European Heart Journal (2013) **34**, 191–200
doi:10.1093/eurheartj/ehs362

QRS duration and QRS fractionation on surface electrocardiogram are markers of right ventricular dysfunction and atrialization in patients with Ebstein anomaly

Gabriele Egidy Assenza[1,2,3], Anne Marie Valente[1,2], Tal Geva[1], Dionne Graham[1], Francesca Romana Pluchinotta[1], Stephen P. Sanders[1], Camillo Autore[3], Massimo Volpe[3,4], Michael J. Landzberg[1,2‡], and Frank Cecchin[1*‡]

[1]Department of Cardiology, Children's Hospital Boston, Harvard Medical School, 300 Longwood Avenue, Boston, MA, 02115, USA; [2]Division of Cardiology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [3]Department of Clinical and Molecular Medicine, Sant'Andrea Hospital, 'Sapienza Universita' di Roma' University, Rome, Italy; and [4]IRCCS Neuromed, Pozzilli, Italy

Received 21 June 2012; revised 28 August 2012; accepted 2 October 2012; online publish-ahead-of-print 1 November 2012

Background Ebstein anomaly is a rare and heterogeneous congenital heart defect affecting the tricuspid valve and right ventricular (RV) myocardium. Few studies have analysed the electrocardiographic features of Ebstein anomaly and none has addressed correlations with disease severity.

Methods Patients with Ebstein anomaly who had undergone electrocardiography and cardiac magnetic resonance (CMR) within 6 weeks between 2001 and 2009 were included. Exclusion criteria were: associated congenital cardiac defect, previous RV myoplasty and/or reduction surgery, class I anti-arrhythmic drug therapy, and paced/pre-excited QRS. Standard electrocardiogram (ECG) findings were correlated with CMR-based RV measures and clinical profile.

Results The mean age of the 63 study patients was 22 ± 13 years. An RV conduction delay (rsR′ pattern in right precordial leads) was present in 45 patients (71%). The QRS duration correlated with anatomic RV diastolic volume ($r = +0.56$, $P < 0.0001$) and inversely with RV ejection fraction (EF; $r = -0.62$, $P < 0.0001$). The presence of QRS fractionation predicted greater atrialized RV volume (80 ± 31 vs. 45 ± 37 mL/m^2, $P < 0.001$). Normal QRS duration was associated with smaller anatomic RV diastolic volume (150 ± 57 vs. 256 ± 100 mL/m^2; $P < 0.0001$), higher RV EF (48 ± 6 vs. 34 ± 14%; $P < 0.0001$), higher oxygen consumption (VO_2) at cardiopulmonary exercise (25.8 vs. 21.8 mL/kg/min, $P = 0.05$) and lower incidence of oxygen desaturation with exercise (25 vs. 65%, $P = 0.02$).

Conclusion Delayed and prolonged depolarization of the RV is common in patients with Ebstein anomaly. The QRS duration is a marker of RV enlargement and dysfunction. QRS fractionation is associated with a greater atrialized RV volume. A preserved surface ECG identifies a subset of patients with Ebstein anomaly with mild morphological and functional abnormalities and better clinical profile.

Keywords Ebstein anomaly • Heart defect • Congenital • Magnetic resonance imaging • Electrocardiography

‡ The authors contributed equally to the study.

* Corresponding author. Tel: +1 617 355 6508, Fax: +1 617 739 8632, Email: frank.cecchin@cardio.chboston.org

Introduction

Ebstein anomaly is uncommon, occurring in 1 per 200 000 live births and accounting for <1% of congenital heart defects.[1] This rare anomaly serves as a model of right ventricle (RV) dysfunction and altered atrial and ventricular coupling.

The major morphological features of Ebstein anomaly include failure of delamination of tricuspid valve leaflets and downward (apical) displacement of the tricuspid valve attachments (functional annulus); atrialization of part of the RV sinus; redundancy, fenestration and tethering of the anterior tricuspid valve leaflet; and dilation of the anatomic (true) valve annulus. Physiological consequences include tricuspid valve regurgitation, stenosis, or both. Subsequent dilation and dysfunction of the right atrium and ventricle are accompanied by progressive patchy myocardial atrophy and fibrosis, which leads to generation of an abnormal endocardial electrogram.[1–5] The clinical spectrum of Ebstein anomaly is broad, ranging from mild disease to more severe forms with massive tricuspid regurgitation and severe cardiomegaly. Exercise limitation, congestive heart failure, arrhythmia, and sudden death have been thought to correlate with right heart dysfunction. Treatment increasingly targets preservation of myocardial function and depends on an accurate assessment of cardiac chamber size and function via advanced imaging techniques.[2–11] A simple non-invasive marker of disease severity could improve our current clinical stratification in this disease and would help to identify patients who might benefit from advanced imaging and surgery.

Few studies have analysed the electrocardiographic features of Ebstein anomaly and none has correlated the electrocardiogram (ECG) with morphology. The goals of this investigation were (i) to describe ECG features in patients with Ebstein anomaly and (ii) to investigate correlations between the ECG and the morphological features identified on cardiac magnetic resonance (CMR) imaging.

Methods

Patients

We searched the Children's Hospital Boston Cardiology database to identify all patients with Ebstein anomaly of the tricuspid valve who underwent CMR and ECG within 6 weeks of each other between 2001 and 2009. Ebstein anomaly was defined as apical displacement of the septal and posterior leaflets of the tricuspid valve >8 mm/m^2 in relation to the anterior mitral valve leaflet.[1] Variables recorded included baseline demographics, clinical information, surgical history, cardiopulmonary exercise data (when available), cardiac symptoms, history of arrhythmias (defined as sustained atrial or ventricular arrhythmias requiring intervention or any invasive procedure to ablate an arrhythmic substrate), and medical treatment at the time of evaluation. Patients with one or more of the following conditions were excluded: (i) an associated congenital cardiac defect (other than secundum atrial septal defect or patent foramen ovale); (ii) history of a surgical procedure involving RV myoplasty and/or reduction; (iii) use, at time of ECG acquisition, of medication known to affect the QRS complex; (iv) paced ventricular rhythm; (v) ventricular pre-excitation.

The study was approved by the Scientific Review Committee of the Department of Cardiology and by the Children's Hospital Boston Committee on Clinical Investigation.

Electrocardiogram analysis

12-lead ECGs were acquired using standard lead position and recorded at 25 mm/s−0.1 mV/mm, using a commercially available digital recording and storage system (Marquette® 12SL™, GE Healthcare). Dedicated software with a resolution of 1 ms on the horizontal axis and 0.01 mV on the vertical axis was used to measure standard intervals and amplitudes directly on the digital ECG. ECGs were enlarged ×4 for analysis. The detection of onset and termination of pertinent ECG complexes was manually performed and the QRS duration was measured in each precordial lead; the averaged value was used for analysis. Intervals were measured in two consecutive beats (excluding atrial or ventricular premature beats) and averaged. Two additional depolarization parameters were recorded: 'S-wave upstroke time' was measured in the right precordial leads as the longest interval from the nadir of the S-wave to the point of intersection of the upstroke portion of the S-wave with the isoeletric line (*Figure 1A*)[12]; 'QRS fractionation' was diagnosed when a distinct, low-voltage wave

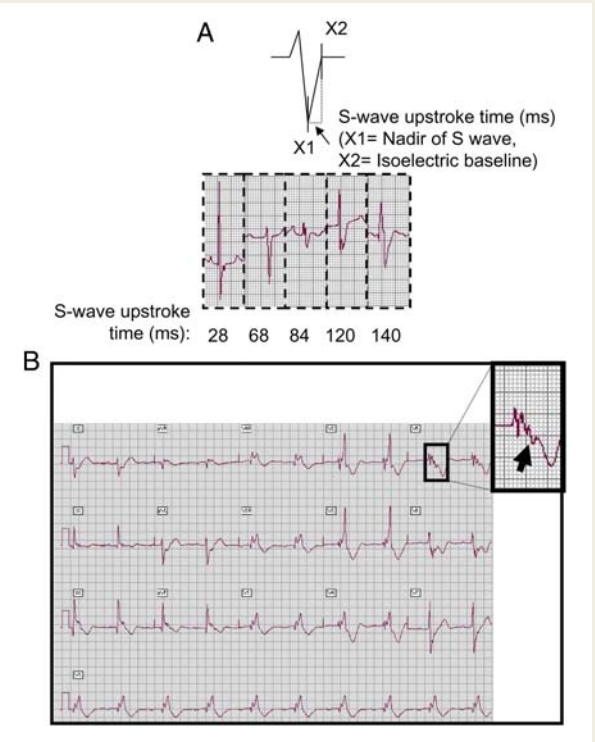

Figure 1 S-wave upstroke time and QRS fractionation. (*A*) Operative definition of S-wave upstroke time as the time between the nadir of the S-wave (X1) and the isoelectric baseline (X2). In the bottom panel, five representative electrocardiograms from our cohort are presented with S-wave upstroke time comprised between 28 and 140 ms. Modified from ref. (12). (*B*) Representative electrocardiogram obtained from a patient with Ebstein anomaly, showing rsR′ pattern in V1, prolonged QRS duration and abnormal, 'slurred', terminal wave, best seen in the left precordial leads, at the end of the QRS (QRS fractionation). The higher magnification shows details of the QRS fractionation.

(<0.5 mV) was observed in the terminal portion of the QRS complex or the early ST-segment (*Figure 1B*). All the ECGs were analysed by the same investigator blinded to CMR results. In 10 randomly selected patients, QRS duration measurements were repeated in a blind fashion by the same investigator (G.E.A.) and by a second blinded observer (F.C.) to assess intra- and inter-observer variability.

To investigate the relationship between clinical profile and ECG features, the following criteria defined a 'preserved' ECG: the simultaneous presence of: (i) sinus rhythm with normal atrioventricular conduction time (<200 ms); (ii) normal intra-ventricular conduction time (<120 ms); and (iii) absence of QRS fractionation. Patients not matching these pre-specified criteria were considered to have an 'abnormal' ECG.

Cardiac magnetic resonance analysis

Studies were performed using a commercially available 1.5-T scanner (Philips Healthcare, Best, the Netherlands). The details of the CMR technical parameters used in our laboratory for assessment of patients with congenital heart defects have been published previously.[13] Briefly, steady-state free precession cine imaging of the ventricles was performed during breath-holding in ventricular two-chamber, four-chamber, and short-axis planes. The short-axis stack provided complete coverage from base to apex of both ventricles (12–14 equidistant slices, typical slice thickness 8 mm).

For volumetric analysis, the RV was divided into anatomic and functional components (*Figure 2*). The anatomic volume encompassed the entire RV from the anatomic tricuspid valve annulus to the pulmonary valve, including the atrialized part of the RV cavity. The functional RV volume was measured from the functional attachments (annulus) of the tricuspid valve to the pulmonary valve. The atrialized RV cavity volume was calculated as the difference between anatomic and functional diastolic RV volumes. The end-diastolic volume (EDV) and end-systolic volume (ESV) were measured in the short-axis view. The majority of the RV trabeculae were excluded from the blood pool. All ventricular volume measurements were indexed to body surface area (BSA).

A single investigator (A.M.V.), blinded to the ECG and clinical data, analysed the CMR data using commercially available software (MASS version 6.2, Medis, Leiden, the Netherlands). Left ventricular (LV) and RV EDV, ESV volume, and ejection fraction (EF) were measured as described by Alfakih *et al.*[14]

In 10 randomly selected patients, RV and LV volume measurements were randomly repeated in a blinded fashion by the same investigator (A.M.V.) and by a second blinded observer (G.E.A.) to assess intra- and inter-observer variability.

Heart histology

A heart from an adult with Ebstein anomaly and an age-matched normal heart fixed in 10% buffered formalin were selected from the anatomic collection of the Children's Hospital Boston Cardiac Registry. A full thickness section of the 'atrialized' ventricular septum extending across the atrioventricular junction was removed from the Ebstein heart, and a comparable section was obtained from the normal heart. The sections were embedded in paraffin and 5 μm sections mounted and stained with Masson trichrome.

Data analysis

Continuous variables are reported as mean ± SD and categorical variables are reported as counts and percentages. Comparisons of demographic, ECG, and CMR variables were made between groups using a

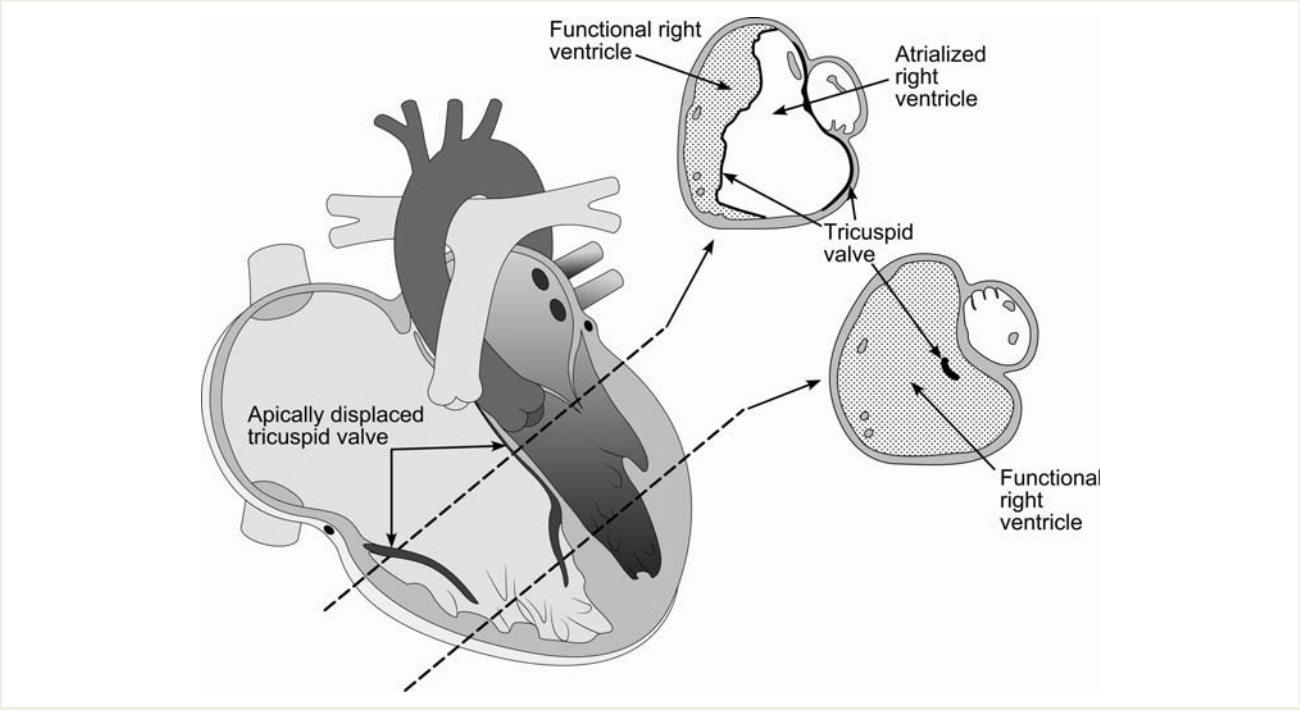

Figure 2 Ebstein anomaly anatomical features. On the left, a four-chamber view is used to exemplify the apically displaced tricuspid valve. Two short-axis views are carried at different distance from the anatomic annulus of the tricuspid valve. The spatial relationship between the functional and anatomic RV cavity is illustrated.

t-test or analysis of variance (ANOVA), given approximately normal distributions. Comparisons of categorical variables were made with Fisher's exact test. The association between continuous ECG and CMR variables was measured with Pearson's correlation coefficient. A *P*-value of <0.05 was considered statistically significant. All tests were two-sided. Analyses were performed using SAS software, version 9.2, for Windows (SAS Institute, Inc., Cary, NC, USA). Intra- and inter-observer variability were determined using intra-class correlation coefficients (ICCs), which is the degree to which repeated measurements on the same subject, either by the same rater (intra-observer) or different observers (inter-observer), correlate with one another.

Results

Baseline characteristics

Of the 225 patients with Ebstein anomaly seen at our institution during the defined study period, 112 underwent CMR. Forty-nine patients were excluded from the analysis due to the following reasons: an associated congenital defect (29, including 12 patients with congenitally corrected transposition of the great arteries); RV myoplasty or reduction surgery at the time of tricuspid valve repair (11); paced ventricular rhythm (5), overt ventricular pre-excitation at the baseline ECG (4).

Sixty-three remaining patients met inclusion criteria. The baseline features of the study population are summarized in *Table 1*. Sixty per cent of the patients were >18 years of age and 80% had not undergone surgical intervention prior to CMR. Accessory pathway ablation was successfully performed in four patients (6%), in coordination with a surgical procedure in three cases and by catheter radiofrequency ablation in one case.

Electrocardiographic features

The ECG features of the 63 patients included in the study are summarized in *Table 1*. All patients were in sinus rhythm except an 8-year-old boy with an ectopic atrial rhythm, a heart rate in the physiologic range for age, a normal PR interval, and no history of surgery or radiofrequency ablation. The nine patients (15%) with a P-wave amplitude >2.5 mm in lead II were younger than the general cohort (mean age 10.8 ± 6.3 vs. 24.7 ± 13.4 years, $P < 0.0001$).

The atrioventricular (AV) conduction time ranged from 100 to 276 ms. Prolongation of AV conduction time >200 ms was noted in 11 patients (17%).

The QRS duration ranged from 76 to 207 ms. The QRS duration was abnormally prolonged >120 ms in 31 (49%) of the patients.

The S-wave upstroke time ranged from 20 to 140 ms. The S-wave upstroke time was highly correlated with the QRS duration ($r = +0.64$, $P < 0.0001$).

The QRS fractionation was present in 18 patients (29%), all of whom had a QRS duration of >120 ms, significantly longer than in patients without QRS fractionation (110 ± 25 vs. 163 ± 24 ms, $P < 0.0001$).

Analysis of QRS duration for inter- and intra-observer variability showed high agreement (inter-coefficient class of 0.88 and 0.90, respectively). There was an excellent agreement for the detection of QRS fractionation, with kappa coefficients of 1 for both inter- and intra-observer variability.

Table 1 Patient characteristics

	Overall cohort ($n = 63$)
Age at CMR (years)	22 ± 13
Sex, male, *n* (%)	26 (41)
Height (cm)	151 ± 35
Weight (kg)	62 ± 29
BSA (m^2)	1.61 ± 0.47
Surgical procedures	
Increase of pulmonary blood flow, *n* (%)	2 (3)
Tricuspid valve repair, *n* (%)	5 (8)
Tricuspid valve replacement, *n* (%)	1 (1.5)
Atrial septal defect closure, *n* (%)	6 (10)
History of accessory AV pathway ablation, *n* (%)	4 (6)
Cardiothoracic ratio	0.58 ± 0.08
P-wave amplitude in lead II (mm)	1.7 ± 0.99
AV conduction time (ms)	174 ± 40
QRS morphology, *n* (%)	
Normal	16 (26)
rsR′ pattern	45 (71)
IVCD	2 (3)
QRS duration (ms)	125 ± 34
QRS amplitude in the precordial leads (mm)	16 ± 7
QRS amplitude in the limb leads (mm)	12 ± 5
S-wave upstroke (ms)	48 ± 24
QRS fractionation, *n* (%)	18 (29)

Values are *n* (%) or mean ± SD.
CMR, cardiac magnetic resonance; BSA, body surface area; AV, atrioventricular conduction time; IVCD, intra-ventricular conduction delay.

Cardiac magnetic resonance features

Table 2 summarizes pertinent volumetric and functional CMR findings. The indexed anatomic RV EDV ranged from 29 to 448 mL/m^2, the indexed functional RV EDV ranged from 10 to 412 mL/m^2, and the indexed atrialized RV cavity ranged from 10 to 185 mL/m^2.

The functional RV EF ranged from 3 to 68%, and correlated inversely with the anatomic RV EDV ($r = -0.51$, $P < 0.0001$).

LV EDV ranged from 46 to 118 mL/m^2 and the LV EF from 20 to 71%. LV EF was ≤60% in 32 patients (48%). In this sub-group, the anatomic RV EDV was significantly greater than in patients with normal LV EF (224 ± 98 vs. 171 ± 88 mL/m^2, $P = 0.02$).

There was excellent agreement among observers for both anatomic and functional RV EDV (inter-coefficient class of 0.98 and 0.95, respectively). Similarly, the intra-observer variability was extremely low (inter-coefficient class of 0.97 and 0.95 for anatomic and functional RV EDV, respectively).

Table 2 Cardiac magnetic resonance volumes and function for the entire patient cohort and stratified by QRS duration and age at cardiac magnetic resonance

	Overall cohort ($n = 63$)	QRS duration at CMR			Age at CMR		
		QRS duration ≤120 ms (33)	QRS duration ≥120 ms (30)	*P*-value	≤18 years ($n = 25$)	≥18 years ($n = 38$)	*P*-value
Indexed, diastolic anatomic RV volume (mL/m^2)	200 ± 96	149 ± 57	256 ± 100	<0.0001	206 ± 113	196 ± 85	0.71
Indexed, diastolic functional RV volume (mL/m^2)	145 ± 75	111 ± 42	182 ± 85	0.0001	142 ± 83	147 ± 70	0.81
Functional RV EF (%)	42 ± 14	48 ± 8	34 ± 14	<0.0001	43 ± 14	41 ± 13	0.60
Indexed, atrialized RV volume (mL/m^2)	55 ± 39	38 ± 29	74 ± 40	0.0001	64 ± 48	49 ± 31	0.18
Indexed, diastolic LV volume (mL/m^2)	72 ± 18	70 ± 17	75 ± 19	>0.85	71 ± 20	73 ± 17	0.70
LV EF (%)	57 ± 8	60 ± 6	55 ± 10	0.01	55 ± 11	59 ± 6	0.14

Values are mean ± SD.
CMR, cardiac magnetic resonance; RV, right ventricle; LV, left ventricle.

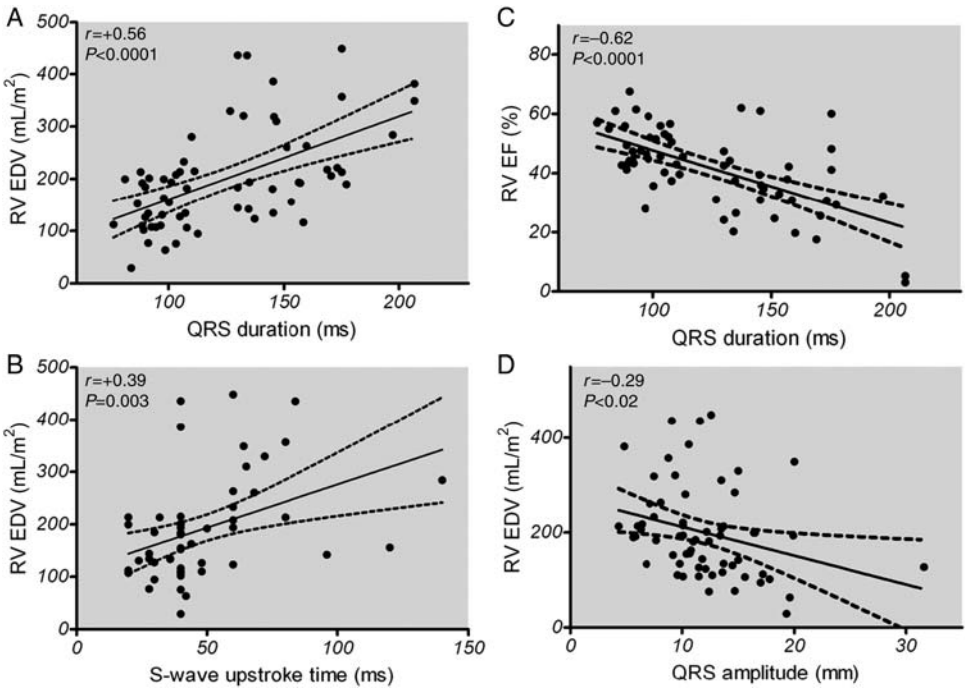

Figure 3 Electrocardiogram and cardiac magnetic resonance correlates. (*A*) Linear, direct relationship between indexed anatomic RV volume (mL/m^2) and QRS duration (ms). (*B*) Linear, direct relationship between indexed anatomic RV EDV volume (mL/m^2) and S-wave upstroke time (ms). (*C*) Inverse, linear relationship between functional RV EF (%) and QRS duration (ms). (*D*) Inverse, linear relationship between indexed anatomic RV EDV (mL/m^2) and QRS amplitude in the peripheral leads (mm).

Morphological correlates between electrocardiogram and cardiac magnetic resonance features

Both QRS duration and S-wave upstroke time were positively correlated with the indexed anatomic RV EDV (*Figure 3A* and *B*, respectively). The functional RV EF was inversely related to the QRS duration (*Figure 3C*). QRS amplitude in the limb leads was inversely related to the indexed anatomic RV EDV (*Figure 3D*).

The atrialized RV cavity volume was significantly larger in patients with evidence of QRS fractionation compared with patients without QRS fractionation (80 ± 31 vs. 45 ± 37 mL/m^2,

$P < 0.001$). In addition, the indexed, anatomic RV EDV was larger (268 ± 76 vs. 173 ± 90 mL/m^2, $P = 0.0002$), and the RV EF lower (28 ± 12 vs. $47 \pm 11\%$, $P < 0.0001$) in patients with QRS fractionation.

Prolonged AV conduction time (>200 ms) was present in 11 patients (17%) and was associated with larger indexed anatomic RV EDV (265 ± 110 vs. 188 ± 91 mL/m^2, $P = 0.03$).

The QRS duration was normal in 32 patients (51%). *Table 2* demonstrates RV volumes and systolic function, according to the QRS duration. The anatomical RV EDV was significantly smaller in patients with a normal QRS duration compared with those with the QRS duration of >120 ms); in addition, RV EF was significantly higher and the atrialized RV volume was significantly smaller in patients with normal QRS duration compared with patients with the QRS duration of >120 ms.

LV EF was only weakly inversely associated with the QRS duration ($r = -0.28$, $P < 0.02$), as was the ratio of LV EDV to anatomic RV EDV ($r = -0.37$, $P = 0.003$). Neither LV EDV nor LV EF differed clinically as a function of the QRS duration (*Table 2*).

Clinical patient profile based on electrocardiogram findings

Table 3 summarizes patient clinical profile stratified by ECG characteristics. Patients with an abnormal ECG were more likely to have advanced NYHA functional class at the time of ECG recording (35 vs. 11%, $P = 0.05$), reduced peak oxygen consumption during maximal effort (21.8 ± 7 vs. 25.8 ± 6 mL/kg/min, $P = 0.05$), a trend toward steeper VE/VCO2 slope (35 ± 10 vs. 30 ± 4, $P = 0.12$). In addition, patients with an abnormal ECG displayed lower oxygen saturation at peak exercise (86 ± 12 vs. $94 \pm 8\%$, $P = 0.02$) with higher rate of exercise-induced desaturation, defined as haemoglobin saturation <90% at peak exercise (65 vs. 25%, $P = 0.02$).

Interaction between age, cardiac magnetic resonance findings, and electrocardiogram parameters

Of the 63 study patients, 25 (40%) were younger than 18 years of age at the time of ECG (range 0.6–17.6 years). To confirm that indexing RV volumes for the BSA was an effective method to account for the heterogeneity in the RV volumes in this wide age spectrum, a regression analysis was performed between age at CMR and the indexed RV EDV. No correlation was noted between these two parameters ($r = +0.02$, $P > 0.85$).

Table 2 summarizes CMR findings based on age sub-groups at the time of the evaluation. To assess whether age was affecting the relationship between RV size, function, and ECG features, a separate regression for RV EDV and QRS duration was performed in the younger group. This confirmed that regardless of age, RV EDV remained strongly associated with the QRS duration ($r = +0.58$, $P = 0.002$).

Interaction between history of tricuspid valve repair, cardiac magnetic resonance findings, and electrocardiogram parameters

To investigate whether there was any confounding effect of history of tricuspid valve surgery prior to CMR on the relationship between CMR findings (RV morphology and function) and ECG parameters (namely QRS duration), we performed a separate regression analysis and found no significant interaction ($P = 0.8$ for interaction).

Table 3 Patient clinical profile according to electrocardiogram

	Overall cohort ($n = 63$)	Preserved ECG ($n = 32$)	Abnormal ECG ($n = 31$)	*P*-value
NYHA > 2, *n* (%)	14 (22)	3 (11)	11 (35)	0.05
Baseline O_2 saturation, %	95 ± 6	96 ± 4	94 ± 7	0.2
Cyanosis, *n* (%)	7 (11)	2 (6)	5 (16)	0.22
History of arrhythmias, *n* (%)	14 (22)	6 (19)	8 (26)	0.23
Cardiopulmonary exercise data	$n = 41$	$n = 19$	$n = 22$	
Peak RER	1.17 ± 0.04	1.19 ± 0.08	1.15 ± 0.09	0.25
Peak VO_2 (mL/kg/min)	23.6 ± 7	25.8 ± 6	21.8 ± 7	0.05
Peak HR (bpm)	168 ± 23	173 ± 24	165 ± 22	0.27
Peak HR (% predicted)	93 ± 10	94 ± 10	91 ± 10	0.45
VE/VCO_2	33 ± 8	30 ± 4	35 ± 10	0.12
O_2 saturation at peak exercise (%)	89 ± 11	94 ± 8	86 ± 12	0.02
Exercise-induced O_2 desaturation, *n* (%)	17 (41)	4 (25)	13 (65)	0.02
Severe tricuspid regurgitation, *n* (%)[a]	34 (54)	12 (37)	22 (71)	0.1
History of tricuspid valve surgery, *n* (%)	6 (10)	3 (9)	3 (10)	0.53

ECG, electrocardiogram; NYHA, New York Heart Association class; O_2, oxygen; RER, respiratory exchange ratio; VO_2, oxygen consumption rate; HR, heart rate; VE/VCO_2, minute ventilation-carbon dioxide production ratio slope.

[a]Severity of tricuspid regurgitation was defined as a regurgitant volume of >40%, measured using CMR-derived RV and LV stroke volume comparison, in the absence of additional significant valvular disease or intra-cardiac shunt.

Cardiothoracic ratio on chest radiograph, electrocardiogram, and cardiac magnetic resonance findings

Thirty-eight patients had a postero-anterior chest radiograph available for review. The median cardiothoracic ratio was 0.58 (interquartile range 0.51–0.65) with a range of 0.44–0.78, including 11 patients with a cardiothoracic ratio of >0.65. The mean QRS duration was not significantly different according to cardiothoracic ratio subgroup (124 ± 5 vs. 137 ± 13, $P = 0.8$). The cardiothoracic ratio had a moderate positive correlation with indexed, anatomic RV EDV ($r = 0.37$, $P = 0.01$). Atrialized RV volume was not significantly different between the two cardiothoracic ratio subgroups (93 ± 13 vs. 99 ± 25, $P = 0.9$).

Discussion

This study demonstrates that RV dysfunction and degree of atrialization in Ebstein anomaly correlates with the QRS duration and QRS fractionation on surface ECG. Delayed depolarization and abnormal activation of the RV are common findings in this disease and correlate with the RV size and function. Accordingly, a preserved ECG identifies a group of Ebstein patients with better exercise capacity and higher oxygen saturation during exercise.

Previous studies, mostly in adults with other congenital heart defects, have highlighted the correlation between the QRS duration and right ventricular size and clinical outcomes. Gatzoulis, in a seminal observation in survivors with repaired tetralogy of Fallot,[15] showed that the QRS duration correlated with the cardiothoracic ratio and RV diastolic volume on echocardiography, leading to the concept of electrical–mechanical interaction. Sung *et al.* showed that the rsR′ pattern and prolonged QRS duration in secundum atrial septal defect is not due to actual right bundle branch block, but is likely an effect of RV dilation.[16] A similar relationship between the QRS duration and right ventricular size and function has also been reported in patients with systemic RV.[17,18]

Right ventricular enlargement, dysfunction, and electrical instability, across the spectrum of congenital heart defects, predict a poor functional status and long-term prognosis.[19,20] Data from a large series of tricuspid valve interventions in patients with Ebstein anomaly confirmed that increased QRS duration was associated with increased mortality during the long-term follow-up.[21,22]

Abnormal RV activation has been reported in Ebstein anomaly.[8] Cappato *et al.*[23] reported pre-ablation intra-cavitary recordings during sinus rhythm in 21 patients with Ebstein anomaly. They observed fragmented electrograms recorded at the AV (anatomic) annular region, with a progressive change to normal activation on moving out of the posterior atrialized RV. Others have also reported delayed and abnormal electrograms recorded from the posterior part of the atrialized RV.[24]

We identified QRS fractionation in 18 of 63 patients (29%). QRS fractionation or notching has been described in various cardiac diseases, including dilated ischaemic and non-ischaemic cardiomyopathy, arrhythmogenic RV cardiomyopathy.[25,26] Although the exact mechanism of QRS fractionation remains speculative, it could be caused by inhomogeneous ventricular activation due to myocardial scar and/or ischaemia. Kastor *et al.*[9] found that, while activation within the atrialized portion of the RV could occur throughout most of the QRS phase, in the majority of patients studied, delayed depolarization in the atrialized RV correlated with slurring of the terminal portion of the QRS complex (denoted the 'second QRS'). Similarly, Tede *et al.*[27] have reported a high prevalence of late positive (and often 'bizarre'), low-voltage, signal-averaged potentials following the 'normal' QRS complex, in patients with Ebstein anomaly. These late potentials disappeared in all patients who underwent plication and resection of the atrialized right ventricle. Histological analysis of the resected atrialized RV in these patients demonstrated clustering of cardiomyocytes within a fibrous matrix. The increase in the QRS duration in Ebstein anomaly seems to be largely due to the increase in the terminal portion of the QRS (reflecting RV activation), as suggested by the strong correlation between the QRS duration and S-wave upstroke time.

Arrhythmogenic RV cardiomyopathy is a genetic model for RV disease in which progressive microscopic disruption of the RV myocardium and electrical conduction leads to unstable, delayed, and asynchronous ventricular potentials. In patients with advanced phenotype, ECG changes resemble those of patients with Ebstein anomaly.[29] We hypothesize that both these conditions share similar features such as anisotropic electrical conduction, fragmented electrical activity, and delayed prolongation of the electrical impulse. It is conceivable that in Ebstein anomaly the increase in RV volume (largely due to an enlarged atrialized RV), as well as the progressive myocardial fibrosis and scarring within the atrialized RV wall (*Figure 4*), may represent the morphologic substrate for QRS prolongation and fractionation. Of note, in our study, QRS fractionation was exclusively seen in patients with abnormally prolonged QRS duration.

Implications of preserved electrocardiographic findings

A preserved surface ECG was seen in just over one-half of our cohort. This subgroup had a smaller anatomic RV, higher RV EF, and a smaller atrialized RV. Clinically, these patients had a better NYHA functional class, better exercise tolerance, and less oxygen desaturation with exercise. A relatively preserved surface ECG appears to identify a low-risk group of patients with Ebstein anomaly in whom a more benign clinical course should be anticipated (*Figure 5*). Presently, the most accurate imaging modality to measure RV volume and function in Ebstein anomaly is CMR.[28] However, CMR is resource-intensive, expensive, and not widely available. Our findings indicate that an ECG-based algorithm could be used to stratify patients with more severe disease who require more intensive clinical surveillance from those patients with mild disease who could be followed with less-intensive follow-up.

Cardiothoracic ratio

Increased cardiothoracic ratio on postero-anterior chest X-ray has been associated with worse clinical outcome in patients with Ebstein anomaly.[1] Although this observation comes largely from studies including a large proportion of paediatric patients (including patients with neonatal recognition of the disease), it remains

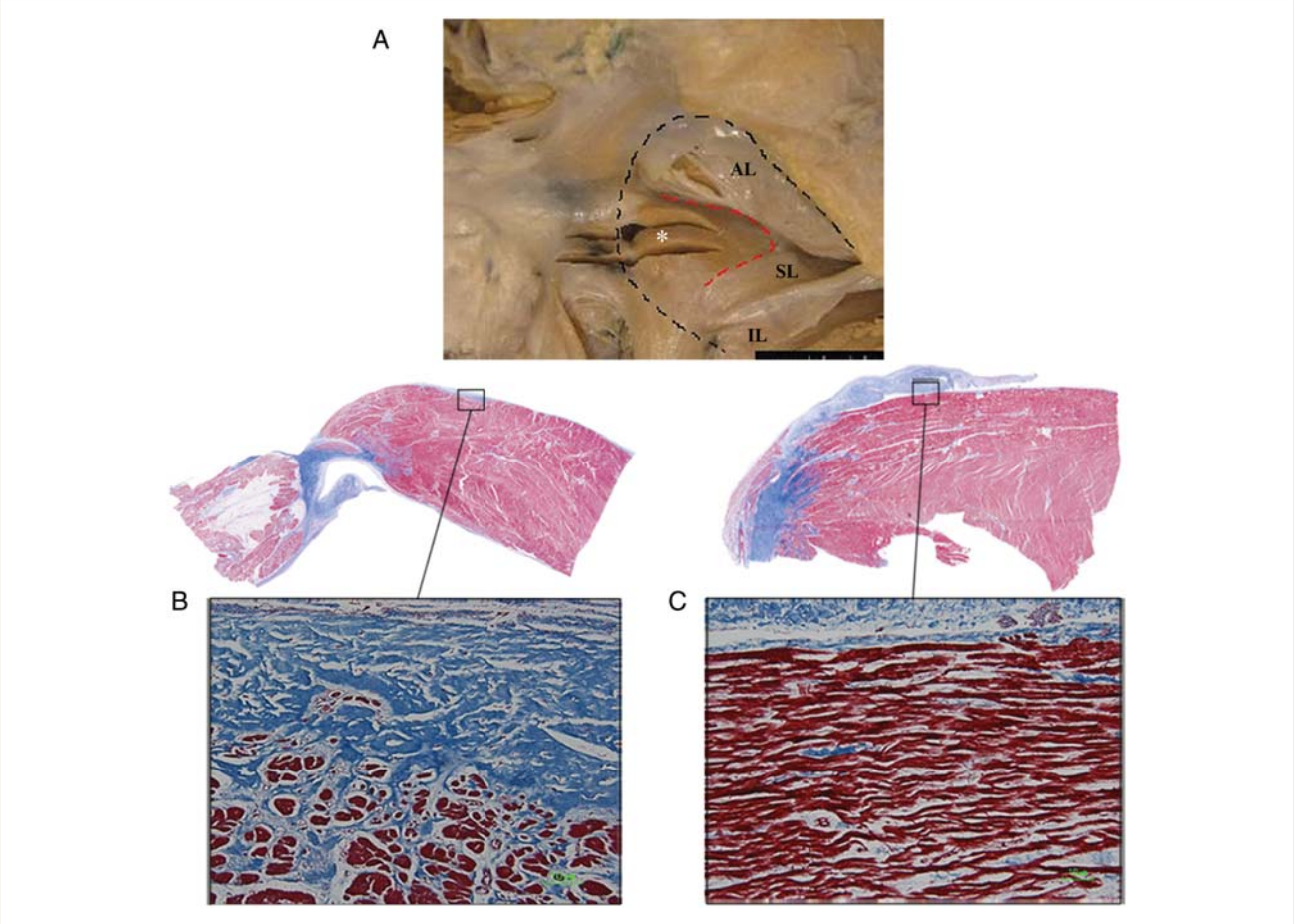

Figure 4 Pathological images of a heart with Ebstein anomaly. These histological sections are obtained from a heart specimen of a 25-year-old man with Ebstein anomaly of the tricuspid valve, not included in the study. (*A*) The right atrium is to the left of the image. The tricuspid annulus is indicated by black dots. The anterior leaflet (AL) and inferior leaflet (IL) attach to the annulus while the septal leaflet (SL) is displaced towards the apex (red dots). The section shown in (*B*) was taken as shown (*) through the atrialized portion of the ventricular septum. (*B*) Section stained with modified Masson trichrome crossing the tricuspid ring and including the portion of the ventricular septum from which the septal leaflet did not delaminate (atrialized portion). The higher magnification (×20) inset shows extensive interstitial fibrosis. (*C*) A similar section from a normal heart showing the formed septal leaflet of the tricuspid valve. The higher magnification (×20) inset shows more organized myocardial architecture, and less-interstitial fibrosis.

plausible that severe cardiomegaly on chest X-ray may be a marker of severe tricuspid valve regurgitation, myocardial dysfunction, and worse clinical outcome in the general population of patients with Ebstein anomaly.

In our study, we found a weak correlation between cardiothoracic ratio and RV EDV; no significant difference in the mean QRS duration and atrialized RV was identified between those patients with very abnormal cardiothoracic ratio (>0.65) and patients with less severe cardiomegaly. Cardiothoracic ratio is influenced by the degree of right atrial enlargement which is not accounted in the atrialized RV volume measure. In addition, severe atrial enlargement does not affect intra-ventricular conduction; this may explain why patients with severe cardiomegaly on chest X-ray may have relatively preserved QRS duration. To this regard, cardiothoracic ratio can be considered a marker of global cardiac enlargement; the ability of this index to measure degree of RV dysfunction and dilation, as well as the degree of RV atrialization, is limited.

Limitations

The cross-sectional design of our study does not allow us to evaluate the relationship between specific clinical outcomes and ECG findings. All related hypotheses are therefore exploratory in nature. In our institution, there is no standardized indication for CMR in patients with Ebstein anomaly. Usual clinical practice is to perform CMR before any intervention on the tricuspid valve or in adult patients with severe tricuspid regurgitation. Since our patients were selected for CMR, this population is likely skewed towards more severe disease severity.

Of note, we did not perform endocardial mapping studies in patients with and without QRS fractionation. Corroboration of our hypothesis that this finding represents delayed activation of

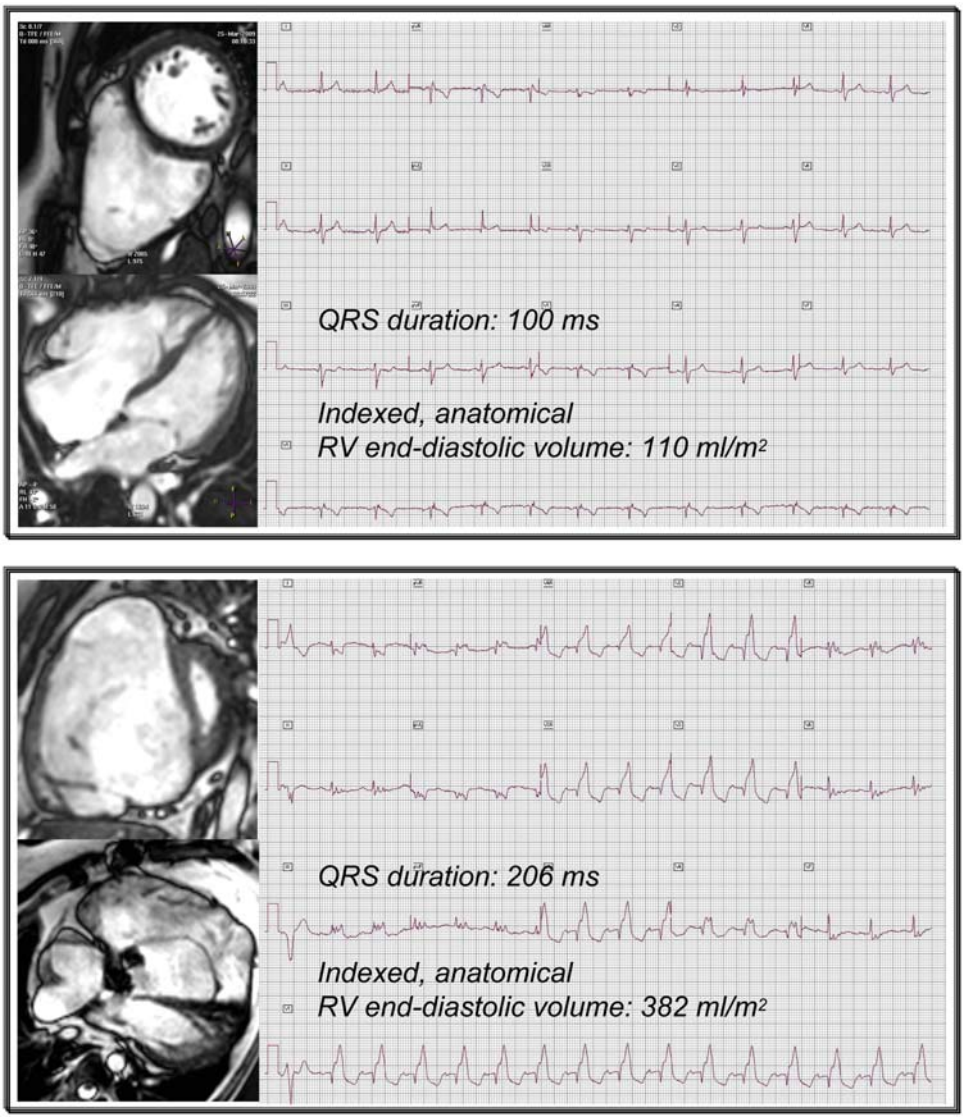

Figure 5 Spectrum of disease. Different representative electrocardiograms obtained from two patients with Ebstein anomaly (both included in the study cohort). These electrocardiograms are coupled with the respective cardiac magnetic resonance short-axis and four-chamber long-axis views. QRS duration and indexed, anatomic RV volumes are reported.

the atrialized RV in Ebstein anomaly requires further invasive study. Lastly, patients with Ebstein anomaly are often referred to congenital heart centres after surgical procedures, including RV or right atrial plasty or plication. As we specifically excluded such post-operative patients from the study, our findings should be cautiously generalized to patients with Ebstein anomaly who have undergone reduction in plasty operations as part of tricuspid valve repair/replacement.

Conclusion

Delayed depolarization and activation of the RV is frequent in patients with Ebstein anomaly. The QRS duration is inversely associated with functional RV systolic performance and is positively correlated with anatomic RV size. The presence of QRS fractionation is associated with a larger atrialized RV volume. Patients with milder ECG abnormalities have lower RV volume and better functional RV systolic performance, better exercise capacity, and less oxygen desaturation with exercise. We suggest that a preserved surface ECG in Ebstein anomaly identifies a subset of patients with milder morphological and functional abnormalities and overall a less-severe clinical profile.

Acknowledgements

We acknowledge the clinical and administrative staff of the Boston Adult Congenital Heart (BACH) and Pulmonary Hypertension Program, the Cardiac Magnetic Resonance Program, the Electrophysiology Service, and the Clinical Research Program of

Children's Hospital Boston, for their invaluable care and support for these patients. We thank David Annese, RT, for technical imaging support and Sue Fernandes, PA-C, for the support and logistics with computer database search. We are grateful to Emily Harris for illustrating the RV morphology in *Figure 2*.

Funding

This study has been supported, in part, by the Dunlevie Fund of the Boston Adult Congenital Heart (BACH) and Pulmonary Hypertension Program, Children's Hospital Boston and Brigham and Women's Hospital, Boston.

Conflict of interest: none declared.

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