Manuscript ID: CDT-2020-RVD-17(CDT-20-592)
Title: Emerging Therapies for Right Ventricular Dysfunction and Failure
Response to Reviewers and Editors comments

Reviewer 1

Comment 1:

Authors nicely reviewed current pharmacological, RNA- and cell-based therapeutic options and their potential to directly target the RV. They further summarized available data for pulmonary artery denervation and mechanical circulatory support.

Reply 1:

We thank the reviewer for her/his positive perception of our manuscript.

Reviewer 2

Comment 2:

In this review article, the authors provide an analysis of current and emerging pharmacological, RNA-, and cell-based therapeutic options for right ventricular dysfunction and failure. They also discuss the role of pulmonary artery denervation and RV mechanical circulatory support.

The authors appear to focus solely on therapies that specifically target the RV myocardium. I am not sure that this is always required in clinical settings. For instance, if the cause of RV failure is pressure overload from pulmonary arterial hypertension, then pulmonary arterial vasodilation would represent an etiological treatment approach. As an example of the above, in the 2nd sentence of Introduction, the authors state: "Yet, specific therapies for right heart dysfunction do not exist.". This statement appears too strong. Specific therapies such as the vasodilatory therapies are currently used in some strata of patients with right heart dysfunction secondary to pulmonary artery hypertension.

Reply 2:

We thank the reviewer for her/his comprehensive evaluation of our manuscript and the constructive comments. We totally agree that vasodilatory drugs are fundamental elements in PH therapy and thus can alleviate RHF via reduction of afterload, as we state in the text, e.g. in the introduction: Indeed, current clinical therapies for PAH mainly pursue a reduction of pressure overload via relaxation of the pulmonary vasculature…. .

With our review we intended to focus on therapies that can directly address molecular mechanisms in the RV independently of hemodynamic regulations, which may provide therapeutic benefit in addition to the treatment of vascular dysfunction.

We rephrased the statement to better point out its intention: Yet, specific therapies that directly target right heart dysfunction are strongly limited.

Comment 3:

1. Page 19, line 10: "Confidentially, inhibitors of SMURF1 are in phase 1 with a major pharma company.". If this is that "confidential", then it should probably not be included into the manuscript.

Reply 3: We apologize for the vague statement. We have rephrased the sentence: Response to Reviewers' comments – CDT-2020-RVD-17(CDT-20-592)

Early clinical studies of BMP-modulating therapies in patients with PAH provide positive proof of concept and the development of novel therapies in the area offers the promise of future patient benefit (sotatercept PULSAR phase 2 late breaking clinical study, American Thoracic Society 2020).

Comment 4:

2. Tables: Please spell out all used abbreviation. For instance, FAO in table 1, PAB and MPO in table 2, CPC and EPC in table 3.

Reply 4:

We have made sure that all abbreviations are explained when used for the first time and in the appropriate legends.

Comment 5:

3. Page 6, line 12: please correct "both … both".

Reply 5:
We have corrected the typo.