulmonary pressures, lower cardiac index and increased mortality [13-15]. A qR pattern was

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associated with worse survival in PAH [30,34] and in our study we found that 30% of the PAH patients had qR pattern in V1 before death.

In patients with idiopathic PAH, ST depression (≥ 1 mm) and T wave inversion suggestive of ischemia or strain are very common in the inferior (18% and 68 %, respectively) and right precordial leads (22% and 88 %, respectively). [30] We observed that negative T waves in the precordial and inferior leads are very common, supporting the findings of Bonderman et al.[9] who used the RV strain pattern on the ECG added to serum NT-proBNP to safely exclude PAH.

PAH patients even with severe forms of the disease tend to remain in sinus rhythm. [29] In a study by Bossone et al. [15] (n=64) most of the patients were in sinus rhythm (97 %); however one patient was in junctional rhythm and another in ectopic atrial rhythm. The authors also observed sinus bradycardia and sinus tachycardia in 5 and 6 subjects, respectively. Tongers et al. [35] evaluated the incidence and clinical relevance of supraventricular tachycardia in 231 PAH or chronic thromboembolic pulmonary disease patients. They observed 31 episodes of supraventricular tachycardia in 27 of these patients (annual risk: 2.8% per patient), including atrial flutter (n=15), atrial fibrillation (n=13) and AV nodal reentry tachycardia (n=3). Mortality was significantly higher in patients with persistent atrial fibrillation [35]. In our study we found that arrhythmias were more common in the ECG closest to time of death, in fact atrial fibrillation, atrial flutter, supraventricular tachycardia and junctional rhythm were mostly seen before death.

Our study has limitations: a) we cannot exclude concomitant coronary artery disease; however, echocardiography did not show left ventricular segmental wall motion abnormalities consistent with this condition, b) findings of this study cannot be generalized to groups of PH other than PAH, and c) electrolyte disorders may occur close to the time of death; however with did not observe major electrolytes abnormalities in these patients and our results remain significant even after adjusting for electrolyte values. The main strength of our study is that it suggests potential new ECG predictors of outcome that deserve further investigation. These include the development of right bundle branch block, negative T wave in the inferior leads, prolongation of PR interval and decrease in the amplitude in lead I.

Conclusion

ECG changes occur between the time of initial PAH diagnosis and just before death. Alone or in combination, these electrocardiographic parameters need further evaluation to identify whether they can be useful biomarkers of poor prognosis in PAH.

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Table 1

ECG characteristics at the time of PAH diagnosis and before death.

Variables	First ECG median (IQR) or n (%) (n=39)	ECG before death median (IQR) or n (%) (n=50)	p (Related samples Wilcoxon Signed Rank Test or McNemar's test, n=39)
Heart rate (bpm)	83 (70-93)	89 (79-103)	0.001
Rhythm			
•NSR	33 (85)	26 (52)	
•Sinus tachycardia	4 (10)	11 (22)	0.01
•Sinus bradycardia	2 (5)	0 (0)	
•A fib / A flutter / SVT / junctional.	0 (0)	13 (26)	
P wave amplitude (DII) (mV)	0.18 (0.1-0.2)	0.16 (0.1-0.2)	0.09
P wave amplitude (V1) (mV)	0.13 (0.1-0.2)	0.16 (0.1-0.2)	0.3
P wave ≥ 0.25 mV (%) ¶	9 (23.1)	6 (12)	0.29
P wave frontal axis (degrees)	58 (48-68)	59 (44-69)	0.83
PR interval (ms)	167 (150-187)	176 (144-191)	0.031
QRS duration (ms)	88 (80-100)	90 (82-110)	0.018
QRS frontal axis (degrees)	97 (42-121)	112 (90-128)	0.003
QRS transition zone	4 (3-5)	4 (3-5)	1
R wave (V1) (mV) *	0.27 (0.2-0.6)	0.4 (0.2-0.6)	0.24
R wave (V2) (mV)	0.48 (0.2-0.7)	0.5 (0.3-0.8)	0.23
R wave (DI) (mV)	0.46 (0.32-0.6)	0.3 (0.2-0.4)	< 0.001
R wave (aVR) (mV)	0.22 (0.12-0.4)	0.2 (0.1-0.3)	0.49
S wave (V1) (mV)	0.28 (0.16-0.7)	0.21 (0.1-0.4)	0.11
R/S ratio (V1)	1 (0.3-3)	2 (0.8-3.6)	0.01
R/S ratio (V1) ≥ 1 (%)	19 (48.7)	37 (74)	0.003
Intrinsicoid deflection (V1) (ms)	50 (40-60)	50 (40-70)	0.27
qR pattern (V1) (%)	5 (12.8)	15 (30)	0.3
rSR' pattern (V1) (%)	17 (43.6)	22 (44)	0.55
qrS pattern (V1) (%)	1 (2.6)	4 (8)	1
RBBB (%)	2 (5.1)	8 (16)	0.031

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Variables	First ECG median (IQR) or n (%) (n=39)	ECG before death median (IQR) or n (%) (n=50)	p (Related samples Wilcoxon Signed Rank Test or McNemar's test, n=39)
S wave (V5-V6) (mV)	0.5 (0.2-0.7)	0.5 (0.3-0.6)	0.78
QTc (ms)	431 (405-458)	444 (414-463)	0.018
T wave frontal axis (degrees)	26 (-3 - +52)	13 (-30 - +58)	0.19
Negative T waves (V1-V3) (%)	31 (79.5)	38 (76)	0.75
Negative T wave (inferior leads) (%)	12 (30.8)	30 (60)	0.004
ST depression (V1) (%)	3 (7.7)	3 (6)	1
ST depression (V2) (%)	5 (12.8)	6 (12)	1
ST depression (inferior leads) (%)	2 (5.1)	4 (8)	1
Normal ECG (%)	3 (7.7)	0 (0)	0.25

Abbreviations: A fib: atrial fibrillation, A flutter: atrial flutter, bpm: beats per minute, NSR: normal sinus rhythm, RBBB: right bundle branch block, SVT: supraventricular tachycardia.

*Tallest R wave in lead V1.

¶P wave amplitude ≥ 0.25 mV in lead II, III, aVF, V1 or V2.

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Table 2

Prevalence of right ventricular hypertrophy by different ECG criteria at the time of PAH diagnosis and before death.

	ECG at PAH diagnosis n (%)	ECG before death n (%)	P (Fisher exact test)
n	39	50	
Butler et al.[22]	33 (85)	50 (100)	0.006
Heikkilä et al. [12,23]	28 (72)	44 (88)	0.06
Lehtonen et al.[12]	34 (87)	50 (100)	0.01
Louridas et al.[24]	33 (85)	43 (86)	1
WHO[25]	33 (85)	44 (88)	0.76

Abbreviations: WHO: World Health Organization.

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Table 3

ECG characteristics at the time of PAH diagnosis, during the course of the disease and before death.

Variable	ECG at PAH diagnosis median (IQR) or n (%) (n=39)	ECG between PAH diagnosis and before death Median (IQR) or n (%) (n=28)	ECG before death median (IQR) or n (%) (n=50)
Months before death	40 (16-77)	27 (15-43)	0 (0-2)
Heart rate (bpm)	83 (70-93)	83 (70-94)	89 (79-103)
Rhythm			
•NSR	33 (85)	20 (71)	26 (52)
•Sinus tachycardia	4 (10)	5 (18)	11 (22)
•Sinus bradycardia	2 (5)	2 (7)	0 (0)
•A fib / A flutter / SVT / junctional.	0 (0)	1 (4)	13 (26)
PR interval (ms)	167 (150-187)	164 (152-184)	176 (144-191)
QRS duration (ms)	88 (80-100)	91 (86-108)	90 (82-110)
QRS frontal axis (degrees)	97 (42-121)	108 (57-129)	112 (90-128)
R wave (DI) (mV)	0.46 (0.32-0.6)	0.39 (2.9-5.1)	0.3 (0.2-0.4)
R/S ratio (V1)	1 (0.3-3)	0.91 (0.2-3.3)	2 (0.8-3.6)
R/S ratio (V1) ≥ 1 (%)	19 (48.7)	10 (48)	37 (74)
RBBB (%)	2 (5.1)	3 (11)	8 (16)
QTc (ms)	431 (405-458)	441 (415-464)	444 (414-463)
Negative T wave (inferior leads) (%)	12 (30.8)	14 (50)	30 (60)
Butler et al.[22]	33 (85)	27 (96)	50 (100)
Heikkilä et al. [12,23]	28 (72)	22 (79)	44 (88)
Lehtonen et al.[12]	34 (87)	22 (79)	50 (100)