Risks and Benefits of Amiodarone in Infants

Song Mi Kyoung

Seoul National University Children's Hospital

Korean Heart Rhythm Society

COI Disclosure

Name of First Author:

Song Mi Kyoung

The authors have no financial conflicts of interest to disclose concerning the presentation

Risks and Benefits of Amiodarone in Infants

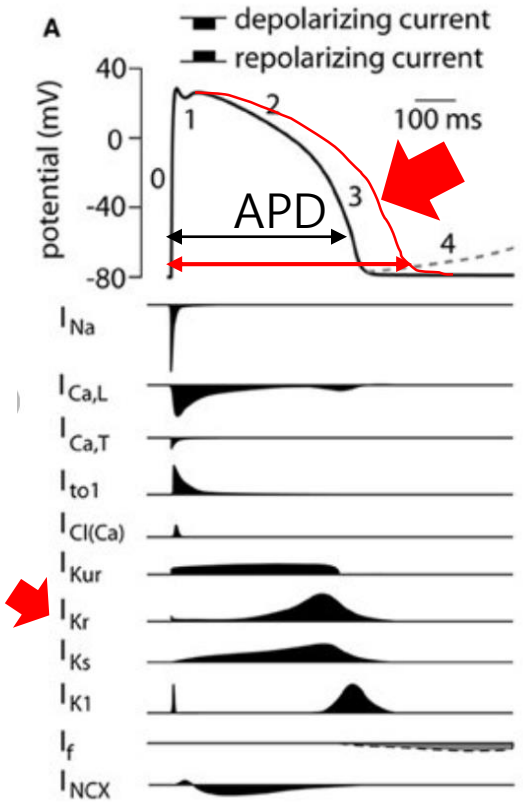
- Identify the mechanism of action of amiodarone.
- Outline the indications for amiodarone use.
- Adverse event profile for patients receiving amiodarone therapy

- Amiodarone indications in infants
- Drug adverse event in infants

Mechanism of Action

- Class III antiarrhythmic drug
  - block multiple K channels → prolonged APD
  →prolonged QT interval

- Blocks beta-adrenergic receptor, Ca++, and Na+ chan.
  → decreased automatism of SA node, AV node conduction velocity
→ inhibits ectopic pacemaker automaticity
→ decreased myocyte excitability



Ventricular Action potential

Mechanism of Action

- Long Half-life: PO ~40 days, IV 9-36 days d/t prolonged terminal elimination phase
- Rapid uptake into lipophilic tissues, wide distribution to tissue (fat, muscle, highly perfused organs) → long loading periods

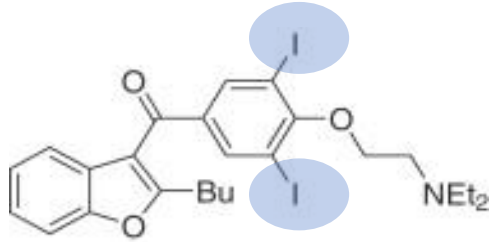
  : onset of action – 2days to 3 weeks

  → 6 weeks for full clinical effects with oral therapy.

  Upon discontinuation, pharmacologic effects could continue for 1-3 months

- Iodine atoms in its molecule : structural analogue of thyroid hormone

  → may interfere with normal thyroid hormone metabolism



Amiodarone

Case> 4 months/Female

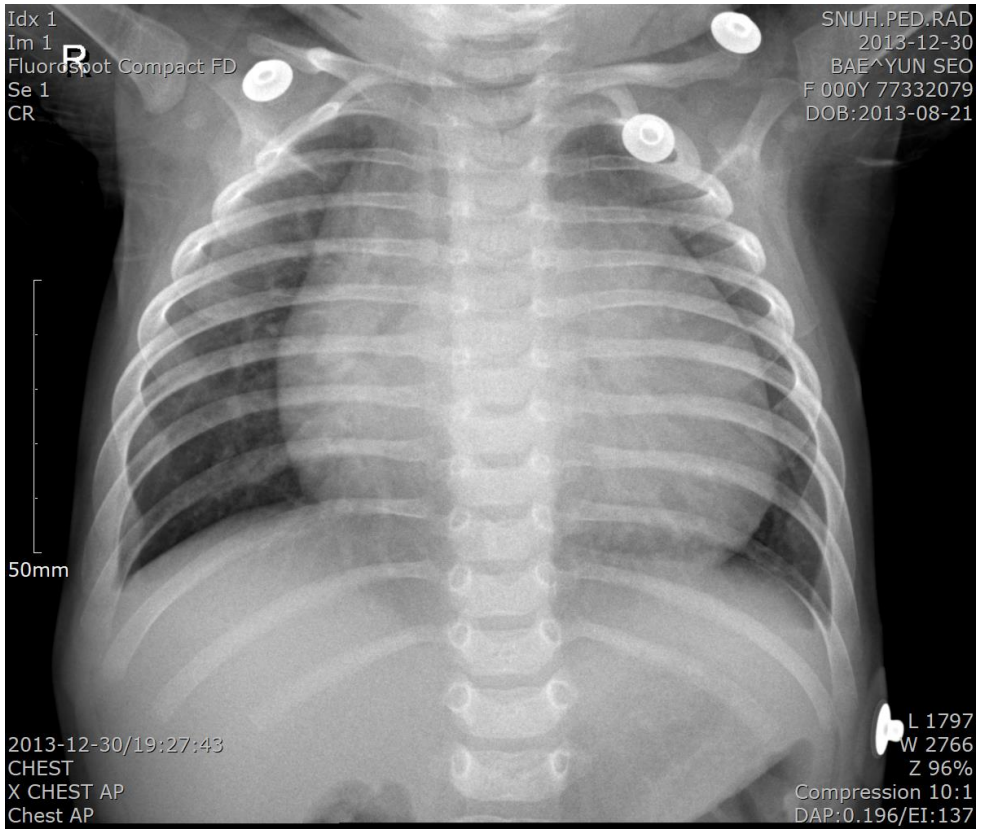
CC> poor oral intake

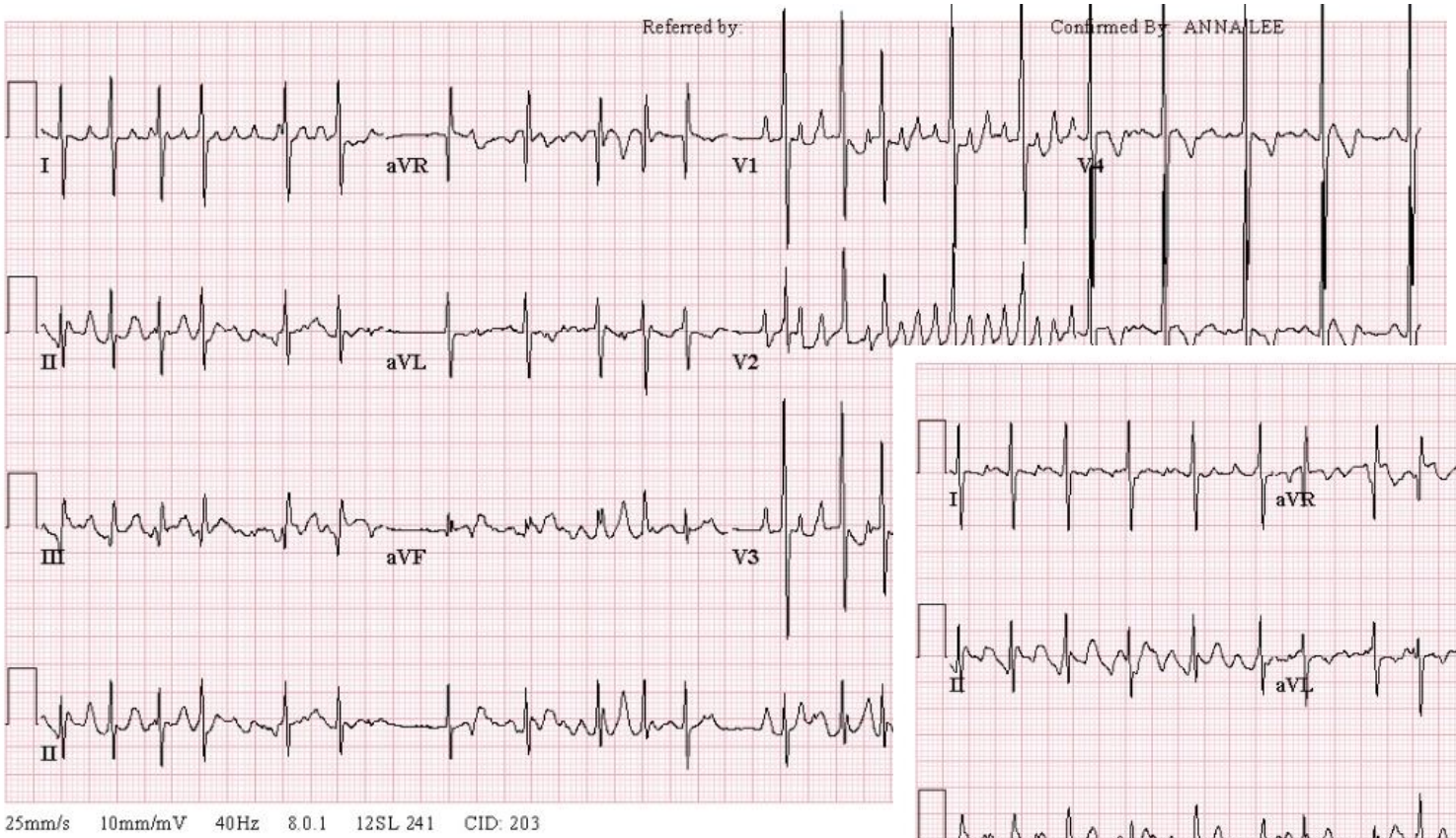
Respiratory difficulty, tachypnea for 2-3 weeks

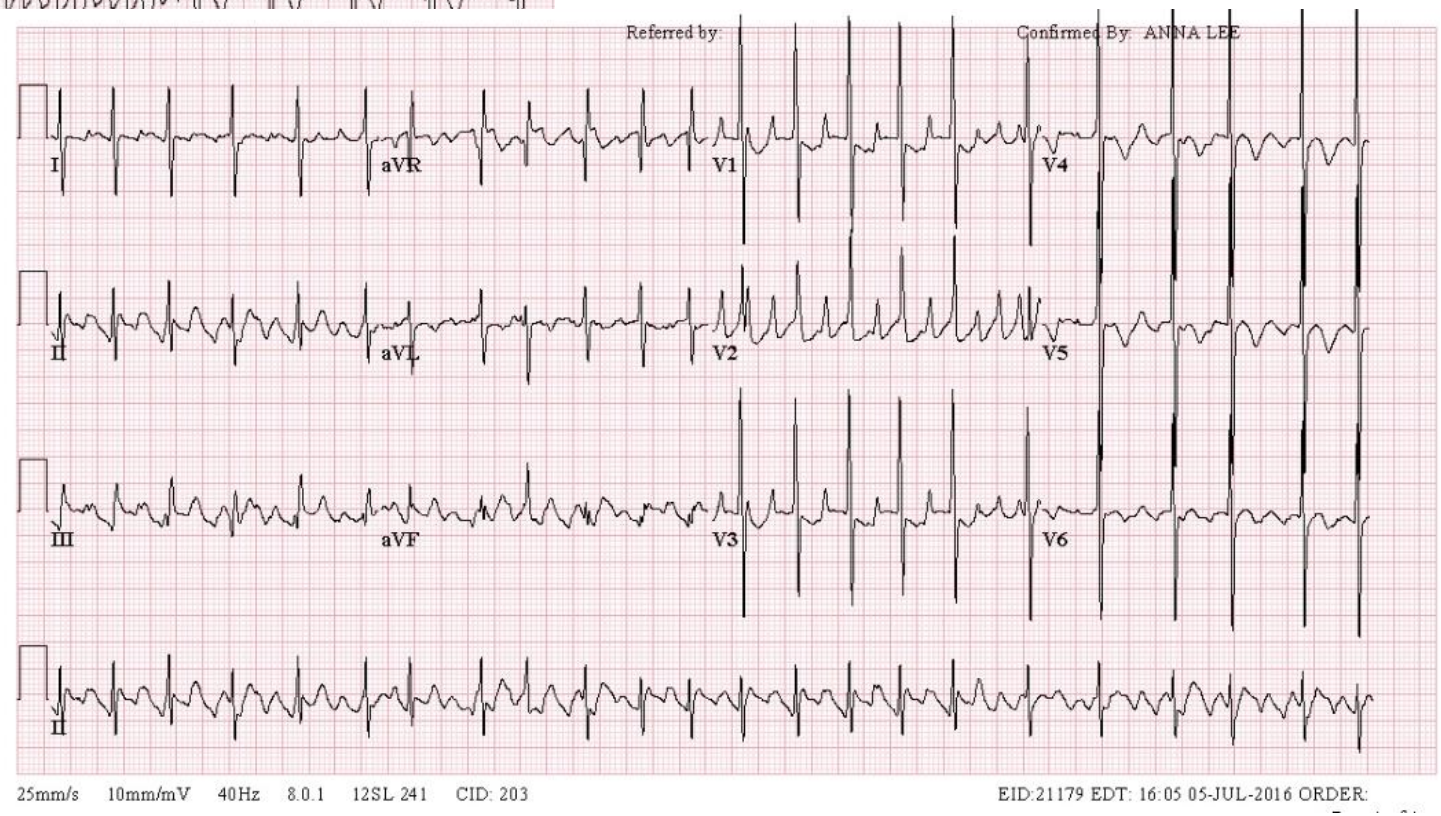
V/S 85/40mmHg, 145 bpm, RR 40/min, no fever

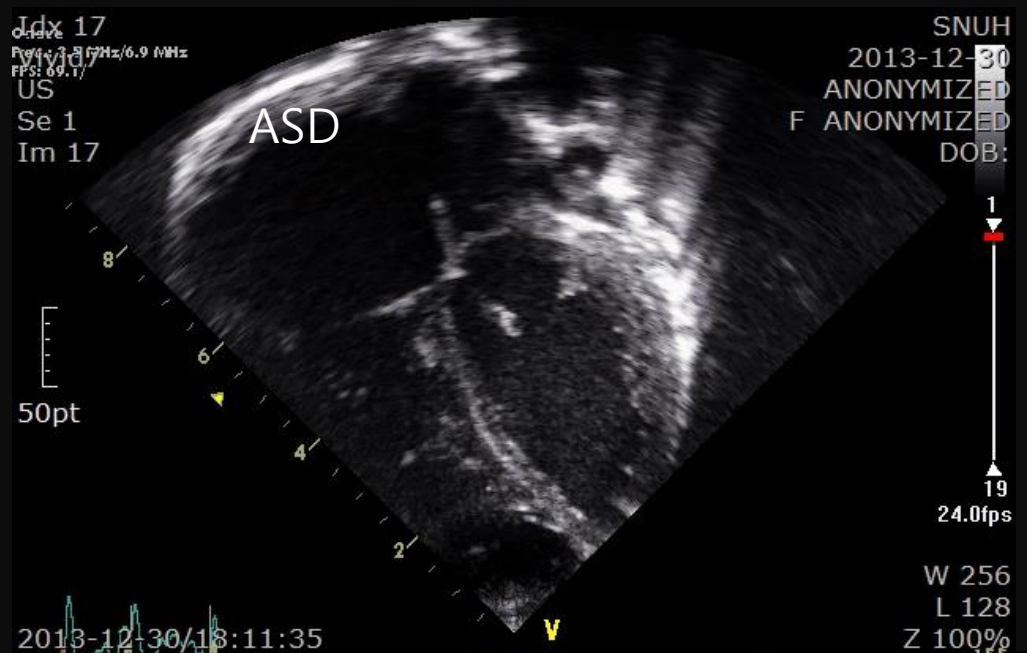
Full term, birth weight 3.4kg

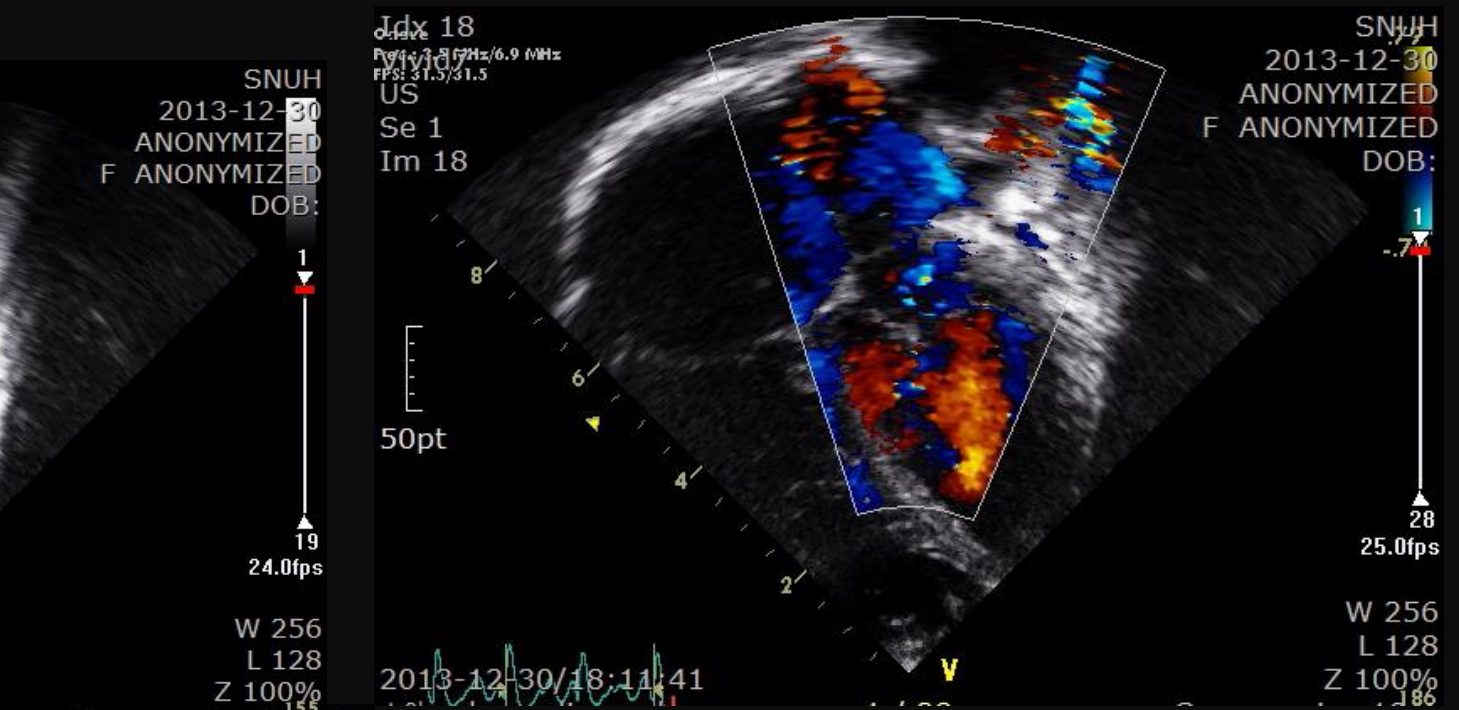
Current Wt 9kg

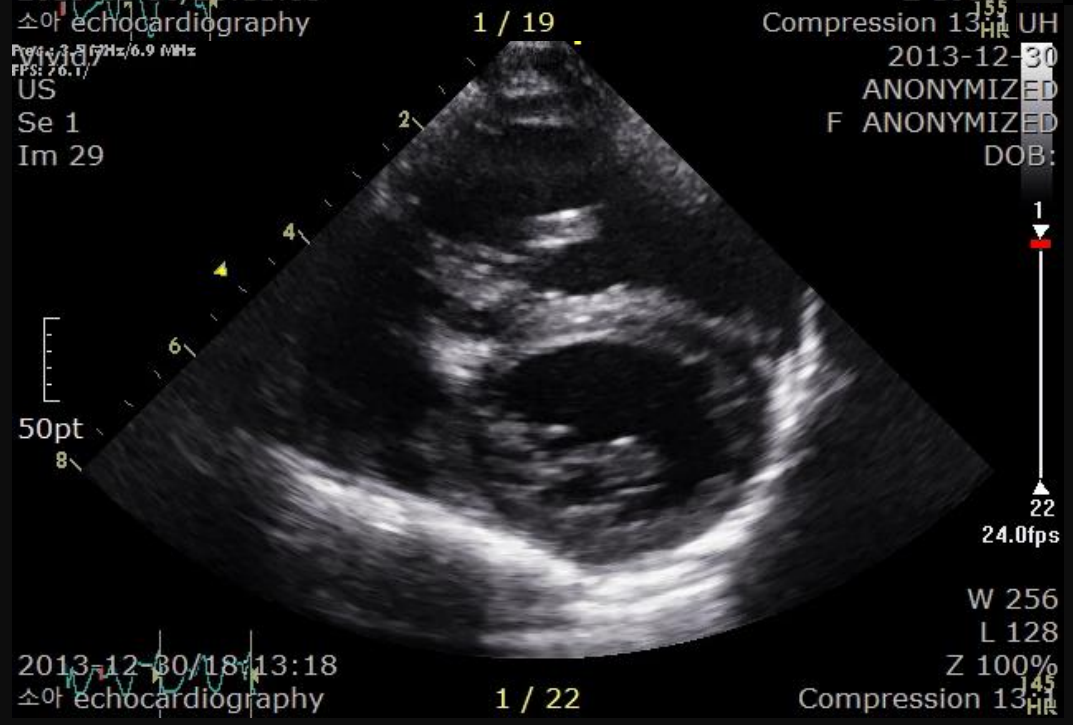


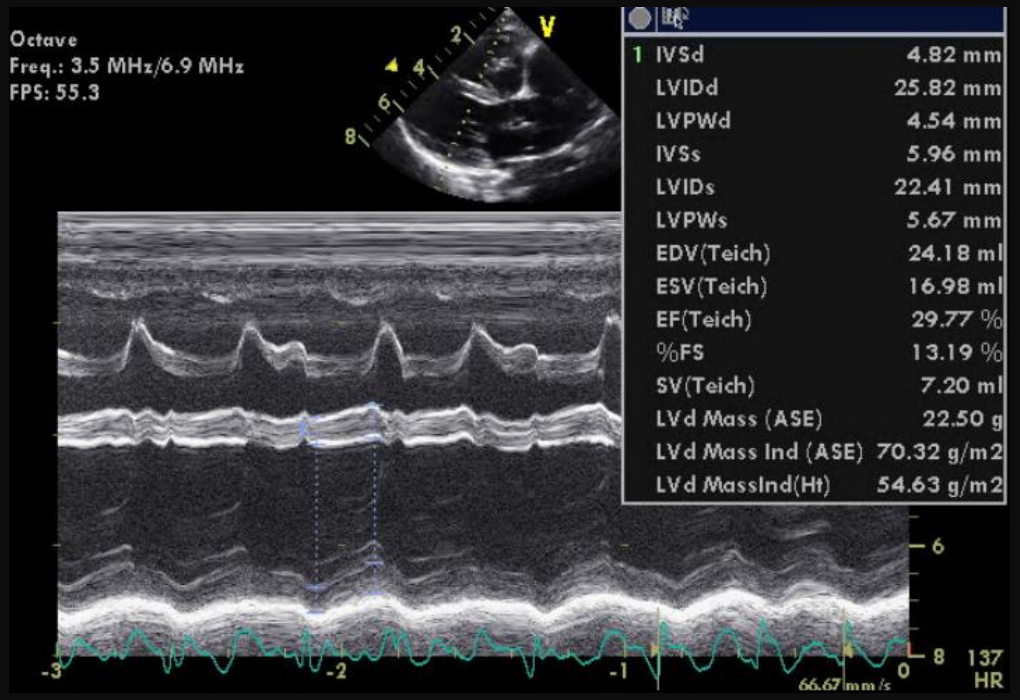

Referred by:
Confirmed By: ANNA LEE
I
aVR
V1
V4
II
aVL
V2
III
aVF
V3
II
25mm/s 10mm/mV 40Hz 8.0.1 12SL 241 CID: 203


Referred by:
Confirmed By: ANNA LEE
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
25mm/s 10mm/mV 40Hz 8.0.1 12SL 241 CID: 203
EID:21179 EDT: 16:05 05-JUL-2016 ORDER:


Idx 17
Vivid7
US
Se 1
Im 17
ASD
SNUH
2013-12-30
ANONYMIZED
F ANONYMIZED
DOB:
50pt
24.0fps
W 256
L 128
Z 100%
2013-12-30/18:11:35
소아 echocardiography
1 / 19


Idx 18
Vivid7
US
Se 1
Im 18
SNUH
2013-12-30
ANONYMIZED
F ANONYMIZED
DOB:
50pt
25.0fps
W 256
L 128
Z 100%
2013-12-30/18:11:41

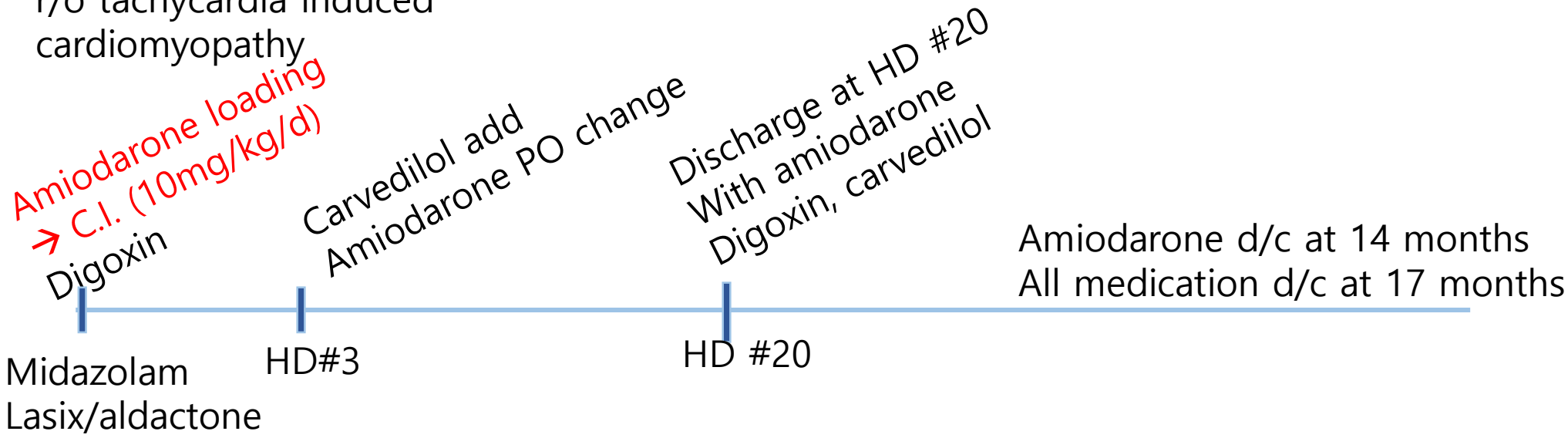

Vivid7
US
Se 1
Im 29
SNUH
2013-12-30
ANONYMIZED
F ANONYMIZED
DOB:
50pt
24.0fps
W 256
L 128
Z 100%
2013-12-30/18:13:18
소아 echocardiography
1 / 22


Octave
Freq.: 3.5 MHz/6.9 MHz
FPS: 55.3
1 IVSd 4.82 mm
LVIDd 25.82 mm
LVPWd 4.54 mm
IVSs 5.96 mm
LVIDs 22.41 mm
LVPWs 5.67 mm
EDV(Teich) 24.18 ml
ESV(Teich) 16.98 ml
EF(Teich) 29.77 %
%FS 13.19 %
SV(Teich) 7.20 ml
LVd Mass (ASE) 22.50 g
LVd Mass Ind (ASE) 70.32 g/m2
LVd MassInd(Ht) 54.63 g/m2
66.67 mm/s
137 HR

MAT

LV enlargement
LV EF 30%
r/o tachycardia induced cardiomyopathy

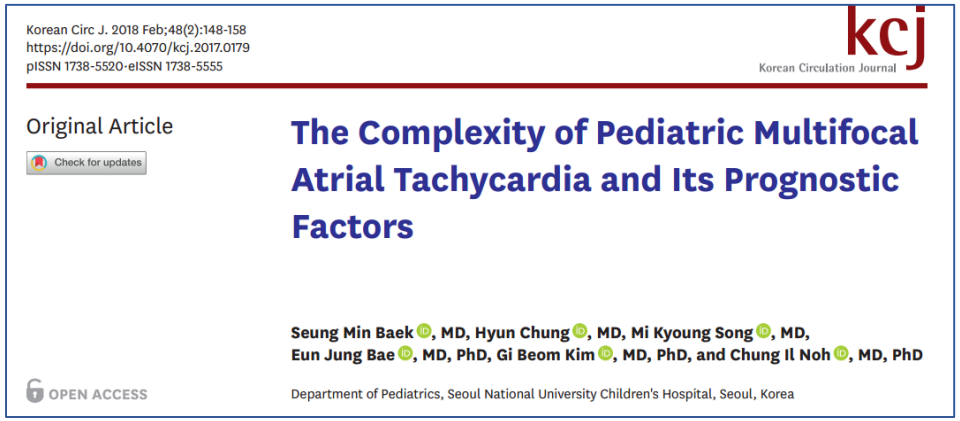
→ Normalized LV function/dimension while rate control



Midazolam sedation
Lasix/aldactone

Multifocal AT

- Infants (m/c)



Korean Circ J. 2018 Feb;48(2):148-158
https://doi.org/10.4070/kcj.2017.0179
pISSN 1738-5520·eISSN 1738-5555

kcj Korean Circulation Journal

Original Article

Check for updates

The Complexity of Pediatric Multifocal Atrial Tachycardia and Its Prognostic Factors

Seung Min Baek, MD, Hyun Chung, MD, Mi Kyoung Song, MD, Eun Jung Bae, MD, PhD, Gi Beom Kim, MD, PhD, and Chung Il Noh, MD, PhD

Department of Pediatrics, Seoul National University Children's Hospital, Seoul, Korea

OPEN ACCESS

Background and Objectives: Multifocal atrial tachycardia (MAT), in general, has a favorable outcome. However, there are insufficient data regarding MAT in a pediatric population. This study sought to determine the clinical course of MAT and identify potential prognostic factors.
Methods: The medical records of MAT patients from 1997–2015 were reviewed. The arrhythmia control rate and factors for unfavorable outcomes were assessed and compared to those in the literature.
Results: Of the 33 included patients (19 boys and 14 girls), 27 were infants less than 1 year of age. The median age at diagnosis was 1.7 months (range, 0 day to 14 years). Fourteen (42%) patients had structural heart disease. Eight (24%) patients had lung disease and 6 (18%) had a syndromic diagnosis belonging to RASopathy. Two patients developed polymorphic ventricular tachycardia, in whom genetic analysis confirmed the presence of the *RyR2* mutation several years later. MAT was controlled in 26 patients (84%) within 3.9 months (median; range, 16 days–18.4 years) using an average of 2.4 medications. There were 3 cases of cardiopulmonary mortality. The arrhythmia control rate was higher in the infant group (85%) than in the non-infant group (67%), although this trend was not statistically significant. There was a significantly lower rate of unfavorable outcomes in the idiopathic infant group (n=11) than in the other groups (p=0.008). Considering the findings of previous studies, the mortality rate was significantly higher in patients with structural heart disease than in patients without (21% vs. 5%, p=0.01).
Conclusion: MAT usually affects infants and has a favorable prognosis, particularly in the idiopathic infant group. However, in the presence of other comorbidities, MAT may have a variable clinical course.

- 33 patients including 27 infants
- Rate control
- Beta-blocker > digoxin & amiodarone

KJC 2018;48(2):148-158

- Infants with MAT: start with digoxin or with a flecainide and propafenon, then using amiodarone as second option (Class I, B)

2013 EHRA, AEPC guideline

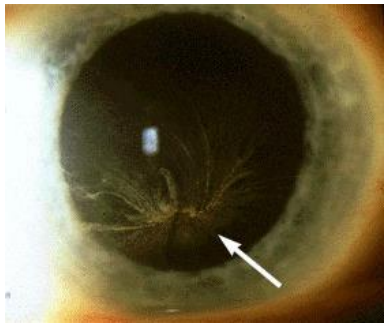
Indications of amiodarone

- Primary drug in pediatric resuscitation
  - effective in treating both life threatening VT/VF (not associated with prolonged QTc)

- Tachyarrhythmia with Hemodynamically unstable patients and patients with congestive HF with reduced LV EF who may be adversely affected by negative inotropic or vasodilating effects of other rate-controlling agents.
- Drug refractory SVT
- Rhythm control in AF/AFL
- Postoperative junctional ectopic tachycardia

Adverse effects

- 15% within the 1st yr of use and 50% for long-term use



10% of these pts actual visual symptoms

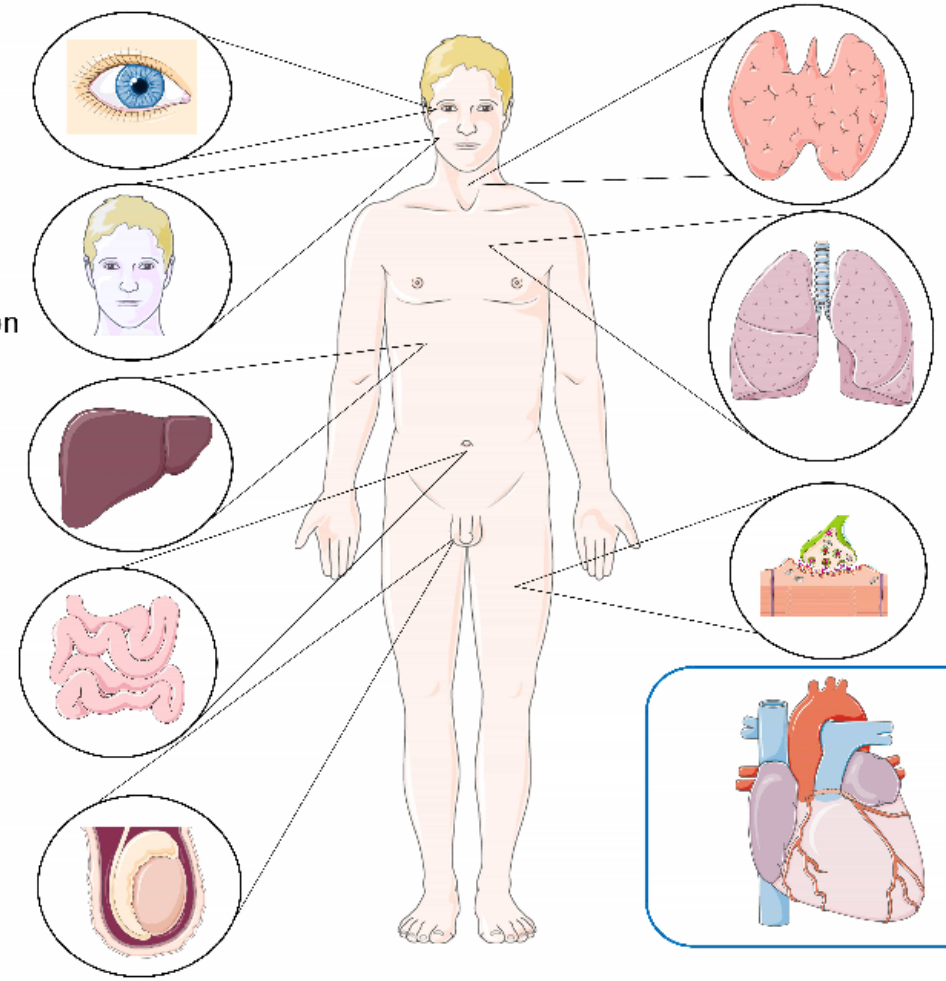
OPTIC TOXICITY
- Optic neuropathy
- Corneal deposits (cat's whiskers)

SKIN ALTERATIONS
- Photosensitivity
- Blue-gray discoloration

HEPATOTOXICITY
- Acute hepatitis
- Chronic liver failure

G.I. DISTURBANCES
- Constipation
- Nausea

G.U. TOXICITY
- Epididimitis



THYROID DYSFUNCTION
- Hypothyroidism (AIH)
- Hyperthyroidism (AIT type I and type II)

LUNG TOXICITY (AIPT)
- Acute pneumonitis
- Interstitial lung fibrosis

PERIPHERAL NEUROPATHY

MYOPATHY

CARDIAC TOXICITY
- Sinus bradycardia
- AV nodal block
- Hypotension
- TdP

Reviews in cardiovascular medicine 2021;22(4):1383-1392

Amiodarone in infants

Intravenous Amiodarone for Incessant Tachyarrhythmias in Children

A Randomized, Double-Blind, Antiarrhythmic Drug Trial

J. Philip Saul, MD; William A. Scott, MD; Stephen Brown, MD; Pablo Marantz, MD; Valeria Acevedo, MD; Susan P. Etheridge, MD; James C. Perry, MD; John K. Triedman, MD; Susan W. Burriss, BSN, MS; Paul Cargo, RN; Jay Graepel, PhD; Eeva-Kaarina Koskelo, PhD; Rebecca Wang, MD; for the Intravenous Amiodarone Pediatric Investigators

Background—Intravenous (IV) amiodarone has proven efficacy in adults. However, its use in children is based on limited retrospective data.

Methods and Results—A double-blind, randomized, multicenter, dose-response study of the safety and efficacy of IV amiodarone was conducted in 61 children (30 days to 14.9 years; median, 1.6 years). Children with incessant tachyarrhythmias (supraventricular arrhythmias [n=26], junctional ectopic tachycardia [JET, n=31], or ventricular arrhythmias [n=4]) were randomized to 1 of 3 dosing regimens (low, medium, or high: load plus 47-hour maintenance) with up to 5 open-label rescue doses. The primary efficacy end point was time to success. Of 229 patients screened, 61 were enrolled during 13 months by 27 of 48 centers in 7 countries. Median time to success was significantly related to dose (28.2, 2.6, and 2.1 hours for the low-, medium-, and high-dose groups, respectively; $P=0.028$). There was no significant association with dose for any arrhythmia subgroup, including JET, but the subgroups were too small for an accurate assessment. Adverse events (AEs) were common (87%), leading to withdrawal of 10 patients. There were 5 deaths in the 30-day follow-up period (2 possibly related to the study drug). Dose-related AEs included hypotension (36%), vomiting (20%), bradycardia (20%), atrioventricular block (15%) and nausea (10%).

- Incessant tachy

  SVT 26, JET 31, VA 4
- Primary efficacy end point: time to success

Circulation. 2005;112:3470-3477

Intravenous Amiodarone for Incessant Tachyarrhythmias in Children

A Randomized, Double-Blind, Antiarrhythmic Drug Trial

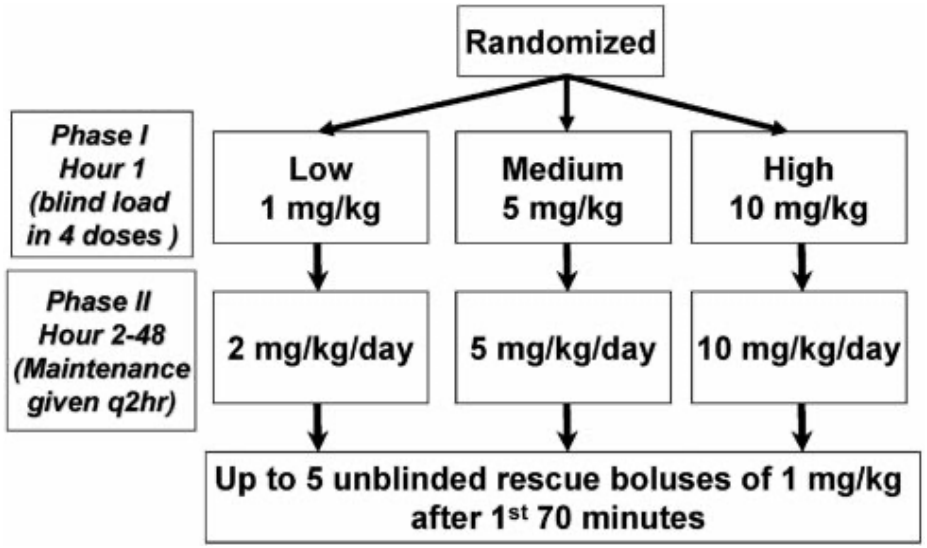


Figure 1. Overall study design. Study drug administration was divided into loading and maintenance phases.

- **Median time to success:**

28.2 (low-dose), 2.6 (medium-), and 2.1 hrs (high-dose)

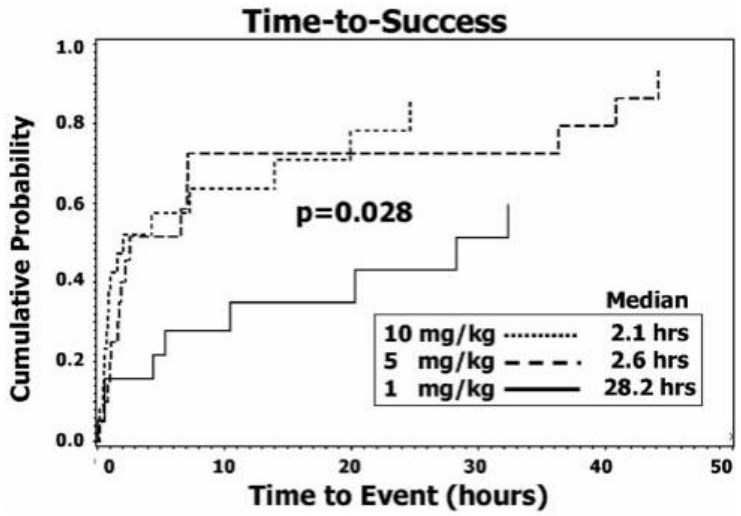


Figure 2. Time to success for the overall ITT population. Abbreviations are as defined in text.

Circulation. 2005;112:3470-3477

Intravenous Amiodarone for Incessant Tachyarrhythmias in Children

A Randomized, Double-Blind, Antiarrhythmic Drug Trial

TABLE 6. AEs by Dose Group

	Dose Group			
	Low (n=19)	Medium (n=20)	High (n=22)	Total (N=61)
≥1 AE, n (%)	17 (89.5)	16 (80.0)	20 (90.9)	53 (86.9)
Hypotension, n (%)	5 (26.3)	7 (35.0)	10 (45.5)	22 (36.1)
Bradycardia, n (%)	0 (0.0)	6 (30.0)	6 (27.3)	12 (19.7)
Atrioventricular block, n (%)	2 (10.5)	3 (15.0)	4 (18.2)	9 (14.8)
Vomiting n (%)	1 (5.3)	3 (15.0)	8 (36.4)	12 (19.7)
Nausea, n (%)	1 (5.3)	1 (5.0)	4 (18.2)	6 (9.8)
≥1 significant AE, n (%)	6 (31.6)	8 (40.0)	10 (45.5)	24 (39.3)
Hypotension, n (%)	0	1 (5.0)	3 (13.6)	4 (6.6)
Bradycardia, n (%)	0	1 (5.0)	2 (9.1)	3 (4.9)
Atrioventricular block, n (%)	1 (5.3)	1 (5.0)	1 (4.5)	3 (4.9)

Adverse events 87%
Significant AEs in 39%
(BP drop, HR fall to <50% for age)
Hypotension, vomiting, brady, AVB, nausea
→ dose related

10 patients withdrwan for significant safety issues
- 4 for hypotension
- 5 for bradycardia
- 3 for AV block

- Hepatic, thyroid, phlebitis → not dose related

Five deaths during the 30 days FU period.
- 2 of the death (1 in the medium and 1 in the high dose) hypotensive AE

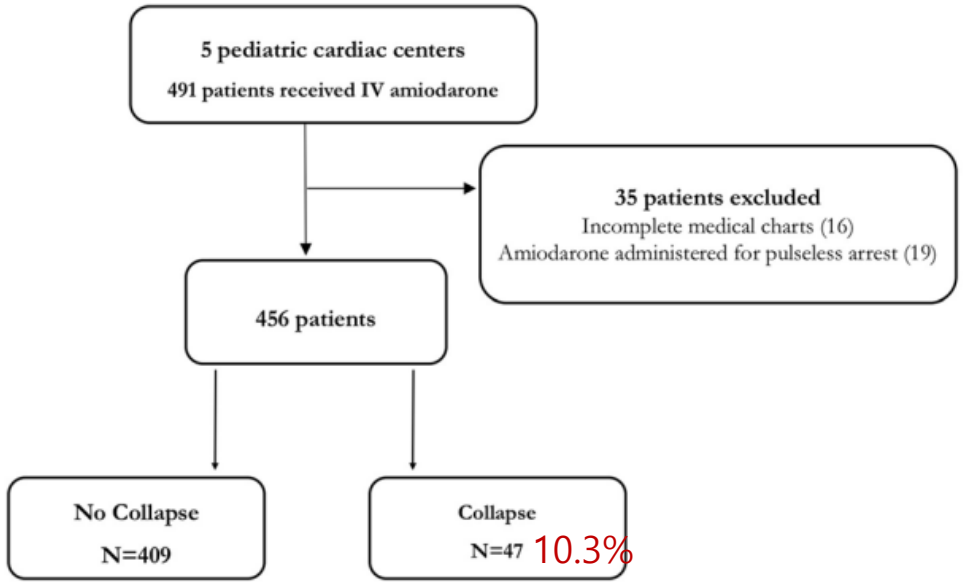
Cardiovascular Collapse with Intravenous Amiodarone in Children: A Multi-Center Retrospective Cohort Study

Khadijah Maghrabi[1] · Orhan Uzun[2] · Joel A. Kirsh[3,4] · Seshadri Balaji[5] · Nicholas H. Von Bergen[6] · Shubhayan Sanatani[7]

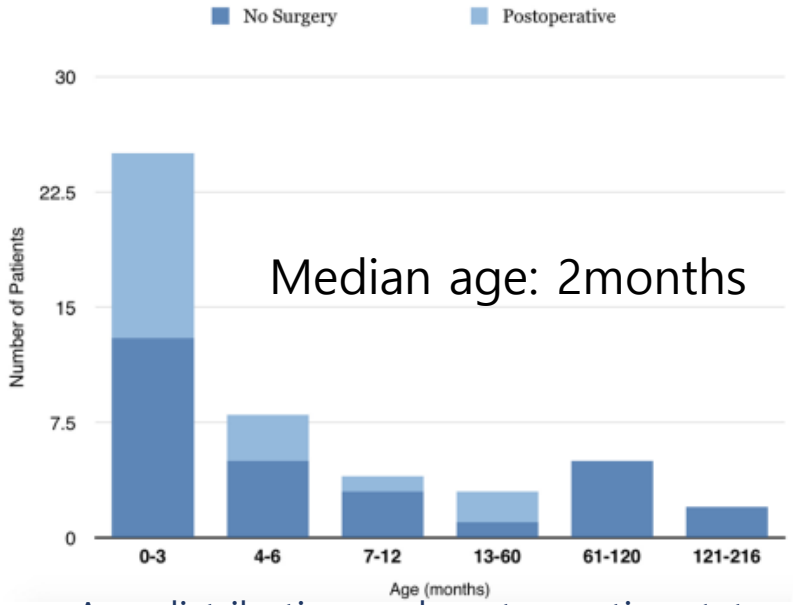
Pediatric Cardiology (2019) 40:925–933

Objective To determine the incidence of cardiovascular collapse in children receiving intravenous (IV) amiodarone and to identify the population at risk.

Design A multicenter study of patients ≤ 18 years of age who received intravenous amiodarone between January 2005 and December 2015. A retrospective analysis was performed to identify patients who developed cardiovascular collapse (bradycardia and/or hypotension).



Bradycardia or hypotension that requires circulatory support (inotropic support or cardiopulmonary resuscitation)



Age distribution and postoperative status among the collapse group

Cardiovascular Collapse with IV Amiodarone in Children: A Multi-Center Retrospective Cohort Study

- Risk factors for collapse in a multivariate analysis

Variable	Multivariate analysis	
	Adjusted odds ratio (95% confidence interval)	*p* value
Age < 3 months	2.7 (1.4–5.2)	0.005
Depressed cardiac function (EF < 35%)	4.6 (2.1–9.9)	< 0.001
Presence of structural heart disease	0.5 (0.17–1.4)	0.18
Postoperative arrhythmia	0.7 (0.2–1.8)	0.12
Method of administration: bolus	7.1 (0.9–52)	0.06
Bolus given over ≤ 20 min	2.1 (1.1–4.1)	0.01
Blood pressure below the 3rd percentile prior to amiodarone administration	4.5 (1.7–12)	0.002
Lactate prior to amiodarone administration > 2 mmol/L	2.0 (0.7–5.2)	0.17

- Mortality rate

-higher in the collapse group (28% vs 8%)

Pediatric Cardiology (2019) 40:925–933

The Effects of Amiodarone on Thyroid Function in Pediatric and Young Adult Patients

Brett Barrett,[1] Colin P. Hawkes,[1,2] Amber Isaza,[1] and Andrew J. Bauer[1,2]

[1]Thyroid Center, Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104; and [2]Perelr
Pennsylvania 19104

Amiodarone impact on thyroid function
1) through iodine excess-associated alterations
2) via direct toxicity to the thyroid gland.

Median age 1.35 yrs

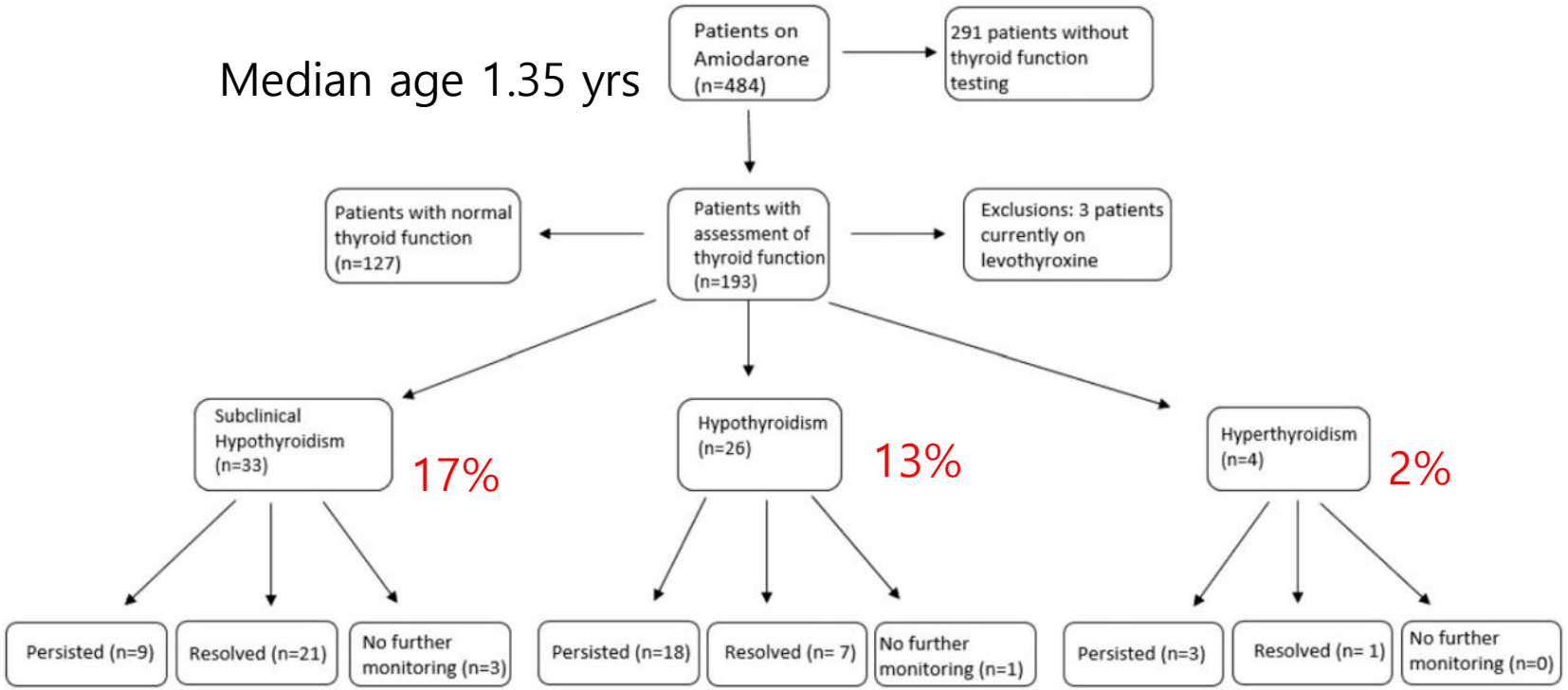


Figure 1. Patients developing subclinical hypothyroidism, AIH, and AIT and resolution.

J Clin Endocrinol Metab 104: 5540–5546, 2019

The Effects of Amiodarone on Thyroid Function in Pediatric and Young Adult Patients

Brett Barrett,[1] Colin P. Hawkes,[1,2] Amber Isaza,[1] and Andrew J. Bauer[1,2]

[1]Thyroid Center, Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104; and [2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Table 3. Clinical Features of Patients Who Developed Each Type of Thyroid Dysfunction

	Hyperthyroidism (n = 4)	Hypothyroidism (n = 26)	Subclinical Hypothyroidism (n = 33)
Duration of amiodarone treatment, n (%)			
Acute, <10 days	1 (25)	3 (11.5)	6 (18.2)
Subacute, ≥10 days to <3 months	2 (50)	16 (61.5)	18 (54.6)
Chronic, ≥3 months	1 (25)	7 (26.9)	9 (27.3)
Days on amiodarone before thyroid dysfunction, mean (SD)	9.00 (11.8)	19.38 (32.0)	16.09 (20.6)
Resolved,			

Conclusions: This study looks at a pediatric and young-adult population in an effort to describe the natural history of amiodarone-induced thyroid dysfunction. Based on our data, we recommend that a complete thyroid-function panel be obtained within the first week and then at weekly intervals for the first 5 weeks after initiation. The majority of thyroid dysfunction was noted within the first 35 days of treatment. (***J Clin Endocrinol Metab*** **104: 5540–5546, 2019)**

Patterns of amiodarone-induced thyroid dysfunction in infants and children

Ana Creo, MD,* Heather Anderson, MD,† Bryan Cannon, MD, FHRS,† Aida Lteif, MD,*
Seema Kumar, MD,* Peter Tebben, MD,*‡ Anoop Mohamed Iqbal, MBBS,*
Akhila Ramakrishna, MBBS,* Siobhan Pittock, MBBCh*

*From the *Division of Pediatric Endocrinology and Metabolism, Mayo Clinic, Rochester, Minnesota, †Division of Pediatric Cardiology, Mayo Clinic, Rochester, Minnesota, and ‡Division of Endocrinology, Diabetes and Metabolism, Mayo Clinic, Rochester, Minnesota.*

Table 2 Thyroid function tests in children receiving amiodarone

	Patients with TFTs checked	Patients developing an elevated TSH*	Time to first abnormal TSH (d)	Initial TSH (mIU/L)	Peak TSH (mIU/L)	FT4 at peak TSH (ng/dL)
All patients (n = 150)	63 (58)	50.8	7 (3–19)	4.8 (2.8–8.8)	11.4 (6.4–23.3)	1.6 (1.2–1.8)
Neonates (n = 27)	12 (44)	66.7	12 (6–20)	10.3 (6.8–26.4)	28.8 (11.4–40)	1.5 (1.1–1.6)
Infants (n = 25)	11 (46)	36.4	4 (3–17)	4.3 (2.9–5.1)	14.3 (9.4–211.7)	1.6 (1.2–1.9)
Young children (n = 27)	18 (67)	38.9	7 (5–57)	3.0 (2.3–4.9)	6.0 (5.0–8.0)	1.8 (1.6–2.4)
Older children (n = 71)	23 (32)	56.5	10 (2–17)	5.9 (2.2–9.1)	9.6 8.3–18.3)	1.2(1.2–1.4)
Short-term therapy (3–30 days)						
All ages (n = 109)	31 (28)	54.8	5 (2–14)	5.9 (2.7–9.8)	15 (8.7–26.8)	1.35 (1.0–1.6)
Neonates (n = 21)	7 (33)	57.1	6 (4–17)	9.2 (6.0–22.9)	23.5 (11.4–63.1)	1.25 (0.9–1.5)
Infants (n = 17)	5 (29)	40.0	N/A	4.2 (1.1–4.4)	N/A	N/A
Young children (n = 10)	3 (30)	33.3	N/A	2.8 (2.5–5.8)	N/A	N/A
Older children (n = 61)	16 (26)	62.5	5 (2–11)	6.15 (2.4–9.5)	10.3 (9.2–15.6)	1.2 (1.0–1.5)
Long-term therapy (>30 days)						
All ages (n = 41)	32 (78)	46.9	15 (6–20)	4.5 (2.9–6.9)	8.9 (5.2–18.8)	1.6 (1.4–2.3)
Neonates (n = 6)	5 (83)	80.0	17 (7–20)	11.4 (7.5–25.6)	28.8 (11.4–34.4)	1.85 (1.6–2.1)
Infants (n = 8)	6 (75)	33.3	4 (3–17)	4.6 (3.3–5.3)	14.3 (9.4–211.7)	1.6 (1.2–1.9)
Young children (n = 17)	15 (88)	40.0	7 (5–57)	3.1 (2.3–4.8)	6.0 (5.0–8.0)	1.8(1.6–2.4)
Older children (n = 10)	7 (70)	42.9	19 (18–30)	4.4 (2.2–7.7)	8.9 (5.2–16.1)	1.3 (1.3–1.4)

TSH above the reference range

*In patients who had thyroid testing performed.

Heart Rhythm 2019;16:1436–1442

Patterns of amiodarone-induced thyroid dysfunction in infants and children

Ana Creo, MD,* Heather Anderson, MD,† Bryan Cannon, MD, FHRS,† Aida Lteif, MD,*
Seema Kumar, MD,* Peter Tebben, MD,*‡ Anoop Mohamed Iqbal, MBBS,*
Akhila Ramakrishna, MBBS,* Siobhan Pittock, MBBCh*

Most patients who developed elevated TSH values
→within the first 2 weeks of amiodarone exposure.

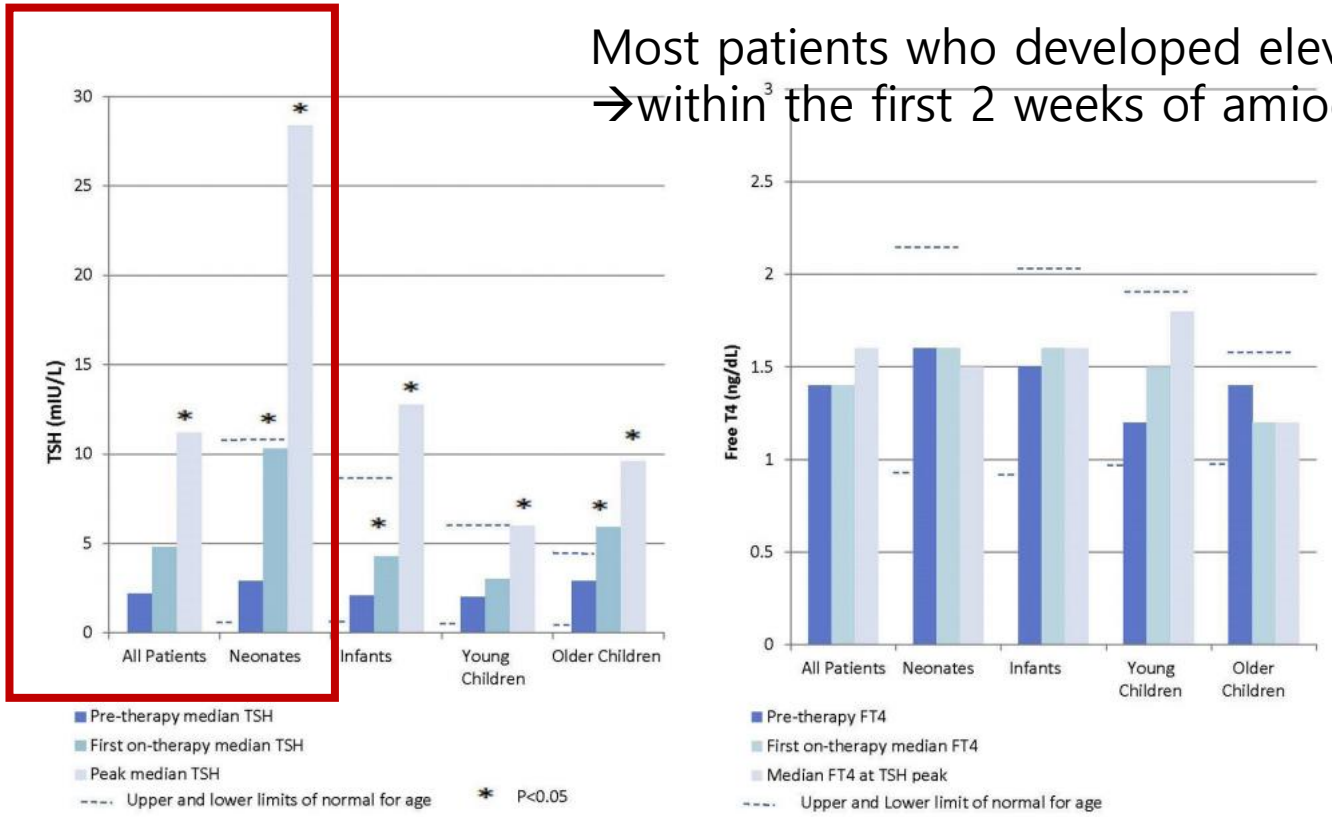


Figure 1 Thyroid function tests by age. FT4 = free thyroxine; TSH = thyroid-stimulating hormone.

Heart Rhythm 2019;16:1436–1442

Amiodarone-induced thyroid dysfunction in children

- Adequate thyroid hormone levels on brain development in the first 3 years of life

→ Rigorous thyroid function test monitoring is required in these population

Table 1. Amiodarone-induced hypothyroidism screening diagnosis, screening recommendations and treatment

	Amiodarone-induced hypothyroidism
Timing of onset	Early (within weeks of amiodarone use)
Risk factors	Iodine sufficient region, female, underlying Hashimoto's thyroiditis
Diagnosis	Elevated TSH greater than 10 mIU/l with low-fT4
Treatment	Levothyroxine – lower starting dose with slow dose escalation to decrease the risk of precipitation or exacerbating arrhythmia. Goal is normalization of TSH.
Screening recommendations for amiodarone-induced thyroid dysfunction in pediatrics	Baseline TSH, free T4, T3 and reverse-T3 (rT3) Weekly TSH, FT4, T3, and rT3 for the first 5 weeks after initiation of amiodarone. If thyroid dysfunction is not detected in the first 5 weeks, then thyroid-function testing could then be performed less frequently, such as every 1–3 months, with decreasing frequency based on results and clinical status Thyroid autoantibodies (antithyroglobulin and antithyroid peroxidase) for patients older than 2 years of age

J Clin Endocrinol Metab 2019;104:5540–5546.
Curr Opin Pediatr 2021, 33:436–441

Summary

- Amiodarone is a potent antiarrhythmic drug
- Effective in the patients with life-threatening incessant tachycardias, postop junctional tachycardia, and incessant SVT
- Neonates and infants were prone to developing complications
- Caution and careful hemodynamic monitoring is recommended when

using IV amiodarone, especially in young infants, hemodynamically compromised patients, and in patients receiving rapid amiodarone bolus administration.

- Thyroid function abnormalities is common complication in infants.

Baseline and weekly TFT for the first 5 weeks after initiation of amiodarone is recommended