Cardiol Young 2001; 11: 683–686

ISSN 1047-9511

Brief Report

Use of terbutaline in the treatment of complete heart block in the fetus

Blair V. Robinson,[1] José A. Ettedgui,[2] Frederick S. Sherman[3]

[1]*University of North Carolina at Chapel Hill, NC;* [2]*Children's Hospital of Pittsburgh, Pittsburgh, PA;* [3]*Magee-Women's Hospital, Pittsburgh, PA, USA*

Abstract Between 1989 and 2000, 21 fetuses were diagnosed with complete atrioventricular block. Seven women with fetal ventricular rates of less than 60 were given oral terbutaline, and 6 of these had an initial increase in the fetal ventricular rate. Four fetuses (57%) maintained an increased average rate of 60 beats per minute and survived. Two fetuses returned to rates below 55 and died. The final fetus, with hypertrophic cardiomyopathy, was unresponsive. Terbutaline, therefore, is initially effective in raising the fetal ventricular rate, but this effect may be transient.

Keywords: Congenital; heart block; fetal; echocardiography

THE INCIDENCE OF CONGENITAL COMPLETE HEART block has been reported to be approximately 1 in 20,000 newborn infants,[1] and its aetiology appears to be multi-factorial. The association of congenital heart block with the abnormal development of the atrioventricular junction and nodal conduction tissue, as well as maternal connective tissue disease, is widely recognized.[2–4]

Over the past 15 years, efforts have been made to improve the outcome in fetuses with heart block. By the mid 1990's, reports appeared[5,6] in which sympathomimetic medications had been used to raise the ventricular rate in several fetuses. Other reports have shown some success in improving atrioventricular conduction in a limited number of fetuses by giving corticosteroids to women with autoantibodies.[7,8] Plasmapheresis[9] and fetal ventricular pacing[10] have been used with limited success, and neither has gained widespread usage. This study represents a single institutional experience over the past 11 years with fetal complete heart block, and our experience with both corticosteroid and sympathomimetic therapies.

Correspondence to: Blair Robinson, MD, Pediatric Cardiology Department, 311 Burnett-Womack Bldg. CB# 7220, Chapel Hill, NC 27599-7220, USA. Tel: 919 966 4601; Fax: (919) 966-6894; E-mail: brobins@med.unc.edu

Accepted for publication 9 May 2001

Methods

We reviewed the fetal echocardiographic database, identifying all cases of complete heart block. Atrial and ventricular rates had been determined using M-mode recordings simultaneously through the atrial and ventricular wall.

Beginning in 1995, oral terbutaline therapy was begun in women with fetal heart block and a ventricular rate less than 60. A starting dose of 2.5 mg every 6 hours was used, and the dose was increased to a maximum of 7.5 mg every 6 hours. Adjustments in dosage were made based on the fetal ventricular response. Maternal and fetal heart rates, as well as possible side effects, were monitored.

Statistical analysis was performed using SPSS for Windows Version 8.1. Values are expressed as a mean ± standard deviation. Continuous variables were analyzed using the Student's *t*-test. Categorical data were organized in contingency tables and analyzed using Fisher's exact probability test. A p value < 0.05 was considered significant.

Results

Over 3,700 women were referred for fetal echocardiograms at Magee-Women's Hospital in Pittsburgh between 1989 and 2000, and 21 fetuses were found to have complete heart block (Table 1). The average

Table 1. Twenty-one fetuses with complete heart block.

#	Gest. age	Initial V.R.	Mat. CTD	Anatomical anomaly	Hydrops fetalis	Terb / max dose	Dex.	Last V.R.	Outcome	Pacer
1	26	45	+	−	+	−	+	40	Died in-utero	
2	21	71	+	−	−	−	+	51	Died in-utero	
3	15	40	−	−	+	−	−	40	Died in-utero	
4	37	45	−	−	+	−	−	45	Died at birth	
5	20	38	−	−	−	−	−	38	Died in-utero	
6	33	52	−	−	−	−	−	55	Survived	−
7	24	64	+	−	−	−	−	62	Survived	−
8	23	62	+	−	−	−	−	60	Survived	−
9	23	48	+	−	−	+/7.5 mg qid	+	58	Survived	−
10	19	57	+	−	+	+/7.5 mg qid	+	53	Died in-utero	
11	22	48	+	−	−	+/5.0 mg qid	−	61	Survived	+
12	26	40	−	−	+	+/7.5 mg qid	−	43	Delivered 30 weeks; CHF, pacer; died 2 days of age	+
13	20	64	+	−	Developed 35 weeks	+/2.5 mg qid	−	64	Delivered 35 weeks; severe RDS, ECMO; died 3 weeks	+
14	22	58	+	−	−	+/2.5 mg qid	−	68	Survived	−
15	22	50	−	HCM	−	+/7.5 mg qid	−	50	Survived; Noonan's syndrome	+
16	17	70	−	CC-TGA	−	−	−	67	Survived	−
17	23	52	−	AVSD	+	−	−	52	Died in-utero	
18	33	60	−	Trisomy 18, DORV, AVSD	+	−	−	60	Died in-utero	
19	30	80	−	CC-TGA, VSD	+	−	−	84	Survived	−
20	20	50	−	AVSD, Truncus arteriosus	+	−	−	50	Therapeutic abortion	
21	28	55	−	CC-TGA, VSD, PS	−	−	−	48	Survived	+

Gest. age = Gestational age in weeks at time of diagnosis; Initial V.R. = ventricular rate at diagnosis; Mat. CTD = maternal connective tissue disease; Terb. = terbutaline therapy; Dex. = dexamethasone therapy; Last V.R. = ventricular rate at last fetal echo; pacer = required pacemaker; + = positive or present; − = negative or absent; HCM = Hypertrophic cardiomyopathy; AVSD = atrioventricular septal defect; CC-TGA = congenitally corrected transposition of the great arteries; DORV = double outlet right ventricle; VSD = ventricular septal defect; PS = pulmonic stenosis

gestational age at diagnosis was 24 weeks, with a range from 15 to 37 weeks. Seven were found to have complex structural lesions. Of the 14 with structurally normal hearts, the mean ventricular rate at presentation was 52 ± 10, with a range from 38 to 71. Eight (57%) of these died during fetal life or in the immediate newborn period, and they had a mean ventricular rate at presentation of 50 ± 12, compared to 56 ± 7 ($p = 0.4$) for the survivors. The mean ventricular rate for the non-survivors at last fetal echo was 47 ± 9, compared to 61 ± 5 ($p = 0.01$) for the survivors.

Between 1995 and 2000, 7 women were treated with terbutaline for fetal ventricular rates less than 60. An initial dose of 2.5 mg every 6 hours was used in all 7 women. The fetal ventricular rate after 1 week of terbutaline therapy increased from a mean of 51 ± 7 to a mean of 60 ± 6 ($p = 0.02$).

Of the 7 fetuses treated with terbutaline, 6 had an initial increase in their ventricular rate, and one had no response. Four of these 6 maintained an average ventricular rate of 60 (Fig. 1). Three are doing well postnatally and have not required a pacemaker. Despite a ventricular rate of 64, the fourth fetus developed hydrops and was delivered at 35 weeks gestation. She developed severe respiratory distress syndrome, and despite ventricular pacing and extracorporeal support, she died at 3 weeks of age.

After several weeks of response to therapy, 2 of the six had a return to their baseline ventricular rates of less than 55 (Fig. 2). At this point, the terbutaline was increased to 5 mg every 6 hours and then to 7.5 mg every 6 hours. There was no increase in ventricular rate and these fetuses died. In the one fetus with no initial response to therapy, the dose was eventually increased to 7.5 mg every 6 hours. Due to a lack of increase in the ventricular rate, the terbutaline was discontinued. This fetus subsequently developed hypertrophic cardiomyopathy, and was postnatally diagnosed with Noonan's syndrome. This infant required placement of a pacemaker on the first day of life and survived. Overall, 4 of the 7 (57%) treated with terbutaline survived.

In the 7 women treated with terbutaline, there were no serious side effects reported. Most of the women reported feeling "jittery", but the resting heart rates were within a normal range. There were no sustained tachyarrhythmias observed.

Nine of the 14 women with structurally normal fetal hearts had evidence of connective tissue disease, with either anti-SS-A or anti-SS-B antibodies. Five (56%) of the 9 fetuses survived. Oral corticosteroid therapy using dexamethasone 4 mg per day was instituted in 4 women between 19 and 26 weeks. In these 4 fetuses, there was no change in the degree of atrioventricular block. Two of these 4 also received treatment with terbutaline. The fetal ventricular rate was 54 ± 3 before steroids and 53 ± 9 after treatment. One of these 4 fetuses survived.

Nine of the 21 fetuses developed or presented with hydrops fetalis. Eight (89%) of these died during fetal life or within the immediate neonatal period.

Postnatally, a total of 5 infants had placement of a pacemaker. Three survived and are doing well. The other 2 died in the neonatal period.

Discussion

In our series, the overall mortality was 52%. Previous reports[1,6] have noted that a ventricular rate less than 55 predicts a fatal outcome in both fetuses and children with complete heart block. In our 14 fetuses with structurally normal hearts, 7 of the 8 non-survivors had a ventricular rate below 55 prior to their death. All 6 of the surviving infants had a ventricular rate greater than or equal to 55 on their last fetal echo.

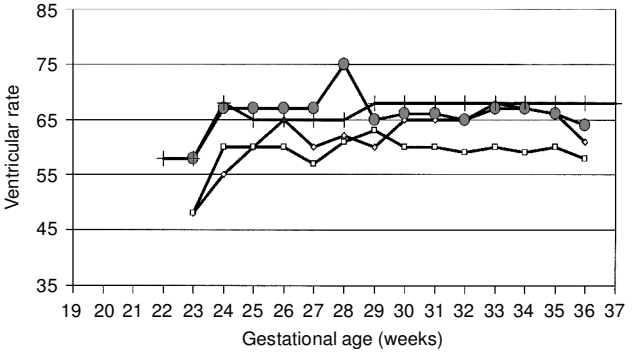

Figure 1.
Four fetuses maintained increased ventricular rates with terbutaline therapy. The initial rate was prior to beginning terbutaline.

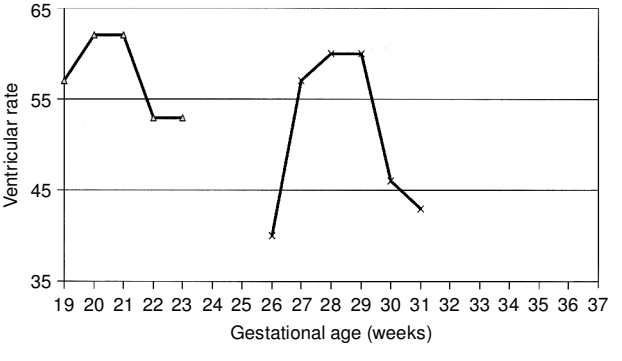

Figure 2.
Two fetuses had an initial increased ventricular rate with terbutaline therapy and then returned to their baseline rates. The initial rate was prior to beginning terbutaline.

https://doi.org/10.1017/S1047951101001123 Published online by Cambridge University Press

In the women treated with terbutaline, there was an initial increase in the ventricular rate in 6 of the 7 fetuses. It is unclear what the difference was between the 4 fetuses that responded to terbutaline and maintained a ventricular rate above 60 and the 2 that had initially responded and then seemed "resistant" with a return to their baseline rate. Perhaps maternal and fetal upregulation of beta-adrenergic receptors played a role in the decreased fetal response to therapy, but this is merely speculation.

In conclusion, complete heart block in the fetus carries a significant mortality. A ventricular rate less than 55 ($p = 0.001$), and/or the presence of hydrops fetalis ($p = 0.02$) are signs of a fatal outcome. Terbutaline therapy was effective in raising the ventricular rates in some fetuses, but this effect was not always sustained, and there was no increase in the overall survival. In mothers with connective tissue disease and autoantibodies, treatment with corticosteroids did not result in improved survival, increased ventricular rate, or a change in the degree of atrioventricular block. We recognize that ours is a small, retrospective series, and thus the power of the conclusions is limited.

References

1. Michaëlsson M, Engle MA. Congenital complete heart block: an international study of the natural history. Cardiovasc Clin 1972; 4: 85–101.
2. Chameides L, Truex RC, Vetter V, Rashkind WJ, Galioto FM, Noonan JA. Association of maternal systemic lupus erythematosus with congenital complete heart block. N Engl J Med 1977; 297: 1204–1207.
3. Scott JS, Maddison PJ, Taylor PV, Esscher E, Scott O, Skinner RP. Connective-tissue disease, antibodies to ribonucleoprotein, and congenital heart block. N Engl J Med 1983; 309: 209–212.
4. Taylor PV, Taylor KF, Norman A, Griffiths S, Scott JS. Prevalence of maternal Ro (SS-A) and LA (SS-B) autoantibodies in relation to congenital heart block. Br J Rheumatol 1988; 27: 128–132.
5. Groves AMM, Allan LD, Rosenthal E. Therapeutic trial of sympathomimetics in three cases of complete heart block in the fetus. Circulation 1995; 92: 3394–3396.
6. Schmidt KG, Ulmer HE, Silverman NH, Kleinman CS, Copel JA. Perinatal outcome of fetal complete atrioventricular block: a multicenter experience. J Am Coll Cardiol 1991; 91: 1360–1366.
7. Bierman FZ, Baxi L, Jaffe I, Driscoll J. Fetal hydrops and congenital complete heart block: response to maternal steroid therapy. J Pediatr 1988; 112: 646–648.
8. Copel JA, Buyon JP, Kleinman CS. Successful in utero therapy of fetal heart block. Am J Obstet Gynecol 1995; 173: 1384–1390.
9. Buyon J, Roubey R, Swersky S, Pompeo L, Parke A, Baxi L, Winchester R. Complete congenital heart block: risk of occurrence and therapeutic approach to prevention. J Rheumatol 1988; 15: 1104–1108.
10. Carpenter RJ, Strasburger JF, Garson A Jr, Smith RT, Deter RL, Engelhardt HT. Fetal ventricular pacing for hydrops secondary to complete atrioventricular block. J Am Coll Cardiol 1986; 8: 1434–1436.