

11th March 2017

RE: Manuscript number 3257 Atrial tachyarrhythmia in adult congenital heart disease

Dear Xiu-Xia Song,

Thank you for considering our manuscript for publication and for allowing us an opportunity to respond to the reviewer's comments. We have revised our manuscript in the light of the comments and suggestions and hope it is now in good shape for publication. Please find our responses to the reviewers below.

Reviewer #2639968 comments:

Karbassi A et al described a management of atrial tachycardia about prevalence, diagnosis and treatment in adult congenital disease. It is well written and interesting. This reviewer has no comments in this literature.

Author response: Thank you for reviewing our manuscript and for your kind comments we are glad you found our manuscript of interest.

Reviewer #875981 comments:

This is an interesting manuscript. Attention to the following should improve it.

Author response: Thank you for reviewing our manuscript and for your constructive feedback.

Minor comment

1. The following paragraph is confusing. "Rhythm control is recommended as an initial strategy in moderate or complex forms of CHD[17]. This relates to concerns about the impact of tachyarrhythmia on hemodynamics and ventricular function as well as the side effects of antiarrhythmic drugs when they are continued long-term[17,26]. Nevertheless, once an ACHD patient has experienced atrial arrhythmias recurrences are not uncommon and in such cases antiarrhythmic drugs may be beneficial". Did you mean "Rate control is recommended as an initial strategy..." Author response: We did mean that rhythm control should generally be the initial strategy for atrial tachycardia in ACHD patients. The paragraph has been rephrased as follows:

"Rhythm control is generally recommended as the initial strategy for patients with moderate or complex forms of CHD^[17]. This is because loss of sinus rhythm, even with a controlled heart rate can adversely and importantly impact both hemodynamics and ventricular function in ACHD patients^[17,27]. However, once an ACHD patient has experienced atrial arrhythmia, recurrences are often seen. In our experience, the initiation of antiarrhythmic drugs, before further cardioversion may be beneficial to the chances of reestablishing sinus rhythm and/or reducing the frequency of recurrence."

Toronto Congenital Cardiac Centre For Adults

Director

Erwin Oechslin, MD

Research Director
Candice Silversides, MD

Fellowship Director
Lucy Roche, MD

Cardiology

Lee Benson, MD Jack Colman, MD
Andrew Crean, MD Eric Horlick, MD
Erwin Oechslin, MD Mark Osten, MD
Andrew Redington, MD Lucy Roche, MD
Candice Silversides, MD Rachel Wald, MD

Congenital Cardiovascular Surgery

Chris Caldarone, MD Tirone David, MD
Chris Feindel, MD Edward Hickey, MD
Osami Honjo, MD Glen Van Arsdell, MD

Interventional Cardiology

Lee Benson, MD Eric Horlick, MD
Mark Osten, MD

Cardiovascular Imaging

Andrew Crean, MD Lorretta Daniel, MD
Melitta Mezody, MD Elsie Nguyen MD
Erwin Oechslin, MD Narinder Paul, MD
Harry Rakowski, MD Lucy Roche, MD
Candice Silversides, MD Rachel Wald, MD
Bern Wintersperger, MD Anna Woo MD

Advanced Practice Nurses

Barbara Bailey, NP
Noorin Janmohamed, NP
Sue Jimeno, APN Angela Lee, NP

Anesthesiology

Eric Goldszmidt, MD Jane Heggie, MD
Patricia Murphy, MD Annette Vegas, MD

Electrophysiology

Douglas Cameron, MD Eugene Downar, MD
Louise Harris, MD Krishnakumar Nair, MD

Genetics

Anne Bassett, MD David Chitayat, MD
Chantal Morel, MD

Heart Failure

Lucy Roche, MD Heather Ross, MD

Marfan

Timothy Bradley, MD Jack Colman, MD
Andrew Crean, MD

Psychology

Adrienne Kovacs, PhD

Pulmonary Hypertension

John Granton, MD John Thenganatt, MD
Erwin Oechslin, MD

Reproductive Program

Jack Colman, MD Cynthia Maxwell, MD
Mathew Sermer, MD Candice Silversides, MD
Samuel Siu, MD Rachel Wald, MD

Supportive Care & Bioethics

James Downar, MD

Cardiovascular Pathology

Jagdish Butany, MD

Hepatology

Eberhard Renner, MD

Booking Office

Tel: 416-340-4393, Fax: 416-340-4127
ACHD@uhn.ca

Program Office

Carole Ryan, Program Co-ordinator
Tel: 416-340-4871, Fax: 416-340-5014
Email: carole.ryan@uhn.ca

Major Comments:

1. Rate is not specific for any tachycardia mechanism. Atrial tachycardias may be focal or macroreentrant. Explain the differences. Then use that information to make it easier for the reader to grasp why ACHD and atrial macroreentry are intimately associated. Author response: We agree with the reviewer that rate does not distinguish between (or diagnose) mechanisms of atrial arrhythmia and did not intend to imply that it does. However, there are factors related to having underlying ACHD that often slow atrial conduction, whether in sinus rhythm or in atrial tachycardia. This is the point we were trying to make and we have rephrased several sentences to clarify.

Since we are targeting our paper towards general cardiologists, emergency physicians and community primary health care providers we have deliberately not gone into much detail regarding electrophysiological mechanisms of arrhythmia, preferring to focus on the caveats and peculiarities of diagnosing and managing arrhythmia in ACHD patients. However, in the light of your comments about macro reentry vs. micro reentry and focal/ectopic arrhythmia we have modified several paragraphs of the paper in the section headed “Types of atrial tachyarrhythmia in ACHD and their mechanisms”, aiming to be more precise in our language and informative around the subject of mechanisms.

2. It is important to recognize that adenosine’s effects on atrial arrhythmias are inconsistent. In reentrant atrial tachycardias (including atrial flutter and fibrillation), the most common response is transient production of, or increased, AV block. Termination, persistence with AV block, or no effect may also occur (see Crit Care Med. 2009 Sep;37(9):2651-2) Author response: We appreciate the point regarding the effect of adenosine on atrial arrhythmias. We have expanded that paragraph to clarify and included the reference you suggest.

“Patients with WPW, orthodromic AVRT and AVNRT, who are hemodynamically stable can be treated with intravenous adenosine, which may terminate the tachycardia and restore sinus rhythm. This is because adenosine slows AV nodal conduction and these tachycardias include the AV node as an obligatory part of their circuit. In contrast, the effects of adenosine on atrial flutter, IART and atrial ectopic tachycardia are inconsistent^[52-Trohman]. Adenosine will not generally terminate these arrhythmias and is more likely to produce transient or increased AV block, which can unmask atrial activity on an ECG and aid diagnosis. It is important that adenosine be given rapidly and in a sufficient dose to reach the coronary circulation.”

3. It is true patients with WPW and orthodromic AVRT, who are hemodynamically stable can initially be treated with adenosine. Mention the risk of precipitating pre-excited atrial fibrillation.

Author response: We have added a reference which discusses the proarrhythmic risks of adenosine and specifically mentioned the risk of precipitating pre-excited AF:

“Adenosine administration is generally safe but rare proarrhythmic and potentially life-threatening effects have been reported^[53-Mallet]. It can precipitate atrial fibrillation, which as already stated, is a risk in patients with an accessory pathway where the atrial rate may be conducted 1:1 to the ventricles. Patients with pre-excited atrial fibrillation are usually treated with urgent electrical cardioversion because of the risk of cardiovascular collapse^[54].”

4. It would be useful to know more specific data about dofetilide in ACHD. Would you choose it instead of sotalol?

Author response: The information regarding the use of dofetilide in ACHD population is based on a multicenter study of 20 patients, which is mentioned in our review paper (Reference #68). There is more experience with use of sotalol in our center. We almost never use dofetilide,

5. You state: “Of note, complex mapping systems often offer information in the form of colors which may deceive”. Consider deleting this sentence. The colors are only misleading if the data entered is incorrect.

Author response: We have deleted this sentence

6. On page 15, you make an important statement about the AV node. How effective are methods to locate the AV node in ACHD? Author response: A new reference (#82) is added to address the use of 3D mapping in locating AV node in ACHD patients and we have revised the text of this section as follows:

“The AV node does not have an intracardiac signal. The His bundle signal is used as its surrogate marker. Locating and identifying the His is often challenging in ACHD as the conduction system is often displaced in many conditions like AV canal defects and congenitally corrected transposition of great arteries. In other conditions like an extracardiac Fontan, the His bundle is not accessible unless a puncture is performed. If located, the His signal can be tagged by using 3D electroanatomic mapping systems. This is especially important in patients with single ventricle palliation where the complication of heart block would often require management with epicardial pacing^[82].”

7. Mavroudis and colleagues’ work is mentioned. It would be interesting to provide more detail. Author response: More information has been added to the text as follows:

“Mavroudis and colleagues have published an excellent and detailed review of arrhythmia surgery in ACHD based on their own experience in 248 patients^[88]. Most of the surgical procedures described are for the treatment of atrial arrhythmia in patients with repaired TOF or a single ventricle circulation. Operative techniques described include, methods for increasing the safety of repeat sternal reentry, direct ablation (cryoablation or radiofrequency), right atrial and biatrial Cox-maze procedures, as well as excision of automatic foci. The paper describes the differing anatomical and electrophysiological variations which need to be taken into account for each congenital cardiac diagnosis and arrhythmia^[88].”

8. Explain the process of deciding whether ACHD is simple, moderate or complex.

Author response: A new reference (#18) is added to the text which addresses the classification of ACHD patients into simple, moderate and complex lesions. This classification is the standard approach across the field of ACHD and was initially outlined by Task Force 1 of the 32nd Bethesda Conference as a means of deciding which patients need to be followed at a tertiary care ACHD centre.

9. The use of anticoagulants during pregnancy is indeed a complex subject. Don’t let it be beyond the scope of the manuscript. Educate the readers.

Author response: Aware of the dangers of oversimplification, we prefer not to delve into the specifics of anticoagulation in pregnancy. We have however expanded the section as follows:

“Pregnancy is a prothrombotic state and sustained atrial arrhythmia will further increase risk of thromboembolic events in pregnancy, therefore anticoagulation should be considered. Specific guidelines and recommendations exist^[100,110] and any decision about anticoagulation during pregnancy should be made with the input of specialist advice and in full consultation with the patient. Different regimens can be recommended depending on patient preference and the individualized balance of risks: obstetric risks (miscarriage, retroplacental hematoma, bleeding during delivery) vs. off-spring risks (warfarin associated embryopathy, premature birth, inter-cranial bleeding) vs. maternal risks (thrombosis and bleeding). The risk of maternal thrombosis and thromboembolism are highest in women who in addition to their atrial arrhythmia, also have either mechanical valves or Fontan circulations.”

We hope these responses and our amendments to the text are sufficient to address any concerns.

Yours sincerely

Drs. Arsha Karbassi and Lucy Roche on behalf of our coauthors