Peer Review File

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Reviewer #1

In Adults with Congenital Heart Disease (ACHD) Heart failure is extremely with respect to morbidity and mortality, causing cause of death up to 25% of patients, either in native CHD or after surgical or interventional treatment.

The underlying pathophysiological changes are multifactorial and determined by the underlying specific CHD. Recognition of heart failure in CHD can be tricky and different from in acquired heart disease.

Moreover, at the same time, there is a considerable uncertainty regarding therapeutic measures in CHD due to the heterogeneity of CHD and the absence of large data from controlled studies. Accordingly, management of FD deviates from the current guideline recommendations in cardiology. For all these reasons, it is important to inform cardiologists and family doctors about the particularities of heart failure diagnosis and treatment in ACHD.

The present, nicely written article, meets these requirement as the authors give an up-to-date overview, including pathoanatomy, pathomechanism, diagnosis, treatment.

The reviewer believes that minor improvements are still possible:

Comment 1: Page 7: The authors might explain in more detail, why "TGA or ccTGA, may have components of both pre- and postcapillary pulmonary hypertension"

Authors response:

To explain this fact more in detail the authors included on page 8 lines 155-158:

"Postcapillary pulmonary hypertension can arise due to a failing systemic right ventricle in case of ccTGA or TGA after atrial switch procedure and precapillary pulmonary arterial hypertension can be associated with shunt lesions or abnormalities of the pulmonary vasculature (1, 2)."

Comment 2: Page 7: The authors might explain in more detail, what the meaning is "Patients with TGA after atrial switch procedure show an impaired capacitance and conduit function of the baffles"

We thank the reviewer for the comments. We included into the manuscript on pages 9 lines 174-175:

"The baffles in patients with Fontan circulation are prone to narrowing or developing stenosis resulting in filling disorders of the single ventricle (1)."

Reviewer Response: This is not about Fontan patients, but Patients with TGA after atrial switch procedure!

Author Response: We thank the reviewer for the important comment and changes the text to: "The baffles in patients with atrial switch in patients with TGA are surgically constructed by using patient related tissue or Dacron and thus have an impaired compliance during growth and increasing demand of blood flow of the patient (1). " on page 8-9 in lines 174-176

Comment 3: Table 1: I would strongly recommend to delete the number "40". In my opinion, this number comes from nowhere and no valid data exist to support this.
Authors response: We omitted table 1 as it might be too close resembling the original tables as shown in the manuscript by Budts et al (3). However, we included on page 10 lines 201-209: "ACHD patients with heart failure and an anatomical left ventricle as systemic ventricle with a reduced ejection fraction <40% are treated with the same medication as recommended in non-ACHD patients (3). Most commonly renin-angiotensin-aldosterone-system blockers are used in addition to beta-blockers, mineralocorticoid receptor antagonists and diuretics or digoxin. If the failing ventricle is an anatomic right ventricle the medication is only used in symptomatic patients (3). Patients with a single ventricle are handled the same way. These patients are treated with the suggested medication if the ventricle is an anatomic left ventricle irrespective of symptoms and in case of an anatomic right single ventricle only if the patient is symptomatic (3). "

Reviewer Response: Again, I doubt that the figure of „40%" is based on valid data and would recommend to eliminate this figure in the text.

Author Response: As suggested by the reviewer we did remove the number from the text. It is suggested by the position paper by Budts et al. but not based on provided data. As such we did remove the number from the text
Page 10, lines 201-208: "ACHD patients with heart failure and an anatomical left ventricle as systemic ventricle with a reduced ejection fraction are treated with the same medication as recommended in non-ACHD patients (3). Most commonly renin-angiotensin-aldosterone-system blockers are used in addition to beta-blockers, mineralocorticoid receptor antagonists and diuretics or digoxin. If the failing ventricle is an anatomic right ventricle the medication is only used in symptomatic patients (3). Patients with a single ventricle are handled the same way. These patients are treated with the suggested medication if the ventricle is an anatomic left ventricle irrespective of symptoms and in case of an anatomic right single ventricle only if the patient is symptomatic (3). "

Comment 4: Page 11: Are there any data that "….. beta-blockers to reduce atrioventricular valve regurgitation" in ACHD ???
Authors response: "The reviewer is correct here. We did change the text on page 11 lines 217-219: "….lacking, asymptomatic patients with a failing systemic right ventricle are often treated with beta-blockers. However, symptomatic patients are treated analogous to patients with a failing morphologic…."

Comment 5:
I would recommend that the following articles of the CDT Journal could be cited:
Neidenbach R, Lummert E, Vigl M, et al; Non-cardiac comorbidities in adults with inherited and congenital heart disease: report from a single center experience of more than 800 consecutive patients. Cardiovasc Diagn Ther. 2018 Aug

Neidenbach R, Niwa K, Oto O, et al; Improving medical care and prevention in adults with congenital heart disease- reflections on a global problem-part I: development of congenital cardiology, epidemiology, clinical aspects, heart failure, cardiac arrhythmia. In Cardiovasc Diagn Ther. 2018 Dec

Singh, S.; Desai, R.; Fong, H.K.;et al.. Extra-cardiac comorbidities or complications in adults with congenital heart disease: A nationwide inpatient experience in the United States. Cardiovasc. Diagn. Ther. 2018, 8, 814–819.

Authors response: We thank the reviewers for their suggestion and included the literature in the introduction section of the manuscript on page 3 line 71.

References

1. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, et al. 2020 ESC Guidelines for the management of adult congenital heart disease. Eur Heart J. 2020.
2. Menachem JN, Schlendorf KH, Mazurek JA, Bichell DP, Brinkley DM, Frischhertz BP, et al. Advanced Heart Failure in Adults With Congenital Heart Disease. JACC Heart Fail. 2020;8(2):87-99.
3. Budts W, Roos-Hesselink J, Radle-Hurst T, Eicken A, McDonagh TA, Lambrinou E, et al. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. Eur Heart J. 2016;37(18):1419-27.