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DIGOXIN: Its Role in Pediatric Heart Failure and Atrial Fibrillation

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Digoxin is the only commonly used oral inotropic agent. Its most important mechanism of action is in its ability to blunt sympathetic nervous system, slow heart rate and increase cardiac filling time.

What do we know about the pharmacological properties of digoxin?

Digoxin was extracted from foxglove plant, D. lanata and D. purpurea, plants that were abundant in Brazil, South Africa and other Mediterranean countries. Its use as a therapy for cardiac ailment dates back in 1250's when ancient Arabs and Romans used the extracts for treatment of dropsy. Also noted was excessive vomiting in people who ingested leaves of this plant when added as an ingredient in the preparation of "omalade". It was in 1785 that a monograph on the use of digoxin entitled "An account of the foxgloves and some of its medical uses with practical remarks on dropsy and other diseases" by William Withering, MD was published in Birmingham, London.

After more than 200 years of experience with digoxin use in cardiac ailment, its mechanism of action is still debatable (Haji and Movahed, 2000). There a number of clinical trials on the use of digoxin in adult patients with heart failure in combination with other drugs, however, randomized controlled trials on its use in children are lacking. Our information are derived from small uncontrolled studies among children with ventricular septal defects (VSD).

The pharmacokinetics (Pk) and pharmacodynamics (Pd) of digoxin is characterized by the following: 70-80% absorption in the proximal part of the small intestine following oral administration, 20-30% bound to serum protein and is extensively distributed in tissues due to its large volume of concentration. The heart and kidneys have high concentration while the skeletal muscles form the largest digoxin storage. Its elimination half-life in persons with normal renal function ranges from 38-48 hours and 60-170 hours in premature neonates. A steady state plateau concentration following maintenance doses is achieved after 4-5 half-lives or 7-10 days in patients with normal renal function. About 70% of the drug is excreted by the kidneys and 30% via fecal route or hepatic metabolism.

Digoxin has a narrow therapeutic range and side effects can be seen in 10-20% of all cases receiving this drug. There are some factors that can modify serum level of digoxin. These are renal clearance of creatinine, bioavailability of drug formulation and volume of distribution, amount of extra renal clearance, body weight, serum albumin concentration, high fiber intake and some drugs like macrolides, metoclopramide, indomethacin and

spironolactone. Digoxin has interactions with some drugs that increase serum digoxin level (AAD, ACEi) or increase drug toxicity (furosemide).

The therapeutic range of digoxin is 0.8-2ng/ml and toxicity is seen at level >2 ng/ml. Mild signs of toxicity can be managed with withdrawal of digoxin, while life threatening signs will require more aggressive interventions. If the patient had a history of acute ingestion of 4mg of digoxin, first line management is administration of digoxin-specific antibody fragments. Ventricular tachycardia may be managed with potassium administration in the presence of hypokalemia, and drugs like lidocaine or phenytoin may be administered. In cases wherein there is sinoatrial arrest or high grade AV block, atropine can be tried and cardiac pacing be considered.

What are the clinical applications of digoxin in pediatric patients? Are there existing evidences or guidelines for its use?

In 1986, Myung Park had an article published in the Journal of Pediatrics about the “Use of digoxin in infants and children with specific emphasis on dosage.”

His conclusions are as follows:

A. Pk studies indicate that somewhat higher doses are required in infants to attain same serum levels as in adults. The more rapid body clearance of digoxin and large volume of distribution are the reasons cited.
B. High serum digoxin levels are not indicated on the basis of decreased myocardial uptake in infant.
C. High levels of serum digoxin (>2ng/ml) are not associated with greater inotropic effects in pediatric patients. Higher dosages are associated with greater frequency of toxic effects especially in infants receiving concomitant diuretic therapy.
D. Classic ECG signs of digitalis toxicity derived from adult patients with coronary artery disease do not apply to immature or healthy cardiac tissue. Common first sign of digoxin toxicity in pediatric patients is prolongation of PR interval.

What are the effects of digoxin in infants with congested circulatory state due to VSD?

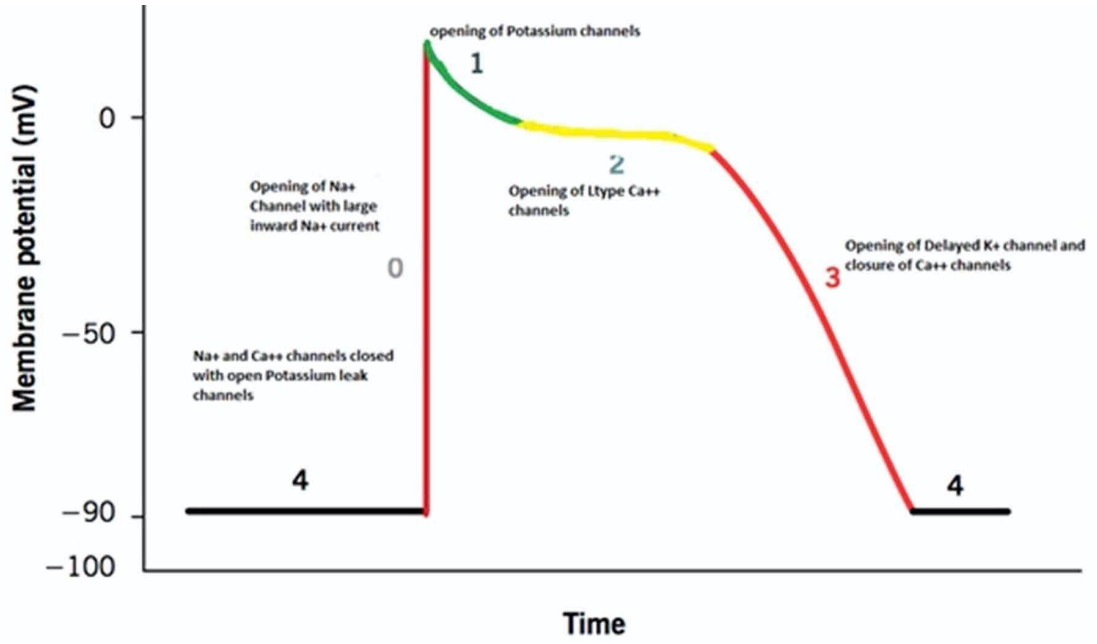
Behrman Jr. et al in 1983 had a study published in NEJM.
They reported their findings in 21 infants, mean age 2.7 months, mean weight 3.8kg with CHD VSD given digoxin to treat congested circulatory state, Dose was adjusted to achieve a mean steady-state concentration of 1.6 to 0.3 ng/ml of serum digoxin level. Mean serum level of Na-K ATPase fell from 23.1 +/- 7 to 12.6 +/- 5.2 nmol/ng/min with treatment. The conclusions from this study are: only 6/21 patients had inotropic response as reflected by echo measurements. Digoxin was of clinical benefit to 12 patients.

How about the effect of digoxin on contractility and symptoms in patents with large VSD?

Kimball, et al in an article that was published in 1991 edition of The American Journal of Cardiology, studied the effect of digoxin in infants with large VSD.
19 infants with symptoms of CHF due to VSD were studied with load-independent indexes during 4 study periods: before any medication, while on chronic diuretics, while on both diuretics and digoxin and while on diuretic alone. 18 infants underwent catheterization with mean QpQs of 3:1. In patients receiving digoxin and diuretics, cardiac index (CI) was significantly greater than in control. In the diuretics alone after digoxin was discontinued, CI was no longer different. Signs and symptoms did not improve significantly by either digoxin or diuretics. It was concluded that infants with large left to right shunt VSD and receiving digoxin and diuretics, CI was significantly greater than in control subjects. Neither diuretics alone nor in combination with digoxin improved symptoms significantly.

The addition of ACE inhibitors to digoxin and diuretics is effective in improving and prolonging the lives of patients with severe heart failure (Gheorgiade, Can J Cardio 1990).

What is the mechanism of action of digoxin when used in patients with heart failure?



In the 2009 issue of Small animal Critical Care Medicine, an extensive review of digoxin by N. Joel Edwards was published. It is said that the mechanism of action of digoxin is multifaceted. This includes (A) positive inotropic effects mediated through its inhibition of the Na-K ATPase pumps located on myocardial cell membrane which results in an increase in intracellular Na, in turn, in exchange for extracellular Ca ions within the myocardial cell thus mediating increased contractility. (B) digoxin also reduces sympathetic nerve activity, renin-angiotensin activity, circulating catecholamines and

regulates baroreceptor function by increasing vagal tone (vagomimetic effect) which decrease rate of sinus node discharge, atrial conduction and AV node conduction through a prolongation of conduction times and refractory periods in these tissues. These form the basis for digoxin's effectiveness at controlling ventricular response in supraventricular arrhythmias.

In patients with chronic MR, maintenance dose of afterloading agents, hydralazine or CCBs are recommended. Diuretics and digoxin are also useful. Digoxin is used to control rate of ventricular response in patients with TR and AF, as well as to improve myocardial contractility.

What are the guidelines in the use of digoxin in HF management in children?

2014 ISHLT Guidelines for evaluation and management of HF in children

Digoxin is a class III recommendation, while diuretics and ACEi are class I recommendations.

2016 ESC Guidelines (GDMT)

LVEF ≤35%: initiate treatment with ACEi/ARB and BB. With persistence of symptoms and LVEF ≤ 35%, recommendation is to use ARNI.
iIvabradine may be initiated when patient is in sinus rhythm and heart rate ≥ 70bpm (resting HR).
If patient still has resistant symptoms, digoxin, hydralazine and isosorbide dinitrate or LVAD or heart transplant be considered.

What is the role of digoxin in children with chronic or stable HF?

ACE inhibitor, low dose furosemide may be initiated with or without digoxin or beta blockade to treat mild symptoms of HF.
Digoxin dose recommended is 0.005 - 0.01 mg/k/day divided twice daily for children younger than 10 years old and not to exceed 0.125 mg - 0.25 mg oral once a day for older children over 10 years old.
Aldosterone antagonist and beta blockers may be considered. Addition of Ivabradine to children with stable symptomatic HF caused by cardiomyopathy who are in sinus rhythm and with elevated HR is also recommended. The goal of therapy is 20% reduction in HR from baseline.

What is another clinical application of digoxin in children?

Atrial fibrillation (AF) with rapid ventricular rate that is not due to an accessory pathway is another indication.

AF, although rare in children, can be seen in patients with associated cardiac conditions such as rheumatic valvular disease, cardiomyopathy, atrial tumors, IE, EFE or CHD. Any condition that will result into atrial structural abnormalities in the form of fibrosis, dilatation, ischemia, infiltration, or hypertrophy can lead to AF.

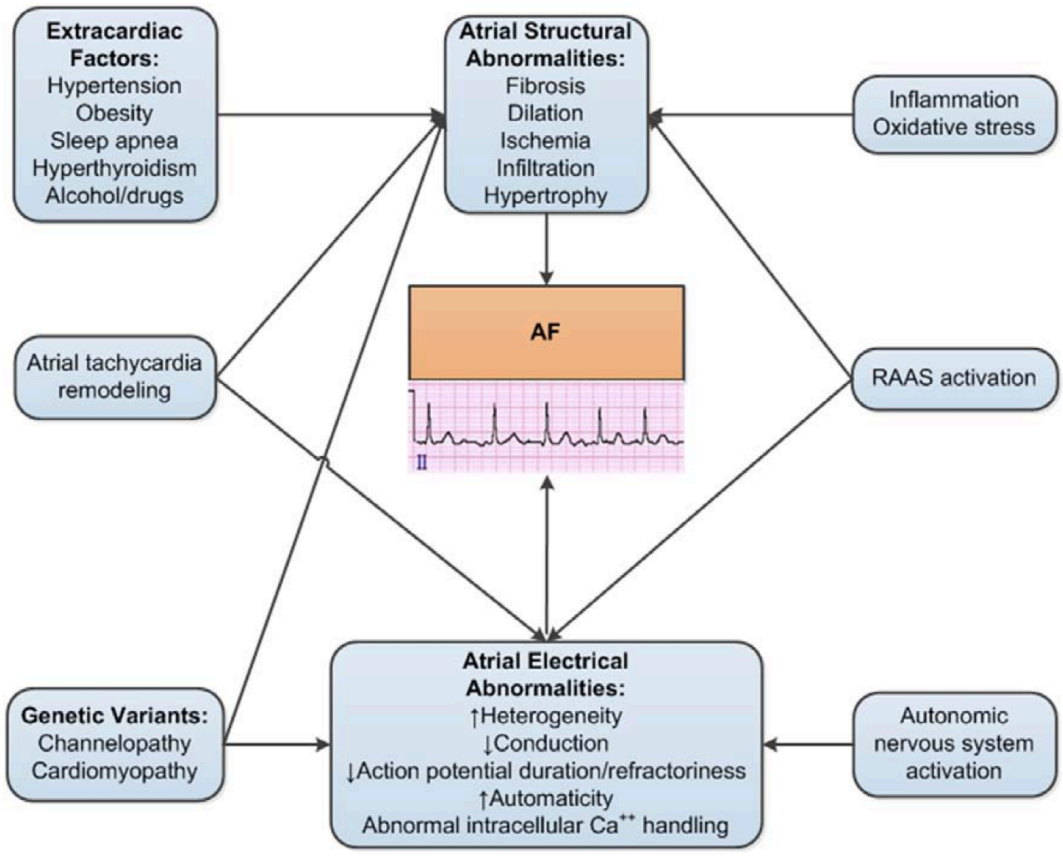


Figure 2. Mechanisms of AF. AF indicates atrial fibrillation; Ca^{++}, ionized calcium; and RAAS, renin-angiotensin-aldosterone system.

What are the indications for digoxin use in AF or atrial flutter?

A. Digoxin is used for rate control in AF or atrial flutter when conventional therapies have not achieved the goal HR.
B. SVT that is not rate controlled by traditional therapies may benefit from digoxin.
C. Fetal tachyarrhythmias, digoxin showed some success
D. Not to be administered in cases of pre-excitation caused b accessory pathways.
E. Ineffective in states of high sympathetic activity.

Are there guidelines on the management of atrial fibrillation for specific patient groups?

2014 AHA/ACC/HRS AF Guidelines (Circulation 2014)

Table 15. Summary of Recommendations for Specific Patient Groups and AF

Recommendations	COR	LOE	References
Hypertrophic cardiomyopathy			
Anticoagulation is indicated in HCM with AF independent of the CHA_2DS_2-VASc score	I	B	50, 457
Antiarrhythmic drugs can be useful to prevent recurrent AF in HCM. Amiodarone or disopyramide combined with a beta blocker or nondihydropyridine calcium channel antagonist are reasonable	IIa	C	N/A
AF catheter ablation can be beneficial for HCM to facilitate a rhythm-control strategy when antiarrhythmics fail or are not tolerated	IIa	B	458–461
Sotalol, dofetilide, and dronedarone may be considered for a rhythm-control strategy in HCM	IIb	C	11
AF complicating ACS			
Urgent cardioversion of new-onset AF in the setting of ACS is recommended for patients with hemodynamic compromise, ongoing ischemia, or inadequate rate control	I	C	N/A
IV beta blockers are recommended to slow RVR with ACS and no HF, hemodynamic instability, bronchospasm	I	C	N/A
With ACS and AF with CHA_2DS_2-VASc score ≥2, anticoagulation with warfarin is recommended unless contraindicated	I	C	N/A
Amiodarone or digoxin may be considered to slow RVR with ACS and AF and severe LV dysfunction and HF or hemodynamic instability	IIb	C	N/A
Nondihydropyridine calcium antagonists might be considered to slow RVR with ACS and AF only in the absence of significant HF or hemodynamic instability	IIb	C	N/A
Hyperthyroidism			
Beta blockers are recommended to control ventricular rate with AF complicating thyrotoxicosis unless contraindicated	I	C	N/A
When beta blockers cannot be used, a nondihydropyridine calcium channel antagonist is recommended to control ventricular rate	I	C	N/A
Pulmonary diseases			
A nondihydropyridine calcium channel antagonist is recommended to control ventricular rate with AF and COPD	I	C	N/A
Cardioversion should be attempted for patients with pulmonary disease who become hemodynamically unstable with new-onset AF	I	C	N/A
WPW and pre-excitation syndromes			
Cardioversion is recommended for patients with AF, WPW syndrome, and RVR who are hemodynamically compromised	I	C	64
IV procainamide or ibutilide to restore sinus rhythm or slow ventricular rate is recommended for patients with pre-excited AF and RVR who are not hemodynamically compromised	I	C	64
Catheter ablation of the accessory pathway is recommended in symptomatic patients with pre-excited AF, especially if the accessory pathway has a short refractory period	I	C	64
IV amiodarone, adenosine, digoxin, or nondihydropyridine calcium channel antagonists in patients with WPW syndrome who have pre-excited AF is potentially harmful	III: Harm	B	493–495
Heart failure			
A beta blocker or nondihydropyridine calcium channel antagonist is recommended for persistent or permanent AF in patients with HF$\downarrow$EF	I	B	269
In the absence of preexcitation, an IV beta blocker (or a nondihydropyridine calcium channel antagonist with HF$\downarrow$EF) is recommended to slow ventricular response to AF in the acute setting, with caution in patients with overt congestion, hypotension, or HF$\downarrow$EF	I	B	502–505
In the absence of pre-excitation, IV digoxin or amiodarone is recommended to control heart rate acutely	I	B	277, 503, 506, 507
Assess heart rate during exercise and adjust pharmacological treatment in symptomatic patients during activity	I	C	N/A
Digoxin is effective to control resting heart rate with HF$\downarrow$EF	I	C	N/A
A combination of digoxin and beta blocker (or a nondihydropyridine calcium channel antagonist with HF$\downarrow$EF) is reasonable to control resting and exercise heart rate with AF	IIa	B	267, 503
It is reasonable to perform AV node ablation with ventricular pacing to control heart rate when pharmacological therapy is insufficient or not tolerated	IIa	B	269, 508, 509
IV amiodarone can be useful to control heart rate with AF when other measures are unsuccessful or contraindicated	IIa	C	N/A

(*Continued*)

In heart failure, digoxin is effective to control resting HR with AF (COR I, LOE C)

Post operative cardiac and thoracic surgery
Digoxin is not recommended, except in post-op AF that is chronic or permanent, to control ventricular rate.
Digoxin is not usually first line therapy for ventricular rate control in patients with AF

For chronic oral therapy, digoxin reduces resting HR but ineffective at controlling ventricular response during exercise.
Digoxin may be combined with BB, CCB to improve ventricular response during exercise.

What is meant by “adequate rate control” in AF management?

Adequate rate control is defined as a HR of 60-80 bpm at rest and 90-115bpm with moderate exercise.

According to ACC/AHA/HRS Guideline, there is no benefit in achieving strict HR control (< 80 bpm at rest and < 110 bpm after a 6 min walk) relative to a more lenient rate control (< 110 bpm at rest).

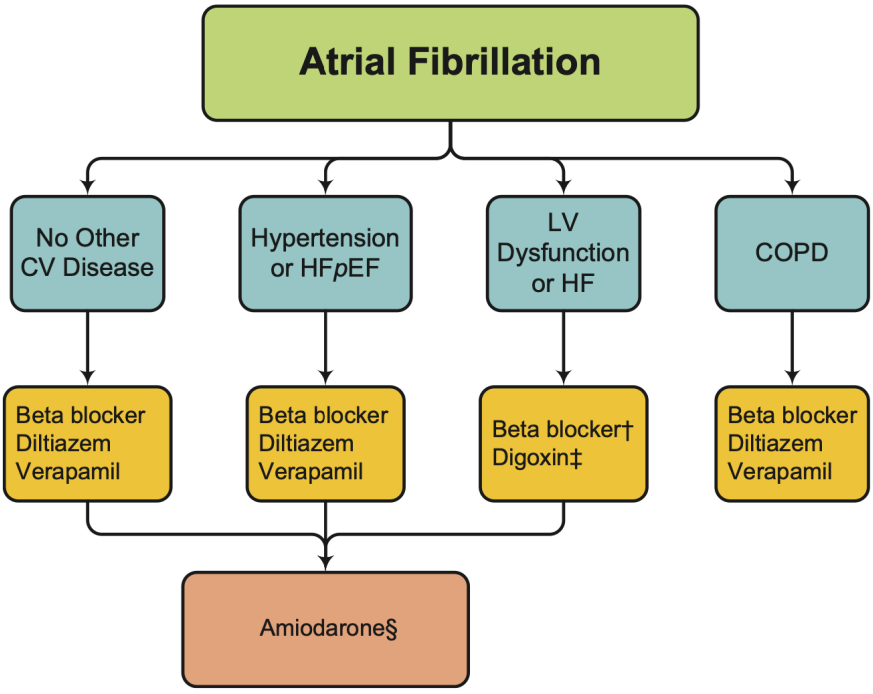
AV nodal blocking drugs are the cornerstones of rate control in long-standing AF in the absence of accessory pathway. Close monitoring of drug levels, serum electrolytes and renal function in sedentary patients given digoxin are recommended.

What are the key messages in the use of digoxin in pediatric patients with HF and/or AF?

HEART FAILURE with REDUCED EJECTION FRACTION (HEFrEF)

A. Digoxin is reserved as a backup drug when first line agents are ineffective.
B. Optimal use of digoxin in the treatment of mild to moderate HF in adult patients to increase myocardial contractility.
C. Digoxin exerts no benefit on mortality
D. Improvement in HF in patients with L to R shunts is achieved in combination with diuretics and ACEi.
E. Digoxin is ineffective in states of high sympathetic activity
F. Conditions considered as contraindications include acute myocarditis, premature infants with impaired renal function, HOCM, WPW with AF, high grade AV Block
G. Use with caution in advanced age, myocardial ischemia, hypothyroidism, hypoxia, electrolyte imbalance, co-administration with drugs inhibiting AV conduction (BB, amiodarone, verapamil, diltiazem)

ATRIAL FIBRILLATION



A. Digoxin use in rate control of AF is usually not a first line therapy
B. Digoxin reduces resting HR but not effective in exercise-induce fast HR
C. Digoxin is contraindicated in AF due to WPW syndrome
D. In post-operative AF, beta blockers and CCBs are class I recommendations (ACC?AHA / HRS guideline 2014)