Published in final edited form as:

Am J Cardiol. 2007 August 15; 100(4): 661–665. doi:10.1016/j.amjcard.2007.03.081.

Atrial and Ventricular Rate Response and Patterns of Heart Rate Acceleration during Maternal–Fetal *Terbutaline* Treatment of Fetal Complete Heart Block

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Abstract

Terbutaline is used to treat fetal bradycardia in the setting of complete heart block (CHB); however, little is known of its effects on atrial and ventricular beat rates or patterns of heart rate (HR) acceleration. Fetal atrial and ventricular beat rates were compared before and after transplacental terbutaline treatment (10 to 30 mg/day) by fetal echocardiography in 17 fetuses with CHB caused by immune-mediated damage to a normal conduction system (isoimmune, n = 8) or a congenitally malformed conduction system associated with left atrial isomerism (LAI, n = 9). While receiving terbutaline, 9 of the 17 fetuses underwent fetal magnetocardiography (fMCG) to assess maternal HR and rhythm, patterns of fetal HR acceleration, and correlation between fetal atrial and ventricular accelerations (i.e., AV correlation). Maternal HR and fetal atrial and ventricular beat rates increased with terbutaline. However, terbutaline's effects were greater on the atrial pacemaker(s) in fetuses with isoimmune CHB and greater on the ventricular pacemaker(s) in those with LAI-associated CHB. Patterns of fetal HR acceleration also differed between isoimmune and LAI CHB. Finally, despite increasing HR, terbutaline did not restore the normal coordinated response between atrial and ventricular accelerations in isoimmune or LAI CHB. In conclusion, the pathophysiologic heterogeneity of CHB is reflected in the differing effect of terbutaline on the atrial and ventricular pacemaker(s) and varying patterns of HR acceleration. However, regardless of the cause of CHB, terbutaline augments HR but not AV correlation, suggesting that its effects are determined by the conduction system defect rather than the autonomic control of the developing heart.

Fetal complete heart block (CHB) is a rare condition, occurring in approximately 1 of 15,000 pregnancies. Fetal CHB that occurs in association with maternal immunoglobulin-G Sjögren antibodies (i.e., isoimmune CHB) is believed to be a result of immune-mediated fibrosis disrupting continuity between the atrium and the atrioventricular (AV) bundle relatively late in cardiogenesis,^{1–3} whereas CHB associated with congenital cardiac malformations such as left atrial isomerism (LAI) is believed to result from maldevelopment of the conduction system early in cardiogenesis, probably during pattern formation of the specialized versus working myocardium.^{4–7} With such morphologic and etiologic

heterogeneity, it might be expected that the electrophysiologic characteristics of the atrial and ventricular pacemakers in fetuses with CHB would differ in response to pharmacologic heart rate (HR) augmentation with a β agonist such as terbutaline.^{8–10} Using the technique of fetal magnetocardiography (fMCG)—the only high-resolution fetal electrocardiography technique with the capacity for beat-to-beat analysis over many hours—we observed patterns of HR accelerations, the atrial and ventricular pacemaker response, and the ventricular rate response to atrial accelerations (i.e., AV correlation) during terbutaline treatment in fetuses with isoimmune and LAI-associated CHB. Our results lead us to postulate a mechanism for the observed difference in acceleration patterns between isoimmune and LAI CHB as it relates to the nature and timing of the conduction system defect.

Methods

We reviewed the perinatal cardiology database from 2 large perinatal centers for fetuses presenting with CHB between 1996 and 2006 that received terbutaline to augment ventricular rate. After the initial diagnosis, fetuses were evaluated by echocardiography (Sequoia; Siemens, Mountain View, California) performed at the referring perinatal center every week. At each visit, atrial and ventricular rates were measured by Doppler interrogation of the outflow tracts (ventricular rate) or M-Mode of the atrium (atrial rate). Mean atrial and ventricular rates were averaged from 10 consecutive cycle lengths. Charts were reviewed for perinatal and neonatal outcome, gestational age at diagnosis, onset of terbutaline treatment, fMCG and delivery, duration of terbutaline treatment, and whether the infant was paced. Pretreatment maternal HR was measured during obstetric visits.

When echocardiography demonstrated a decrease in the mean fetal HR to <56 beats/min, mothers were given terbutaline 2.5 to 7.5 mg orally every 4 to 6 hours (total daily dose 10 to 30 mg). We chose to start terbutaline treatment because of reports suggesting poor outcome of fetuses with HR <56 beats/min.¹¹ Because we anticipated treatment over many weeks, the dose of terbutaline was titrated to maintain a maternal HR at rest between 95 and 115 beats/min. Terbutaline was not well tolerated at higher doses due to frequent maternal complaints of palpitations. During the course of treatment, no mother developed pulmonary edema or glucose intolerance. Mothers with fetal isoimmune CHB also received oral dexamethasone (4 mg/day until 30 weeks, and then the dose was tapered by 1 mg every other week) from the time of diagnosis until 36 weeks' gestation or delivery.

Nine of the 15 terbutaline-treated fetuses underwent fMCG at 20 to 37 weeks of age at the Division of Medical Physics at the University of Wisconsin in Madison using a 37-channel biomagnetometer in a specially constructed low permeability room, as previously described.¹² QRS duration was measured from the signal-averaged fMCG. Five to 10 tracings each of 10 to 15-minute duration were recorded from multiple probe positions then digitized and band-pass filtered (1 to 80 Hz). Maternal HR (mean and range) and rhythm were also measured during fMCG.

Before the beginning of terbutaline treatment, mean beat rates of the fetal atrial and ventricular pacemakers and maternal HRs were measured by echocardiography (fetuses) or auscultation (mothers) and compared with posttreatment values by Wilcoxon signed-rank test for nonnormally distributed data. We compared differences in the atrial and ventricular responses to terbutaline between fetuses with isoimmune CHB and those with LAI CHB by Wilcoxon 2-sample test, a nonparametric equivalent to the independent 2-sample *t* test. Differences in gestational age at delivery and onset of treatment, as well as duration of terbutaline treatment were compared between LAI CHB and isoimmune CHB by *t* test. Data are reported as means $\pm$ SD. A *p* value <0.05 was considered significant.

In the 9 fetuses studied by fMCG, we also qualitatively evaluated patterns of fetal HR acceleration and the correlation between fetal atrial and ventricular accelerations.¹²

Results

Seventeen fetuses diagnosed at 19 to 23 weeks with CHB received terbutaline for mean ventricular rates <56 beats/min (Table 1). Two fetuses with isoimmune CHB (patients 1 and 4) initially had pericardial effusions and ascites that resolved during treatment. Four fetuses with LAI CHB (patients 13 through 16) developed hydrops before terbutaline was given; the hydrops did not improve despite an increased fetal HR. All infants were born alive at 33 to 39 weeks' gestation. Only duration of terbutaline treatment and gestational age at delivery were different between fetuses with isoimmune CHB and LAI CHB.

Sixteen infants received dual-chamber pacemakers and epicardial leads within 24 hours of birth; 1 with isoimmune CHB is still not paced at 9 months of age; 88% of patients with isoimmune CHB survived compared with only 11% of those with LAI CHB.

The mean atrial and ventricular rates after terbutaline treatment differed significantly from pretreatment rates in fetuses and mothers (Table 2). There was no difference between pretreatment atrial or ventricular rates between fetuses with LAI CHB and isoimmune CHB, but the atrial and ventricular rates after terbutaline treatment differed significantly between isoimmune and LAI CHB (Table 3). Specifically, the ventricular rate response to terbutaline was greater for the 9 fetuses with LAI CHB, whereas the atrial rate response was higher for those 8 with isoimmune CHB.

Mean fetal HR was maintained at >60 beats/min during the 6 to 12 weeks of terbutaline treatment in 4 of 6 fetuses, but in 2 fetuses, mean fetal HR decreased back to 55 to 56 beats/min at 33 to 35 weeks' gestation. Because the maternal HR was 120 beats/min and there were no clinical findings of fetal heart failure, the dose of terbutaline was not increased.

Terbutaline was well tolerated by all mothers and continued until delivery. During treatment, 5 of 9 mothers had premature atrial (n = 4) or ventricular heart beats that comprised <1% of the recorded beats during fMCG and were considered benign. Maternal tachyphylaxis was observed in 2 mothers, necessitating an increased dose of terbutaline at 32 and 34 weeks' gestation.

At terbutaline-augmented HRs to >55 beats/min in the fetus with isoimmune CHB, the HR acceleration patterns were almost wavelike, with a gradual return to baseline. In contrast, terbutaline affected fetal HR pattern in LAI CHB in 1 of 2 ways. In 3 fetuses, the ventricular rate was higher, but the acceleration pattern was monotonously flat with no oscillations. In the other 2 fetuses, accelerations were sustained and high in amplitude or the HR oscillated between the baseline and an accelerated rate 9 to 10 beats faster than baseline before decreasing back to baseline level (Figure 1).

Despite the different coupling intervals of the accelerated beats, the QRS morphology and duration of these beats remained normal and did not differ between isoimmune and LAI CHB. The QRS was narrow with a normal duration (Figure 1), which we interpreted as indicating that the subsidiary pacemaker was located in the proximal portion of the conduction system (AV node–His bundle). Because a ventricular escape rhythm is unlikely at these rates and with such morphology, these observations suggest that the accelerated rhythm originated at or near the AV junction.

It has been shown previously in fetal CHB that, if the baseline ventricular rate is >55 beats/min, accelerations in atrial and ventricular rates are correlated. In the current series,

terbutaline restored fetal ventricular rate to >55 beats/min, but AV correlation did not normalize in isoimmune or LAI CHB (Figure 2).

Discussion

The most important finding of this study is that distinct electrophysiologic patterns of fetal HR acceleration, reflecting the underlying pathology of the conduction system dysfunction, are seen after HR perturbation with terbutaline. These patterns can be summarized as follows. When the conduction system is structurally normal but damaged by maternal antibodies late in cardiogenesis (i.e., isoimmune CHB), terbutaline increases fetal HR, but with a pattern of wavelike accelerations with gradual relaxation to baseline level. In fetuses in which conduction system development is altered presumably early in cardiogenesis (i.e., LAI CHB), terbutaline reveals low-amplitude oscillations plus abrupt transitions between 9 to 10 beat accelerations and baseline or it merely increases fetal HR without distinct accelerations.

Previous data and data from this study show that terbutaline, a β -2 agonist, increases atrial and ventricular rates in the setting of CHB.^{8–10} Because the atrial and ventricular responses to HR perturbation vary, it appears that terbutaline, by exerting a differential effect on primary and subsidiary pacemakers, acts locally and does not influence neural control of HR. We postulate that the robust increase in the atrial (i.e., primary) pacemaker but not the ventricular (i.e., subsidiary) pacemakers in isoimmune CHB reflect the pathologic findings of disease in the AV node. Alternatively, the faster ventricular rate seen in fetuses with LAI CHB implies preservation of the components of the distal conduction system serving in the subsidiary pacemaker role, with developmental anomalies of the sinus node responsible for the lower baseline atrial rate and atrial rate response to terbutaline.

In addition to the differential effects on mean atrial and ventricular rate, the HR patterns of acceleration in response to terbutaline also differ. Whereas the mechanism of HR acceleration— β -1 stimulation or reflex mechanism of response to β -2 vasodilation¹³—appears straightforward, the mechanism for the different patterns of HR acceleration in response to terbutaline is more complex. We postulate the existence of a nodal pacemaker, quite proximal to the AV node within the AV junction, with a ventricular rate of >55 beats/min. In the case of isoimmune heart block, ongoing inflammation or fibrosis results in a more distal “locus of automaticity” within the conduction axis. These more distal subsidiary pacemakers may have fewer β -receptors, abnormal innervation, or different underlying channel expression patterns, rendering them unable to sustain a faster rate. This is seen by fewer, less frequent, and lower velocity accelerations in the terbutaline-treated fetus with isoimmune CHB.

These data suggest that the prognosis for isoimmune CHB is extremely favorable and that aggressive transplacental therapy with terbutaline in this population is justified: hydrops was reversed in 2 of 2 fetuses with isoimmune CHB who received terbutaline for fetal ventricular rates <55 beats/min. However, the prognosis of those with LAI AV block even with terbutaline remains very bleak: hydrops progressed relentlessly in 4 fetuses in this group despite terbutaline augmentation of ventricular rate. This suggests that the fetus with LAI CHB and hydrops will require more innovative and extreme therapy to survive.

Acknowledgments

We thank D. Woodrow Benson MD, PhD, who was supported by NIH grant HL69712, for critical reading of the manuscript and valuable suggestions. We thank Mary Maier for fMCG data acquisition; Nana Aba Mensah-Brown, MS; for fMCG data analysis; and Rita Allen, BA, for manuscript preparation.

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Figure 1.

Heart rates during terbutaline treatment in fetuses with isoimmune and LAI CHB. (A) Image from a 29-week fetus with isoimmune CHB. There is a gradual increase in rate, with a slow return to baseline in a wavelike pattern of acceleration. (B) Image from a 29-week fetus with LAI CHB. The accelerations are much more frequent, short-lived, and of higher amplitude and rate than in (A), and oscillate between several different rates. (C) Image from a 31-week fetus with LAI CHB showing a concentrated area of rapid and high-amplitude oscillations, which abruptly ends. (D) The fMCG during the period of intense oscillations presented in (C). Note the QRS morphology is the same even at the shorter coupling intervals, and the PP interval does not vary. The bottom tracing is the maternal signal and the top 2 tracings are the fetal signals.

Figure 2.

An example of AV correlation during atrial accelerations in CHB. *Right*, image from a 29-week untreated fetus with a isoimmune CHB and mean fetal HR of 65 beats/min. Note there is good AV correlation: ventricular accelerations (*bottom tracing*) follow atrial acceleration (*top tracing*). *Left*, in comparison, there is a flat ventricular response to atrial accelerations in this 29-week fetus with isoimmune CHB on terbutaline to maintain a mean fetal HR of 62 beats/min. This impaired AV correlation was also seen with LAI CHB (not shown).

Table 1

Clinical and outcome of 17 fetuses with CHB

Case No.	Gestational Age at Diagnosis (wks)	Gestational Age at Terbutaline Treatment (wks)	Duration of Terbutaline (wks)	Gestational Age at fMCG (wks)	QRS Duration (ms)	Gestational Age at Delivery (wks)	Outcome
Isoimmune CHB							
1	24	24	13	29	56	37	PM, alive
2	19	23	12	24	68	35	PM, alive
3	19	25	12	30	46	37	PM, alive
4	24	24	14	25	49	37	PM, alive
5	24	26	13	32	46	39	PM, alive
6	19	21	14	ND	ND	36	PM, neonatal death
7	22	28	7.5	ND	ND	36.5	PM, alive
8	30	34	4	ND	ND	38	PM, alive
Mean ± SD	22.6 ± 3.8	25.6 ± 4.0	11.2 ± 3.6*	28 ± 3.4		36.9 ± 1.2*	
LAI CHB							
9	20	28	9	31	55	37	PM, alive
10	20	25	9	29	61	34	PM, neonatal death
11	25	29	6	31	60	35	PM, neonatal death
12	19	35	3	38	55	38	PM, neonatal death
13	32	32	1	ND	ND	33	PM, neonatal death
14	23	31	2	ND	ND	33	PM, neonatal death
15	22	35	1	ND	ND	35	PM, neonatal death
16	19	22	8	ND	ND	30	PM, neonatal death
17	27	28	7	ND	ND	36	PM, neonatal death
Mean ± SD	23 ± 4.4	29.4 ± 4.3	5.1 ± 3.4*	32.2 ± 4.0		34.6 ± 2.4*	

ND = not done; PM = pacemaker.

* p < 0.05.

Table 2Effects of terbutaline on maternal heart rate and fetal atrial and ventricular rates (mean $\pm$ SD) in fetal CHB

Rate	No. of Patients	Post-Terbutaline Beat Rate	Post-Terbutaline Beat Rate	p Value
Fetal atrium	17	121.6 $\pm$ 13.3	133.6 $\pm$ 16.9	<0.001
Fetal ventricle	17	52.5 $\pm$ 2.3	63.4 $\pm$ 8.9	<0.001
Maternal	9	74.5 $\pm$ 6.7	98.2 $\pm$ 10.2	0.008

Table 3

Differences in atrial and ventricular rate response (mean $\pm$ SD) to terbutaline between fetuses with isoimmune and LAI CHB

Rate	Isoimmune CHB Beat Rate (n = 8)	LAI-CHB Beat Rate (n = 9)	p Value
Baseline atrial	128.3 $\pm$ 9.9	115 $\pm$ 13.5	0.06
Post-terbutaline atrial	143.9 $\pm$ 14.6	123.3 $\pm$ 12.5	<0.01
Baseline ventricular	51.7 $\pm$ 2.6	53.3 $\pm$ 1.7	0.23
Post-terbutaline ventricular	58.6 $\pm$ 5.0	68.1 $\pm$ 9.6	0.03