Journal of the American Heart Association

ORIGINAL RESEARCH

Fetal Conduction Disease and Arrhythmia in Ebstein's Anomaly and Tricuspid Valve Dysplasia Assessed by Fetal Magnetocardiography

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BACKGROUND: Ebstein's anomaly and tricuspid valve dysplasia are associated with perinatal mortality approaching 50% and are among the most difficult fetal conditions to manage. Prediction of perinatal mortality is difficult and remains an active area of research. The usefulness of electrophysiologic indicators has not been investigated.

METHODS: Eighteen fetuses with a diagnosis of Ebstein's anomaly and tricuspid valve dysplasia were referred for fetal magnetocardiography evaluation. We assessed fetal rhythm, waveform intervals, and heart rate variability and reactivity.

RESULTS: Two subjects were lost to follow-up and 1 remains in utero. Of the other 15, 6 (40%) did not survive: 5 died within the first month of life, and 1 died at 4 months following surgery. Compared with normal fetuses, the Ebstein's anomaly and tricuspid valve dysplasia group exhibited significantly prolonged P-wave duration (P <0.01), PR interval (P <0.03), and QRS duration (P <0.01), along with an increased P/QRS amplitude ratio (P <0.01). The most prominent fetal magnetocardiography abnormalities included tall, broad P-waves suggestive of atrial enlargement and markedly prolonged QRS complexes consistent with bundle branch block. Of the 6 nonsurvivors, 4 had QRS durations ≥90 milliseconds (Z >4), and 4 demonstrated impaired atrioventricular conduction, including PR prolongation and second-degree atrioventricular block. Additionally, 4 showed absent heart rate variability and minimal reactivity. Abnormal findings were more prevalent in the third trimester than earlier in gestation.

CONCLUSIONS: Ebstein's anomaly and tricuspid valve dysplasia manifests distinct conduction and rhythm abnormalities detectable by fetal magnetocardiography but not by echocardiography. These electrophysiologic markers were associated with perinatal mortality and may serve as useful prognostic indicators.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03047161.

Key Words: arrhythmia ■ conduction system disease ■ Ebstein's anomaly ■ fetal magnetocardiography ■ tricuspid valve dysplasia

Fetal Ebstein's anomaly (EA) comprises a spectrum of rare congenital heart defects characterized by varying degrees of apical displacement of the septal and posterior tricuspid valve leaflets into the right ventricle, resulting in tricuspid regurgitation and right ventricular dysfunction.[1–3] Pulmonary atresia and/or insufficiency are frequently present, along with retrograde (left-to-right) shunting across the ductus arteriosus. Tricuspid valve dysplasia (TVD) presents similarly in utero but is anatomically distinct: although the valve leaflets are

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This manuscript was sent to Daniel E. Clark, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 10.

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CLINICAL PERSPECTIVE

What Is New?

- Using fetal magnetocardiography, we showed that fetuses with Ebstein's anomaly/tricuspid valve dysplasia manifest distinct conduction and rhythm abnormalities, such as marked QRS prolongation and atrioventricular block, which generally were not detectable by echocardiography.
- These electrophysiologic markers were associated with perinatal mortality and may serve as useful prognostic indicators.

What Are the Clinical Implications?

- Complex fetal cardiac disease may exhibit significant electrophysiological, as well as hemodynamic, dysfunction and can benefit from the combined use of fetal magnetocardiography and echocardiography.

Nonstandard Abbreviations and Acronyms

CTI	cardiac time interval
EA	Ebstein's anomaly
fMCG	fetal magnetocardiography
TVD	tricuspid valve dysplasia

dysplastic and often fail to coapt, they are not displaced. Perinatal mortality in EA/TVD exceeds that of most other forms of congenital heart disease,[4–7] reaching 45% in a large recent study.[8] Reported fetal risk factors for perinatal mortality include lack of antegrade flow across the pulmonary valve, pulmonary regurgitation, retrograde duct flow, prematurity, and hydrops.[7,9,10]

The association of EA/TVD with both automatic and reentrant arrhythmias, including atrial ectopy, is well known after birth,[11] but prenatally arrhythmias are surprisingly uncommon. Using echocardiography, Celermajer and co-workers reported sustained arrhythmia in only 1 of 21 (5%) cases of EA presenting in utero[12] and Freud and co-workers reported arrhythmia in just 15 of 234 (6%) fetuses with EA/TVD.[8]

In this study, we used fetal magnetocardiography (fMCG) to characterize the electrophysiology of fetuses with EA/TVD. Compared with fetal echocardiography, fMCG provides more precise and comprehensive assessments of fetal heart rate and rhythm, including conduction, repolarization, cardiac time intervals, and fetal heart rate variability.[13–19] The goal was to determine whether occult arrhythmias, repolarization abnormalities, or conduction system disease contribute to poor outcomes in fetuses with EA/TVD.

METHODS

De-identified data that support the findings of this study are available from the corresponding author upon reasonable request. The research was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board. Written informed consent was obtained from all subjects. One author (RTW) had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Subjects

A cohort of 18 subjects was identified from those evaluated at the University of Wisconsin-Madison Biomagnetism Laboratory. All were referred by pediatric cardiologists following a fetal echocardiographic diagnosis of EA or tricuspid valve dysplasia. No referred subjects were excluded from the study. fMCG recordings were performed at the earliest convenient time the subject could travel to the laboratory, typically within 1 week of referral. Medical records were reviewed to obtain fetal echocardiographic findings, pregnancy details, and early neonatal outcomes. Diagnoses (EA or TVD) and severity classifications (mild, moderate, or severe) were assigned by the referring institutions using previously established scoring systems.[20]

Data Acquisition

The fMCG recordings at the University of Wisconsin-Madison were made using a 37-channel SQUID (superconducting quantum interference device) system (Magnes, 4D Neuroimaging, Inc., San Diego, CA) or a 21-channel SQUID system (Model 624, Tristan Technologies, San Diego, CA). Subjects underwent 4 to 6 recordings, each lasting 10 minutes.

Signal Processing and Averaging

A digital filter with a 1 to 80 Hz passband was applied to band-limit the data. Signal processing was used to remove the maternal MCG and other interferences.[21] Signal averaging was performed to increase the signal-to-noise ratio of the waveforms.[22] The waveforms were computed during periods of fetal quiescence, using the QRS complexes as triggers. Typically, 50 to 100 consecutive complexes were averaged, depending on the signal-to-noise ratio of the raw recording.

Cardiac Time Intervals, Waveform Amplitudes, and Repolarization Characteristics

Cardiac time intervals (CTIs), which included the RR interval, P-wave duration, PR interval, QRS duration, QT interval, and heart rate–corrected QT interval, were measured independently from averaged fMCG

Table. **Summary of EA/TVD Cohort**

Subject	Disease severity	Fetal echo and clinical findings	Arrhythmia	Ectopy	STT	BBB	GA (wks)	P (ms)	PR (ms)	QRS (ms)	QTc (ms)	RR (ms)	P/QRS	SDRR (ms)
1	TVD severe	Sustained atrial flutter, digoxin, severe TR			X	X	32–0/7	69†	121	96†	395	411	0.22†	4.3‡
2	EA			Isolated PACs			21–1/7	50	102	48	319	396	0.19†	5.7
3*	EA/Ao stenosis	Hydrops, severe TR and MR, critical aortic stenosis	Intermittent 2° AVB				31–2/7	83†	122†	66†	350	404	0.23†	3.6‡
4*	EA severe	24 wks: mild displacement, mild TR 31 wks: history of atrial flutter, severe TR, PI, moderate hydrops; 34 wks: no flutter, heart enlarged	Low-for-GA heart rate			X	30–6/7	115†	194†	96†	365	501†	0.73†	5.5
5*	EA severe	28 wks: TV in RV, PI, some forward flow, 1:1 tachycardia, digoxin 30 wks: pleural effusion, worsening hydrops	Incessant 2:1 atrial flutter			X	29–5/7	43	139†	102†	318	311‡	0.13	2.1‡
6*	EA severe	25 wks: CT ratio 52%, TD, severe TR, circular retrograde flow; 30 wks: severe TR, PI, no hydrops, CT ratio 57%	Intermittent 2° AVB		X		25–6/7	61†	98	74†	424	417	0.05	3.7
							33–6/7	46	85	102†	429	419	0.08	3.5‡
7	TVD severe	28 wks: non-coaptation, severe TR, marked dilated atrium and ventricle; Follow-up: enlarged heart, 6:10 risk score			X	X	29–6/7	56	104	60†	467	412	0.12	5.4
							34–6/7	58	96	72†	403	428	0.19†	5.8
8	EA mild	Mild displacement and moderate regurgitation					21–2/7	47	93	52	325	400	0.29†	7.0
9	EA severe	30 wks: functional PA, mild to moderate TR, severe RV hypertension, RA mildly enlarged; 36 wks: abnormal ductus venosus flow, PA, worsening RV hypertension					30–4/7	50	119	45	456	412	0.18†	6.0
10	EA moderate	32 wks: RV dysfunction, severe displacement, PA, no hydrops, RA enlarged		Frequent PACs and PVCs			25–2/7	42	110	49	397	424	0.49†	9.0
11	EA moderate					X	30–4/7	69†	117	83†	455	437	0.23†	4.4
12	EA severe	33 wks: severe displacement and TR, 4 mm pericardial effusion, reverse circulation, PI, and low RV pressure				X	22–4/7	73†	108	91†	467	422	0.33†	6.5

(continues)

Table. (Continued)

Subject	Disease severity	Fetal echo and clinical findings	Arrhythmia	Ectopy	STT	BBB	GA (wks)	P (ms)	PR (ms)	QRS (ms)	QTc (ms)	RR (ms)	P/QRS	SDRR (ms)
13	EA	Possible tachycardia		Isolated PVCs	X	X	34–5/7	46	106	81†	407	430	0.14	6.1
14*	TVD moderate	Massive RV dilation, PA, small PA retrograde flow, arrhythmia, died at 4 mo following bilateral PA plasty and shunt revision		Frequent PACs and PVCs		X	31–5/7	53	113	90†	381	453§	0.21†	8.3
15	EA moderate	Born alive			X	X	32–5/7	48	105	64†	401	414	0.14	7.1
16*	EA mild	Sinus tachycardia 170s, PACs, born alive					25–5/7	40	100	41	388	389	0.11	4.2‡
17	EA moderate	Born alive			X	X	31–6/7	62†	117	81†	445	403	0.24†	6.0
							35–5/7	72†	129†	96†	443	412	0.17†	7.6
18‖	EA mild	Possible PACs; in utero				X	30–0/7	43	93	70†	467	433	0.22†	8.3
Mean±SD					33%	61%	30±4	59±18	113±23	75±20	398±58	416±34	0.23±0.15	5.7±1.8

Ao indicates aortic; AVB indicates second-degree atrioventricular block; BBB, bundle branch block; CT ratio, cardiothoracic ratio; EA, Ebstein's anomaly; GA, gestational age; MR, mitral regurgitation; P/QRS, P/QRS amplitude ratio; P, P-wave duration; PA, pulmonary atresia; PAC, premature atrial contraction; PI, pulmonary insufficiency; PR, PR interval; PVC, premature ventricular contraction; QRS, QRS duration; QTc, heart rate–corrected QT interval (Bazett's formula); RA, right atrium; RV, right ventricle; SDRR, standard deviation of RR intervals; STT, ST-T changes; TD, tricuspid dysplasia; TR, tricuspid regurgitation; and TVD, tricuspid valve dysplasia; "X" signifies that the subject exhibited the abnormality.

*Died.

†>95% prediction interval.

‡<95% prediction interval.

§U-wave.

‖In utero.

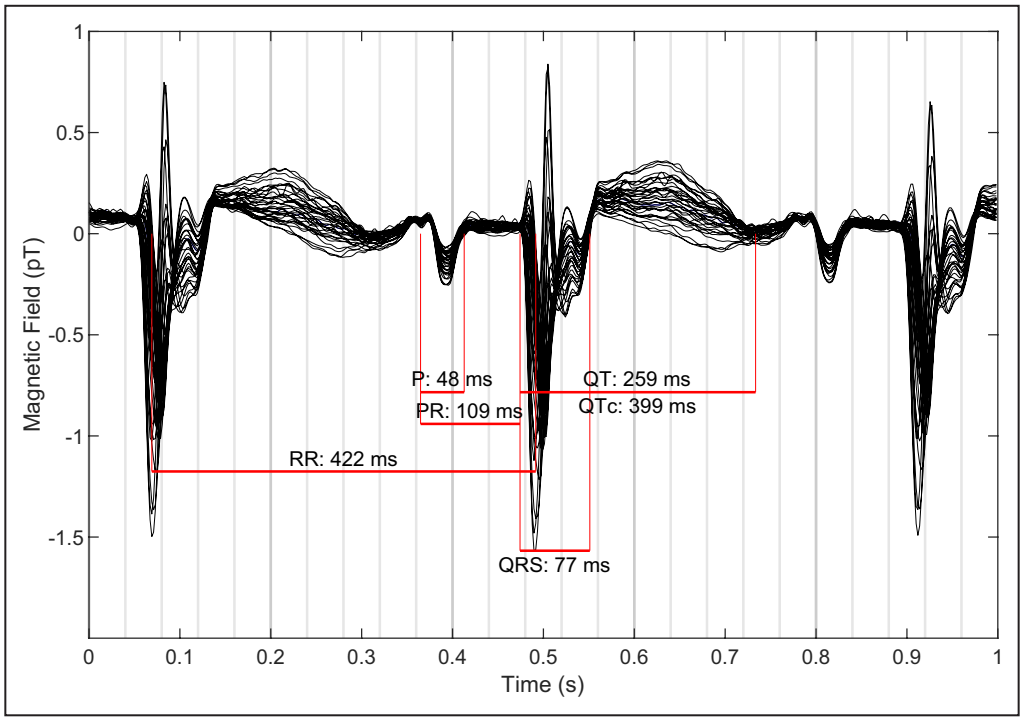


Figure 1. Complete bundle branch block and ST-T changes in fetus #13.
PR indicates PR intervals; QTc, heart rate–corrected QT interval; and RR, RR intervals.

waveforms by 2 pediatric cardiologists (AW-G and JFS). In addition, we measured the peak-to-peak amplitudes of the P-waves and QRS complexes and calculated the P/QRS amplitude ratio. Giant P-waves[23] were defined as P/QRS amplitude ratios with *Z* scores >4, based on gestational age–adjusted prediction intervals derived from normal fetuses.[22] ST-T abnormalities were defined as ST segment depression and/or elevation exceeding 10% of the amplitude of the preceding QRS complex.[24]

Fetal Heart Rate Variability and Reactivity

We assessed fetal heart rate variability by computing the SD of RR intervals in multiple 30-second intervals. This is the simplest of the commonly used measures of heart rate variability.[25,26] Ectopic beats and R-R intervals corresponding to baseline variations >15 bpm were discarded to exclude irregular rhythm, accelerations, and decelerations. Fetal heart rate reactivity was assessed based on the coincidence of fetal heart rate accelerations with fetal movement, using fMCG actography to compute tracings of fetal trunk movement.[27]

Normal Controls

The CTIs were compared with published data from a study of 132 normal fetuses performed by our laboratory,[22] which characterized the gestational age dependence of the CTIs over the last half of pregnancy and established 95% prediction intervals. Fetal heart rate variability was compared with data from a separate cohort of 61 consecutive recently studied normal fetuses because the aforementioned study of 132 fetuses did not assess fetal heart rate variability. *Z* scores were computed to normalize measurements relative to gestational age and to identify values that deviated substantially from the age-specific mean. Each *Z* score was calculated as $Z=(X-\mu)/\sigma$, where X is the observed value, μ is the gestational age-adjusted mean, and σ is the gestational age–adjusted SD. The mean±SD at each gestational age were estimated from the regression line and 95% prediction interval (corresponding to $Z=1.96$), assuming a normal distribution.

Statistical Analysis

Continuous data are presented as mean±SD. Comparison of cardiac time intervals, P/QRS amplitude ratio, and fetal heart rate variability between the EA/TVD subjects and normal subjects was performed using 2-tailed, 2-sample Welch's *t* tests. For fetal heart rate variability, a subanalysis was performed to compare EA/TVD and normal fetuses before and after the onset of the third trimester. One subject (#5) with incessant atrial flutter was excluded from the statistical analysis. For subjects with serial data, only data from the last session were used to avoid biasing the results. A 1-tailed paired *t* test was used to determine whether CTIs increased between sessions in subjects with

serial data. A P value <0.05 was considered statistically significant for all tests. Statistical analyses were performed using MATLAB (R2024a, The MathWorks Inc., Natick, MA).

RESULTS

Eighteen fetuses with a diagnosis of EA or TVD met the inclusion criteria. Fifteen underwent a single evaluation, while 3 were studied twice, yielding a total of 21 recording sessions (Table). The mothers were healthy with no reported family history of structural heart disease or arrhythmia. Their mean age was 29.0±4.0 years. The mothers of subjects #4 and #10 were Hispanic; the others were White. The mothers of subjects #1 and #5 were taking digoxin for fetal atrial flutter. The mean gestational age at the time of measurement was 29.0±4.0 weeks. Two subjects were lost to follow-up. Of the 16 with follow-up, 6 (40%) died postnatally: 1 (subject #6) in the delivery room immediately after birth, 4 (subjects #3, #4, #5, #16) within the first month before undergoing surgery, and 1 at 4 months following surgical intervention.

Rhythms and Conduction and Repolarization Abnormalities

The fetuses were predominantly in sinus rhythm, except for subject #5, who showed incessant 2:1 atrial flutter at a rate of 193 bpm and did not return for a follow-up study. In addition, 2 fetuses showed intermittent 2° atrioventricular block, 1 at 24 weeks gestation showed a baseline fetal heart rate of 120 bpm (<5th percentile), and 4 showed ventricular and/or atrial ectopy (Table). Fetus #1 was referred with a diagnosis of atrial flutter and was treated with transplacental digoxin, but did not show tachycardia during the fMCG. The most common conduction abnormality was bundle branch block, seen in 12 of 18 fetuses (67%). Repolarization abnormalities, consisting of ST-T changes, were seen in 6 of 18 (33%; Figure 1).

Cardiac Time Intervals, P/QRS Amplitude Ratio, and Heart Rate Variability

Compared with normal fetuses, the EA/TVD fetuses showed increases for the following parameters: P-wave duration (59.3±19.2 milliseconds versus 43.8±8.8

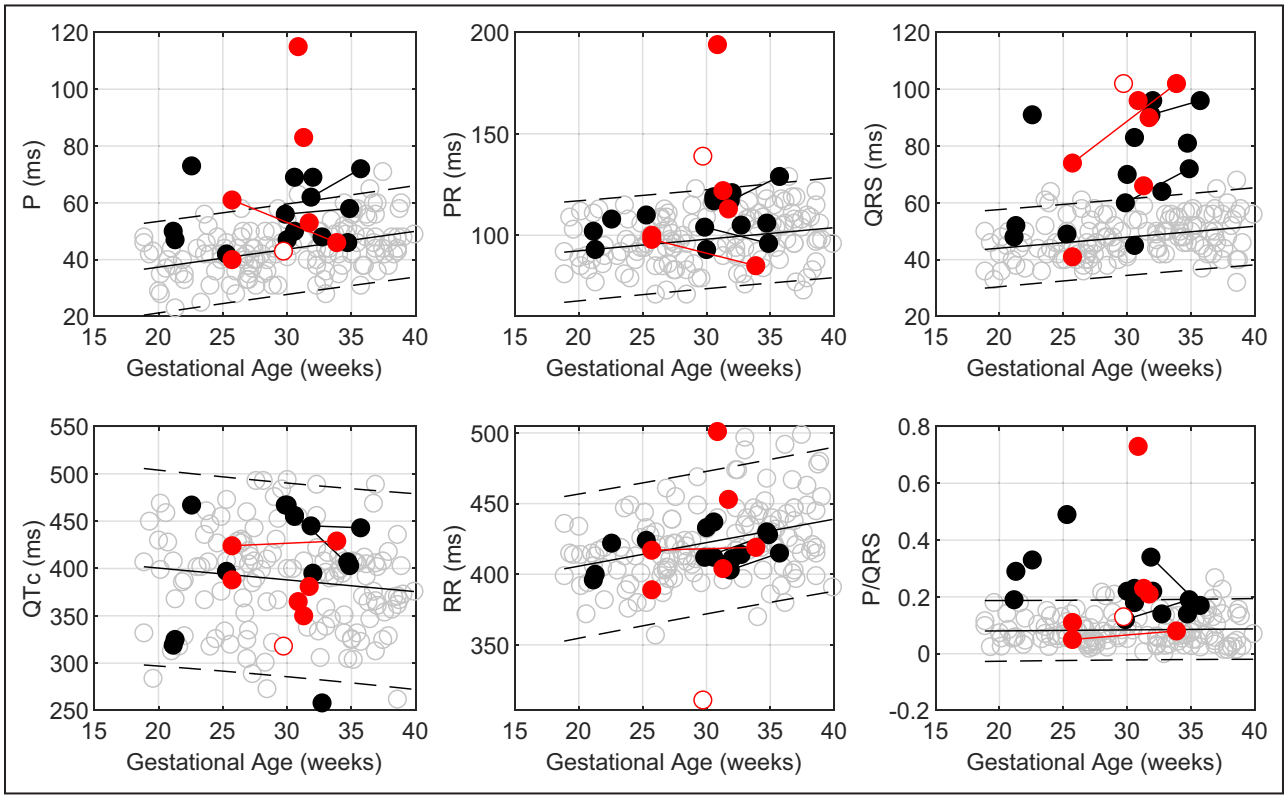


Figure 2. Fetal cardiac time intervals and P/QRS amplitude ratio in EA/TVD subjects.
Normal fetus data are shown as gray open circles and their linear regression line is shown as a solid line. The correlations with gestational age were significant for P (R^2=0.17, P <0.001), PR (R^2=0.07, P=0.0025), QRS (R^2=0.10, P <0.001), and RR (R^2=0.13, P <0.001), but not for QTc or P/QRS amplitude ratio. The 95% prediction interval (Z=±1.96) is shown by the dashed lines. The red dots correspond to subjects #3, #4, #6, #14, and #16 that died. The red open dot corresponds to subject #5 that died and had incessant atrial flutter. Serial data from 3 subjects are connected by lines. EA indicates Ebstein's anomaly; QTc, heart rate–corrected QT interval; PR, PR intervals; RR, RR intervals; and TVD indicates tricuspid valve dysplasia.

milliseconds, P <0.01), PR interval (112.5±24.1 milliseconds versus 98.1±12.7 milliseconds; P <0.03), QRS duration (73.7±20.6 milliseconds versus 47.9±7.1 milliseconds; P <0.01), and P/QRS amplitude ratio (0.24±0.16 versus 0.08±0.05; P <0.01). Among subjects with serial data (n=3), QRS duration was significantly longer in the follow-up session (90.0±13.0 milliseconds), compared with the first (71.7±8.7 milliseconds; P <0.05).

Figure 2 illustrates the variation of the CTIs and P/QRS amplitude ratio with gestational age. Many individual data points from the EA/TVD fetuses exceeded the normal range, as defined by the 95% prediction intervals derived from the data of normal fetuses, with most outliers occurring during the third trimester. The most visually striking waveform features pertained to the P-waves and QRS complexes. P-waves were tall in 13 of 18 EA/TVD fetuses (73%) and wide in 7 of 18 (39%), relative to the upper bound of the 95% prediction intervals. Giant P-waves, defined by a P/QRS amplitude ratio with a Z score >4, were observed in 4 of 18 cases (22%). Prolonged QRS complexes were seen in 13 of 18 fetuses (73%), with 6 (33%) exhibiting durations >90 milliseconds, corresponding to Z scores >4.

Fetal heart rate variability was significantly lower in EA/TVD fetuses (6.02±1.70 milliseconds) compared with normal fetuses (7.28±1.98 milliseconds; P <0.05). As illustrated in Figure 3, fetal heart rate variability increased with gestational age in normal fetuses, reflecting maturation of the autonomic nervous system.[14] This trend, however, is notably absent in the EA/TVD data. Before 28 weeks' gestation, there was no significant difference (P=0.66) in fetal heart rate variability between EA/TVD (6.45±1.77 milliseconds) and normal fetuses (6.06±1.40 milliseconds). After 28 weeks, however, heart rate variability was significantly lower in the EA/TVD fetuses (5.84±1.72 milliseconds), compared with normal controls (8.37±1.80 milliseconds, P <0.01).

FMCG Characteristics of Nonsurvivors

One subject (#16) that died was studied at 25–5/7 weeks and showed a normal fMCG. The other 5 nonsurvivors were studied after this time and showed multiple abnormal characteristics. All 5 showed QRS prolongation (>95th percentile), and 4 showed QRS duration ≥90 milliseconds, corresponding to Z >4. Another notable feature was impaired atrioventricular conduction. Subject #3 showed PR prolongation and intermittent second-degree atrioventricular block. Subject #4 showed extreme PR prolongation (194 milliseconds; Figure 4A), as well as a fetal heart rate <5th percentile for gestational age. Subject #6 showed intermittent second-degree atrioventricular block (Figure 4C). Subject #5 with atrial flutter and 2:1 atrioventricular conduction showed conducted beats with a PR interval of 139 milliseconds (Figure 4B), which is much longer than the PR interval seen in fetuses with atrial flutter and structurally normal hearts.[28] Fetal heart rate variability was also abnormal in 2 nonsurvivors (#4, #6). They showed extended periods of flat, nonreactive heart rate tracings (Figures 5A and 5C) not seen after 28 weeks' gestation in normal fetuses. One other fetus that died (#5) also showed reduced heart rate variability and reactivity (Figure 5B); however, this fetus was in tachycardia, which is commonly associated with low heart rate variability.

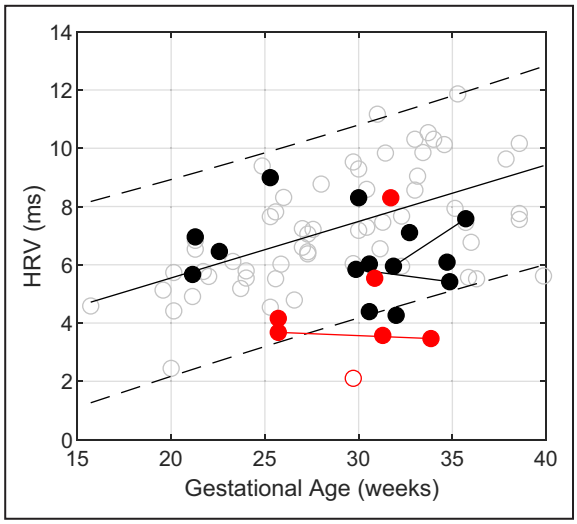


Figure 3. Fetal heart rate variability measured as the SD of the RR intervals.
Normal fetus data are shown as gray open circles, and their linear regression line is shown as a solid line. The correlation with gestational age was statistically significant (R^2=0.32, P <0.01). The 95% prediction interval is shown by the dashed lines. The red dots correspond to subjects that died. The red open dot corresponds to subject #5 that died and had incessant tachycardia. Serial data from 3 subjects are connected by lines. HRV indicates heart rate variability.

DISCUSSION

In this fMCG study of fetuses with EA/TVD, perinatal mortality (6/15 with follow-up) and the incidence of arrhythmia and occult conduction abnormalities were high. Predictors of demise included poor hemodynamic status identified by fetal echocardiography and extreme QRS prolongation, often accompanied by impaired atrioventricular conduction and low fetal heart rate variability.

The fMCG frequently showed tall, wide P-waves and PR prolongation compatible with atrial enlargement and wide QRS complexes indicative of bundle bunch block. While these features are known to occur postnatally in EA/TVD,[1,29] the degree of QRS prolongation seen here was remarkable. Four of 6 nonsurvivors



Figure 4. fMCG rhythm strips from subjects that died and were studied after 28 weeks' gestation. **A**, Subject #3 showed intermittent second-degree atrioventricular block. (**B**), Subject #4 showed giant P-waves and extreme PR and QRS prolongation, **(C)** Subject #5 showed incessant atrial flutter with wide QRS complexes indicative of bundle branch block. The nonconducted P wave is obscured by the QRS. The PR interval of the conducted beats is 140 milliseconds. (**D**), Subject #6 showed several episodes of second-degree atrioventricular block. Notice that PP is shorter for PP intervals that embrace QRS complexes than for those that do not, indicative of ventriculophasic sinus arrhythmia. **(E)** Subject #14 showed frequent ectopy and U-waves. fMCG indicates fetal magnetocardiography.

showed QRS duration ≥90 milliseconds, corresponding to Z >4. The QRS complexes were wider than we have observed in any other fetal arrhythmia except for ventricular rhythms in severe cases of cardiomyopathy, atrioventricular block, or long QT syndrome.

PR interval was significantly prolonged compared with that of normal fetuses, and 4 of 6 fetuses that died showed impaired atrioventricular conduction, including overt PR prolongation and intermittent second-degree atrioventricular block, in conjunction with QRS prolongation. These findings were unexpected. EA/TVD is much more commonly associated with tachyarrhythmia than bradyarrhythmia.[3,30,31] Among our subjects, the referral diagnoses noted tachyarrhythmia in 5 fetuses and bradyarrhythmia in none. It is likely that second-degree atrioventricular block is often missed by ultrasound because of its intermittency and ability to mimic V-shaped sinus deceleration. In contrast, these events are readily captured by fMCG. We speculate that impaired atrioventricular conduction is a sign of more extensive damage to the conduction system and can serve as a useful prognostic indicator. The mechanism of impairment is uncertain but may involve malformation of the conduction system[32] or mechanical stress on the atrioventricular node and conduction system resulting from ventricular pressure imbalance or apical displacement of the tricuspid valve leaflets. Another novel finding was low fetal heart rate variability and low and/or abnormal reactivity, which are ominous indicators of fetal distress. Four fetuses that died showed extended periods of flat heart rate tracings and abnormal reactivity not seen in normal third trimester fetuses.

One subject that died had a normal fMCG at 25–5/7 weeks' gestation. The other nonsurvivors were

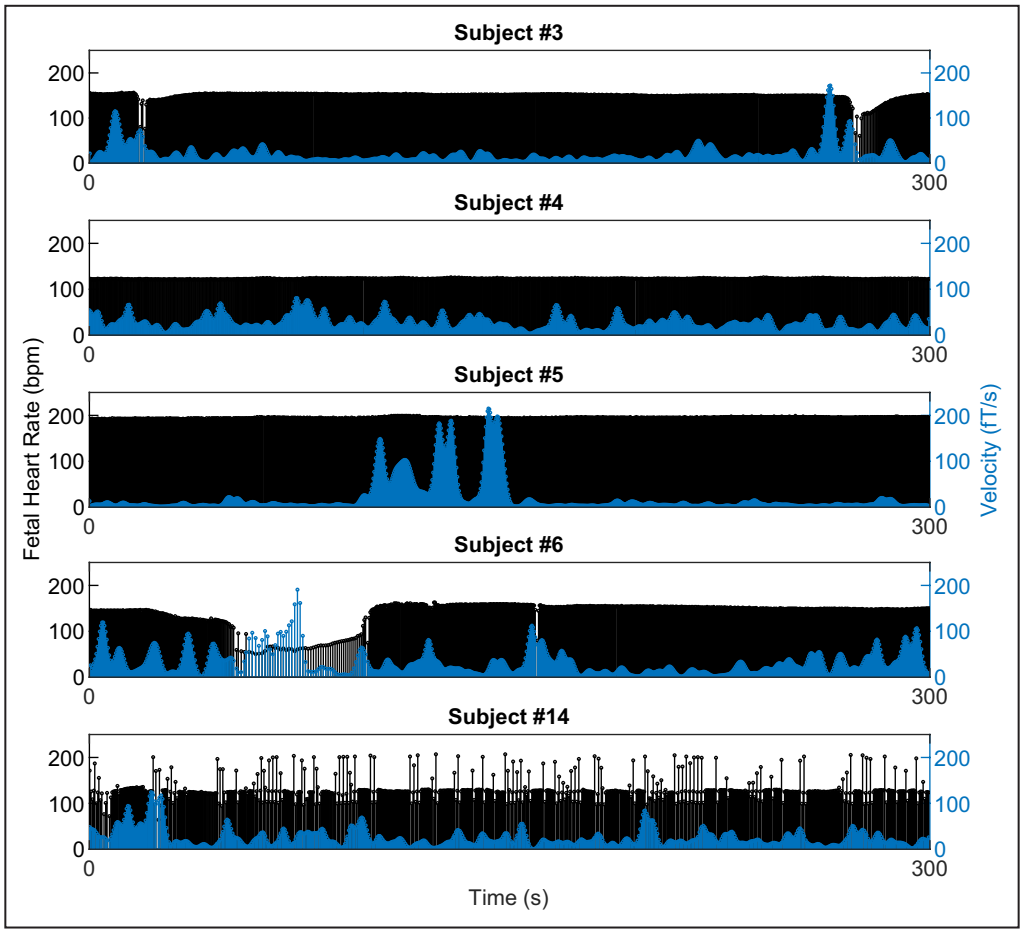


Figure 5. Fetal heart rate (black) and movement (blue) tracings from 5 subjects that died and were studied after 28 weeks' gestation.
A, Subject #3 showed flat heart rate tracings with brief episodes of type II second-degree atrioventricular block. These episodes were associated with fetal movement but, in contrast to normal heart rate reactivity, the heart rate decelerated before atrioventricular block. **(B)**, Subject #4 showed periods of flat, nonreactive fetal heart rate tracings in sinus rhythm. **(C)**, Subject #5 showed flat nonreactive fetal heart rate tracings in tachycardia, **(D)** Subject #6 showed an extended period of second-degree atrioventricular block, preceded by sinus slowing, and periods of flat nonreactive fetal heart rate tracings. **(E)**, Subject #14 showed an irregular heart rate and rhythm due to frequent ectopy.

studied later in pregnancy and all had abnormal fMCGs. In general, QRS prolongation, impaired atrioventricular conduction, low heart rate variability, and other indicators of compromise were more common after ≈28 weeks. Three subjects had serial data, and they showed progression of QRS prolongation between sessions. These findings are compatible with those of Tierney and coworkers, who noted that echo indices obtained before 24 weeks were not reliable indicators of physiologic status later in pregnancy. They concluded that progressive hemodynamic compromise was common, and that the absence of factors associated with poor outcome early in pregnancy may be falsely reassuring.

The mortality and morbidity of EA/TVD exceeds that of other predominantly right-sided lesions such as Tetralogy of Fallot, pulmonary atresia, and double-outlet right ventricle.[33] In a multicenter study of 243 fetuses with EA/TVD diagnosed at mean gestational age 27±6 weeks, Freud and co-workers[8] reported 41 fetal demises (17%), 15 terminations (6%), and 11 lost to follow-up (6%). Of 176 live-born patients, 56 (32%) died before neonatal hospital discharge, yielding an overall perinatal mortality of 45%, similar to our study. Multifactor analysis showed pulmonary regurgitation, indicative of circular shunt physiology, to be the most powerful hemodynamic indicator of risk.

EA/TVD encompasses a complex spectrum of disorders with variable presentations. Prognosis, prenatal counseling, and management are difficult and potentially can benefit from additional physiological assessments. In this regard, the relevance of electrophysiologic indicators contributing to poor outcome in EA/TVD was previously unknown because they could not be assessed using echocardiography. Using fMCG, we

showed that EA/TVD manifests conduction and heart rate abnormalities (STT changes, atrioventricular block, bundle branch block, and low heart rate variability) that can aid in prediction of ventricular dysfunction and sudden death. These were more common during the third trimester, suggesting a need for increased vigilance during late pregnancy. The usual practice of delivering at term, which improves outcomes for most types of congenital heart disease, may be inadvisable for some fetuses with EA/TVD.[34] Ultimately, new pharmacologic and surgical strategies may be needed in the treatment of the most severely affected fetuses. Nonsteroidal anti-inflammatory drugs to restrict retrograde duct flow are one such strategy currently under evaluation.[35,36]

Limitations of the study include the modest sample size, possible referral bias, limited serial data, and incomplete follow-up data. EA/TVD is a rare disease, and subjects were referred from multiple centers. It is possible that referrals were biased toward severe cases; however, the mortality of our cohort is slightly lower than that of a large recent study, suggesting that our cohort did not have a higher-than-normal incidence of severe disease. Most subjects traveled several hours or longer to participate, which limited the number of serial studies. Involvement of multiple centers also increased the difficulty of obtaining postnatal follow-up data.

In conclusion, our study is novel in its use of fMCG to directly assess electrophysiology in fetuses with EA/TVD. This enabled diagnosis of conduction system disease, including atrioventricular block and severe bundle branch block, which was unexpected and associated with perinatal demise. The findings exemplify the usefulness of fMCG as an adjunct to fMCG for evaluation of fetal cardiac disease.

ARTICLE INFORMATION

Received May 9, 2025; accepted June 26, 2025.

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Sources of Funding

This work was supported by NIH grants R01HL063174 and R01HL143485.

Disclosures

None.

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