Flecainide versus digoxin for fetal supraventricular tachycardia: Comparison of two drug treatment protocols

Shankar Sridharan, MRCPCH,[*] Ian Sullivan, FRACP,[*] Viktor Tomek, MD,[†] Joanne Wolfenden, PgDip Medical Ultrasound,[*] Jan Škovránek, MD, PhD,[†] Robert Yates, MBBCh, BSC MED, FRCP,[*] Jan Janoušek, MD, PhD,[†] Troy E. Dominguez, MD,[*] Jan Marek, MD, PhD, FESC[*†]

From the [*]Great Ormond Street Hospital and Institute of Cardiovascular Sciences, UCL, London, United Kingdom, and [†]University Hospital Motol, Prague, Czech Republic.

BACKGROUND The optimal treatment for fetal supraventricular tachycardia (SVT) with 1:1 atrioventricular relationship is unclear.

OBJECTIVE We compared the effectiveness of transplacental treatment protocols used in 2 centers.

METHODS Pharmacologic treatment was used in 84 fetuses. Maternal oral flecainide was the primary therapy in center 1 (n = 34) and intravenous maternal digoxin in center 2 (n = 50). SVT mechanism was classified by mechanical ventriculoatrial (VA) time intervals as short VA or long VA. Treatment success was defined as conversion to sinus rhythm (SR), or rate control, defined as >15% rate reduction.

RESULTS Short VA interval occurred in 67 fetuses (80%) and long VA in 17 (20%). Hydrops was present 28 of 84 (33%). For short VA SVT, conversion to SR was 29 of 42 (69%) for digoxin and 24 of 25 (96%) for flecainide ($P = .01$). For long VA SVT, conversion to SR and rate control was 4 of 8 (50%) and 0 of 8, respectively, for digoxin, and 6 of 9 (67%) and 2 of 9 (cumulative 89%) for flecainide ($P = .13$). In nonhydropic fetuses, digoxin was successful in 23 of 29 (79%) and flecainide in 26 of 27 (96%) ($P = .10$). In hydrops, digoxin was successful in 8 of 21 (38%), flecainide alone in 6 of 7 (86%, $P = .07$ vs digoxin), and flecainide ± amiodarone in 7 of 7 (100%) ($P = .01$). Intrauterine or neonatal death occurred in 9 of 21 hydropic fetuses treated with digoxin (43%), compared to 0 of 7 ($P = .06$) treated with flecainide.

CONCLUSIONS Flecainide was more effective than digoxin, especially when hydrops was present. No adverse fetal outcomes were attributed to flecainide.

KEYWORDS Fetal supraventricular tachycardia; Prenatal treatment; Fetal ultrasound

(Heart Rhythm 2016;13:1913–1919)

Introduction

The incidence of sustained fetal tachycardia is uncertain, but it may occur in about 1 in 1000 pregnancies. The loss of normal atrioventricular (AV) synchrony and increased heart rate in sustained fetal supraventricular tachycardia (SVT) is thought to increase central venous pressure and reduce combined cardiac output, resulting in progressive fetoplacental circulatory failure, hydrops, and even fetal demise. There are no satisfactory natural history studies, but it was reported that more than half of fetuses with sustained tachycardia, and gestation less than about 34 weeks at diagnosis, developed hydrops.[1] Hydrops in this situation has been associated with 20%–46% intrauterine or neonatal mortality despite treatment.[2,3]

Transplacental antiarrhythmic therapy of fetal tachycardia, using digitalis, was first reported in 1980[4] and it was soon confirmed that transplacental antiarrhythmic therapy could be effective.[5,6] Since then, numerous drug treatment protocols have been described, mainly using digoxin, flecainide, sotalol, amiodarone, or a combination thereof.

Published reports have usually been from single centers, with relatively small numbers, and have used a variety of drug treatment regimens. Importantly, successful or adverse outcomes have been attributed, at least by implication, to the treatment used. There have been no controlled studies. A recent position statement from the American Heart Association reported that there "is no study to support which is the

This study was supported by MH CZ-DRO, University Hospital Motol, Prague, Czech Republic 00064203. **Address reprint requests and correspondence:** Dr Shankar Sridharan, Consultant Cardiologist, Cardiothoracic Unit, Great Ormond Street Hospital for Children, London, UK. E-mail address: shankar.sridharan@gosh.nhs.uk.

1547-5271/$-see front matter

http://dx.doi.org/10.1016/j.hrthm.2016.03.023

best initial therapy" and there is "little data to support the specific treatment protocol that is likely to be the most effective and to carry the lowest risks."[7]

In this study, we aimed to compare 2 different drug protocols used to treat similar patient cohorts during the same era in 2 tertiary institutions and provide informative data regarding the preferred therapy.

Methods

Retrospective analysis of fetal tachycardia, defined as ventricular rate greater than 180 beats per minute, presenting to 2 fetal cardiac centers between 1998 and 2012 (center 1) and between 1987 and 2011 (center 2) identified 158 consecutive cases. Of these, 129 had intermittent or sustained tachycardia with a 1:1 AV relationship, defined as SVT, and 29 had an AV relationship greater than 1, which was defined as atrial flutter. Of these, 84 fetuses with SVT, present for more than 50% of scanning time or with evidence of fetal cardiac compromise, were treated with antiarrhythmic therapy and were assessed according to the protocol used.

At center 1, 34 outpatient mothers received oral flecainide, usually at an initial dose of 300 mg daily in 3 separate doses. A maternal electrocardiogram was recorded prior to the initiation of treatment. Follow-up was arranged in 1–7 days from treatment onset according to physician judgment. Flecainide dose was decreased to 100 mg twice daily or less following conversion to fetal sinus rhythm (SR). If tachycardia persisted at first review, or if the dose was increased subsequently, maternal plasma level (trough) was requested. Addition of amiodarone or digoxin was considered if reversion to SR was not achieved.

At center 2, 50 hospital inpatient mothers received intravenous digoxin in a protocol proposed by the Fetal Working Group of the Association of European Paediatric Cardiology.[8] The initial digoxin dose was 1.5 mg/24 hours in 3 divided doses, increasing up to 2.0 mg/24 hours in 2 divided doses if required. Digoxin was administered intravenously in short continuous infusions until a maternal plasma level of 2.0–3.0 ng/mL was achieved. Maternal plasma levels and electrocardiogram were checked daily at the initial phase of treatment. Once the therapeutic plasma level was obtained, digoxin was administered orally if treatment had been successful, or a second-line drug (usually sotalol) was introduced.

The arrhythmia mechanism was classified using echocardiographic[9] or pulsed Doppler identification of atrial and ventricular contraction.[10,11] When the ventriculoatrial (VA) interval was less than the AV interval, short VA tachycardia was diagnosed, assumed to be atrioventricular reentrant tachycardia (AVRT) (Figure 1). When the VA interval was longer than the AV interval, long VA tachycardia was diagnosed. This suggested that the tachycardia mechanism was more likely to be ectopic atrial tachycardia or an unusual type of AV reentry, such as persistent junctional reciprocating tachycardia (Figure 2).

The circulatory status of each fetus was classified into 1 of 3 categories. "*Stable*" was classified when the cardiothoracic area ratio was ≤0.35; there was absence of holosystolic mitral and/or tricuspid regurgitation on color flow Doppler and no evidence of free fluid in the thorax or abdomen. "*Cardiac compromise*" was established if the cardiothoracic area ratio was >0.35, or if there was holosystolic mitral or tricuspid regurgitation, but with absence of free fluid in thoracic or abdominal cavities. "*Hydrops*" required at least

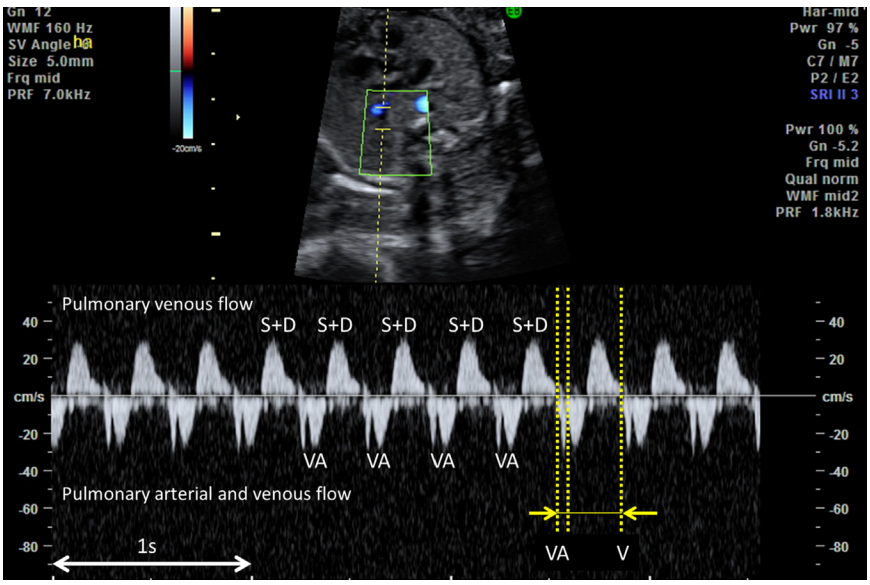

Figure 1 Pulsed Doppler assessment of ventriculoatrial (VA) intervals (short VA tachycardia shown). Diagram indicates measurements of VA intervals registered from simultaneous pulsed Doppler tracing from pulmonary artery and pulmonary vein. Antegrade pulmonary vein flow toward the transducer occurs in systole and early diastole (S+D), whereas retrograde flow, away from the transducer, occurs coincident with atrial contraction (A). Antegrade pulmonary artery flow is away from the transducer (V). As the VA interval is shorter than the atrioventricular (AV) interval, short VA tachycardia was diagnosed, assumed to be atrioventricular reentrant tachycardia.