Digoxin in the management of fetal supraventricular tachycardia

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INTRODUCTION

- Supraventricular tachycardia (SVT) is the most common fetal tachycardia.
- Characterized by a regular rate that is typically between 220 and 260 bpm
- Without intervention, 50% of such fetuses will develop cardiac failure and hydrops fetalis; which eventually leads to death
- The most common mechanism for fetal SVT is a reentrant tachycardia
- The diagnosis of SVT is made by using M-mode echocardiography

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Edgar T. Jaeggi, Julene S. Carvalho, Ernestine De Groot, Olus Api, SallyAnn B. Clur, Lukas Rammeloo et al. Comparison of Transplacental Treatment of Fetal Supraventricular Tachyarrhythmias With Digoxin, Flecainide, and Sotalol: Results of a Nonrandomized Multicenter Study. Circulation. 2011; 124:1747-1754;. AHA.111.026120

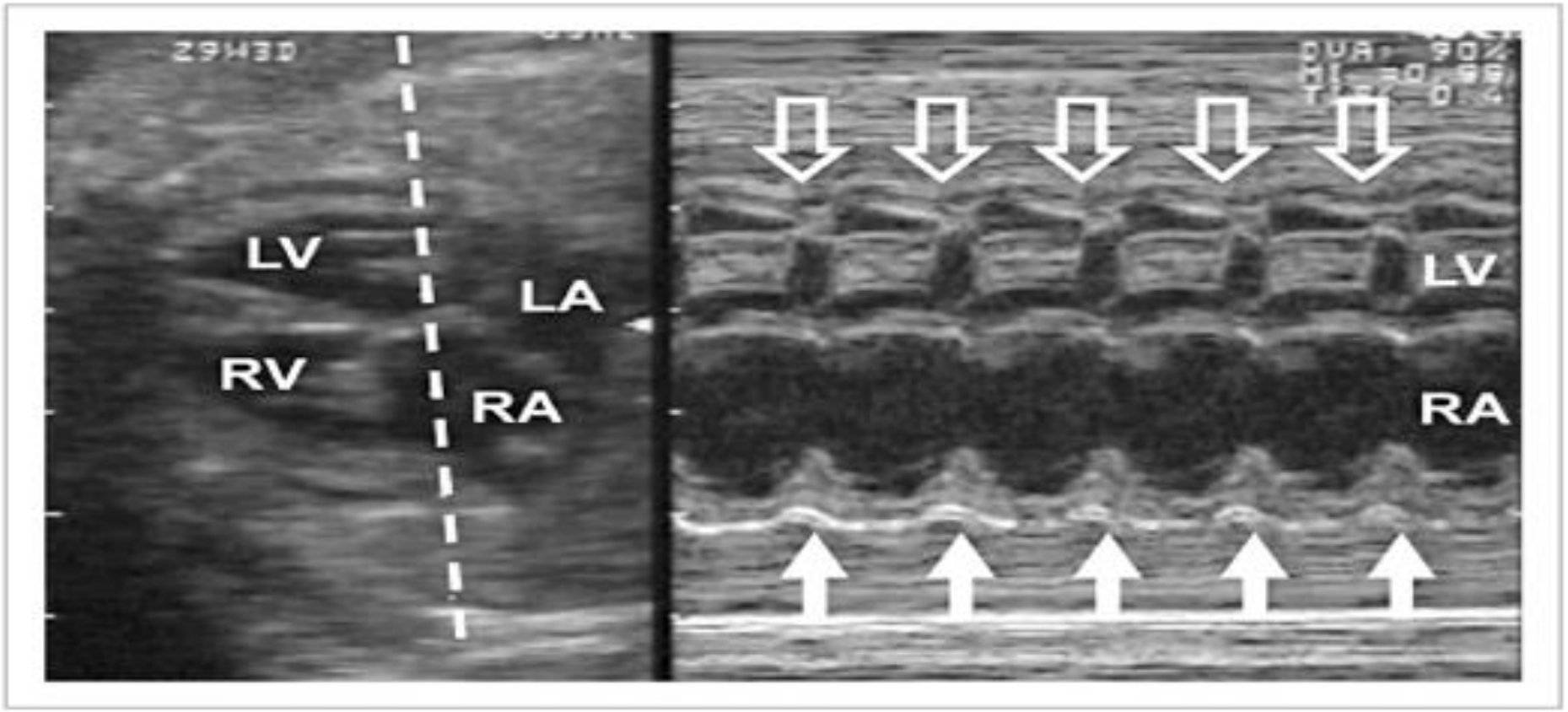

Figure 1.

Simultaneous M-mode recording of both ventricles and atria. M-mode recording in a fetus with supraventricular tachycardia reveals 1:1 relation of atrial (closed arrow) and ventricular contraction (open arrow) with a ventricular rate of 210 bpm. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Maeno, Y., Hirose, A., Kanbe, T. and Hori, D. (2009), Fetal arrhythmia: Prenatal diagnosis and perinatal management. Journal of Obstetrics and Gynaecology Research, 35: 623–629.

DRUG TREATMENT

- The choice of first- and second-line antiarrhythmic therapy are controversial.
- No standards for drug dosing, the need for loading doses, and whether the mother should be hospitalized when therapy is initiated.
- Drug dosing is empiric and depends on maternal, as well as fetal, factors

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Jami C Levine, MD; Mark E Alexander, MD (2016) Overview of the general approach to diagnosis and treatment of fetal arrhythmias, Uptodate 2017

Factors to consider prior to treatment of fetal tachycardia

	Favoring treatment	Favoring observation	Favoring delivery
Tachycardia rate (bpm)	>220	≤200	
Persistence	>50 percent of the day	≤20-25 percent of the day	
Gestational age (weeks)	<34	≥34	Term; mature lungs
Hydrops	Yes	No	
Preeclampsia	No		For maternal safety
Mechanism	Atrial flutter		
	Typical SVT		
		Nonsustained ectopic atrial tachycardia	
		PJRT (slow, frequently terminating)	

BPM: beats per minute; SVT: supraventricular tachycardia; PJRT: persistent junctional reciprocating tachycardia.

DRUG TREATMENT

- Most fetuses with SVT are successfully treated *in utero* by transplacental administration of antiarrhythmic drugs.
- Digoxin is widely accepted as a first-line antiarrhythmic drug.
- Sotalol, flecainide and amiodarone are used as second-line drugs when digoxin fails to achieve conversion to sinus rhythm.
- For fetuses with hydrops, digoxin is rarely effective.

Maeno, Y., Hirose, A., Kanbe, T. and Hori, D. (2009), Fetal arrhythmia: Prenatal diagnosis and perinatal management. Journal of Obstetrics and Gynaecology Research, 35: 623–629.
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Strasburger JF, Cuneo BF, Michon MM *et al.* Amiodarone therapy for drug-refractory fetal tachycardia. *Circulation* 2004; **109**: 375–379.

DRUG TREATMENT

- **AHA 2014**
- In many centers, digoxin, administered maternally either orally or intravenously, is used as first-line therapy
- In some centers, flecainide or sotalol is used as primary therapy.

Oudijk MA, Michon MM, Kleinman CS, Kapusta L, Stoutenbeek P, Visser GH, Meijboom EJ. Sotalol in the treatment of fetal dysrhythmias. Circulation. 2000;101:2721–2726.
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DRUG TREATMENT _ DIGOXIN

Edgar T. Jaeggi (2011)

- A nonrandomized multicenter study reviewed 114 consecutive cases with a prenatal diagnosis of SVT at our tertiary care centers between 1998 and 2008
- The oral loading dose of digoxin was 1.5 to 2 mg over 2 days, followed by maintenance dosages between 0.375 and 1 mg/d, aiming to obtain maternal drug levels in the upper therapeutic range between 2 and 2.5 ng/mL.
- 57% of digoxin-treated SVT were in normal rhythm.
- The median time to conversion of SVT cases was 3 days with digoxin

Jaeggi, E. T., Carvalho, J. S., De Groot, E., Api, O., Clur, S. A. B., Rammeloo, L., ... & Blom, N. A. (2011). Comparison of transplacental treatment of fetal supraventricular tachyarrhythmias with digoxin, flecainide, and sotalol. *Circulation*, *124*(16), 1747-1754.

DRUG TREATMENT _ DIGOXIN

Lê Kim Tuyến 2013

- From Jan 2008 to Dec 2011, there were 39 fetus were diagnosis of arrhythmia at Heart Institute in HCMC. The prevalence of SVT is 14%.
- The oral loading dose of digoxin was 0.75 mg/d (in 3 doses) over 3 days, followed by maintenance dosages 0.5 mg/d, aiming to obtain maternal drug levels in the upper therapeutic range between 1 and 2 ng/mL.
- Digoxin was effective in restoring sinus rhythm in 80%

Lê Kim Tuyến, Phạm Nguyễn Vinh, Châu Ngọc Hoa (2013), "Rối loạn nhịp tim thai: Kinh nghiệm 4 năm tại Viện Tim TP HCM", Tạp chí Y học TPHCM. 17(1), tr. 60

DRUG TREATMENT _ DIGOXIN

Ueda 2017

- A retrospective review of cases of fetal tachycardia that occurred in Japan.
- Thirty-five of the 41 cases (SVT n = 26; and AFL = 9) were treated using digoxin.
- Fetal tachycardia resolved in 90.0% of the cases without fetal hydrops and 90.9% of the cases with fetal hydrops

[3] Ueda, K., Maeno, Y., Miyoshi, T., Inamura, N., Kawataki, M., Taketazu, M., ... & Shimizu, W. (2017). The impact of intrauterine treatment on fetal tachycardia: a nationwide survey in Japan. *The Journal of Maternal-Fetal & NeonatalMedicine*, 1-6.

2001

OBSTETRICS & GYNECOLOGY

Successful Digoxin Therapy of Fetal Supraventricular Tachycardia in a Triplet Pregnancy

Jones, Lisa M. MD; Garmel, Sara H. MD

2008

Europe PMC

Can digoxin and sotalol therapy for fetal supraventricular tachycardia and hydrops be successful? A case report.

Merriman JB, Gonzalez JM, Rychik J, Ural SH

CONCLUSION: Digoxin and sotalol thera… likely nodal reentry in sustained fetal supraventricular tachycardia… some.

2009

JAYPEE JOURNALS

International Scientific Journals from Jaypee

CASE REPORTS

Successful Digoxin Therapy … Supraventricular Tachycardia

[1]Yoginder Singh Rana, [2]Bandana Sodhi, [3]SPS Kochar, [4]D Arora

Digoxin was the first-line drug used in most institutions and was effective in fetal SVT

2015

Intrauterine manage… …praventricular tachycardia (SVT) with cardiac failure

Case Report

Muniswaran Ganeshan, MRCOG (UK)*, Japaraj Robert Peter, MMed (O&G)*, AR Asri Ranga, MRCP (UK), HK Cheong, MRCPCH(UK)*****

CONCLUSION

Indirect maternal administration of digoxin is beneficial in treatment of fetal SVT in cardiac failure.

DRUG TREATMENT _ DIGOXIN

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- 1 to 2 mg (three doses: 0.5 mg, 0.25 mg, and 0.25 mg over 18 to 24 hours).
- The target level is 1 to 2 ng/mL.
- When the fetus is hydropic, it is less likely to respond and higher doses of digoxin may be given.

[1] Kleinman CS, Nehgme R, Copel JA. Fetal cardiac arrhythmias: diagnosis and therapy. In: Maternal-Fetal Medicine, 4th ed, Creasy RK, Resnik R (Eds), WB Saunders Co, Philadelphia 1999. p.301
[2] Strasburger JF, Cuneo BF, Michon MM, et al. Amiodarone therapy for drug-refractory fetal tachycardia. Circulation 2004; 109:375.
[3] Krapp M, Kohl T, Simpson JM, et al. Review of diagnosis, treatment, and outcome of fetal atrial flutter compared with supraventricular tachycardia. Heart 2003; 89:913.

Diagnosis	In Utero Treatment/Management	COR/LOE	Comments
Intermittent tachycardia (not occurring the majority of time or <≈50% of time monitored)			
SVT or AF	Observation	I/B	Frequent FHR auscultation (weekly or more frequently if needed)
VT ≥200 bpm, no LQTS	Antiarrhythmic treatment (see below)	IIa/C	
VT ≥200 bpm, fetal LQTS (suspected or confirmed)	Antiarrhythmic treatment (see below)	IIa/C	
Sustained tachycardia (occurring the majority of time or >≈50% of time monitored)			
Sinus tachycardia	Treat secondary cause	I/A	Check maternal thyroid functions and MCA Doppler for anemia
SVT or atrial flutter with hydrops or ventricular dysfunction	First or second line (transplacental):		See Table 14 for dosing ranges and monitoring recommendations Transplacental transfer of several antiarrhythmic agents decreases with hydrops. Combined therapies have been used for severe drug-refractory cases Consider delivery if near term
	Digoxin	I/B	
	Flecainide	I/B	
	Sotalol	I/B	
	Combination transplacental treatment	IIb/B	
	Third line (transplacental):		
	Amiodarone	I/B	
	Contraindicated: verapamil	III/A	
	Contraindicated: procainamide	III/B	
	Direct fetal treatment:		
	Intramuscular digoxin	IIa/B	
	Intracordal digoxin or amiodarone	IIb/B	
	Contraindicated: intracordal adenosine (deaths reported with intracordal route)	III/B	
SVT ≥200 bpm without hydrops or ventricular dysfunction (most SVT occurs at rates ≥220 bpm; consider other mechanism if rate <220 bpm	First or second line:		See Table 14 for dosing ranges and monitoring recommendations Frequent monitoring of fetal well-being and maternal/fetal drug toxicity Consider delivery if near term
	Digoxin	I/B	
	Flecainide	I/B	
	Sotalol	I/B	
	Third line:		
	Amiodarone	IIb/B	
	Contraindicated: verapamil	III/A	
	Contraindicated: procainamide	III/B	
SVT <200 bpm without hydrops or ventricular dysfunction	Observation	I/B	

Table 14. Antiarrhythmic Drugs

Drug	Therapeutic Maternal Dose Range	Therapeutic Level and Effect	Toxicity
Digoxin	LD: 1200–1500 μg/24 h IV, divided every 8 h MD: 375–750 μg/d divided every 8 to 12 h PO (Fetal intramuscular dose: 88 μg/kg q12 h, repeat 2 times)	0.7–2.0 ng/mL Nausea, fatigue, loss of appetite, sinus bradycardia, first-degree AV block, rare nocturnal Wenckebach AV block	Nausea/vomiting +++, sinus bradyarrhythmia or AV block +++, proarrhythmia Fetal intramuscular: sciatic nerve injury or skin laceration from injection
Flecainide	100–300 mg/d divided every 8–12 h PO	0.2–1.0 μg/mL, Mild P and QRS widening, first-degree AV block, QTc ≤0.48 s, headache	Visual/CNS symptoms, BBB, QTc ≥0.48 s, maternal/fetal proarrhythmia
Sotalol	160–480 mg/d divided every 8 to 12 h PO	Levels not monitored Bradycardia, first-degree AV block, P and QRS widening, QTc ≤0.48 s	Nausea/vomiting, dizziness, QTc ≥0.48 s, fatigue, BBB, maternal/fetal proarrhythmia
Amiodarone	LD: 1800–2400 mg/d divided every 6 h for 48 h PO; lower (800–1200 mg PO) if prior drug therapy MD: 200–600 mg/d PO Consider discontinuation of drug and transition to another agent once rhythm is converted or hydrops has resolved.	0.7–2.8 μg/mL Maternal/fetal sinus bradycardia, decreased appetite, first-degree AV block, P and QRS widening, QTc ≤0.48 s	Nausea/vomiting ++, thyroid dysfunction ++, photosensitivity rash, thrombocytopenia, BBB, QTc ≥0.48 s, maternal/fetal proarrhythmia, fetal torsades with LQTS, fetal goiter, neurodevelopmental concerns
Propranolol	60–320 mg/d divided every 6 h PO	25–140 ng/mL First-degree AV block, bradycardia, increased uterine tone	Fatigue, bradycardia +++, hypotension+++, AV block, fetal growth restriction, increased uterine tone
Lidocaine	LD: 1–1.5 mg/kg IV followed by infusion of 1–4 mg/min	1.5–5 μg/mL	Nausea/vomiting ++, CNS symptoms, proarrhythmia
Mexiletine	600–900 mg/day divided every 8 h PO	0.5–2 μg/mL	Nausea/vomiting ++, CNS symptoms, proarrhythmia
Magnesium sulfate	LD: 2–6 g IV over 20 min followed by 1–2 g/h Treatment for >48 h is not recommended but redosing may be considered if VT recurs	<6 mEq/L Monitor patellar reflex	Fatigue, CNS symptoms, STOP for loss of patellar reflex and/or levels of >6 mEq/L Levels >5 mEq/L associated with maternal changes on ECG and proarrhythmia

FOLLOW-UP

- Close outpatient monitoring is important
- A plan of daily fetal kick counts and frequent prenatal visits (two to three times per week) with nonstress tests.
- ECGs and serum drug levels should be obtained every one to two weeks.

CONCLUSIONS

- Fetal medical therapy should be offered for fetuses with sustained SVT with average heart rates >200 bpm (Class I; Level of Evidence A) (AHA 2014).

- Digoxin was the first-line drug used in most institutions and was effective in fetal SVT (Class I; Level of Evidence B)

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