Summary

Thank you very much for taking the time to review this manuscript. Please find the detailed responses below and the corresponding revisions/corrections highlighted in the re-submitted files.

Point-by-point response to Comments and Suggestions for Authors

Major Comments

Comments 1: Figure 1: the figure is too simplistic and chemically erroneous. The figure should be revised to show the hydroxy-arginine

Response 1: We agree with the reviewer and the image has been modified accordingly

Comments 2: As the authors point out, the cGC-cGMP-PDE-PKG etc pathway is crucial in this regulation by NO and NOS, but no figure describing this pathway in detail is produced in the review. It should be added either as a supplement to figure 1, or as a new figure 2. Contractile proteins must be mentioned as described on lines 155-156

Response 2: We think the reviewer provided a good observation reason why a new image 2 was drafted and added to the manuscript.

Comments 3: Figure 3 is too simplistic and does not add anything as it stands; it needs to be completed with the mechanisms involved. The Riociguat must be linked to the sGC. A figure showing the synthesis with the cGC-cGMP-PDE-PKG pathway and the contractile proteins (previous point), and the action of the 2 types of treatment could be very informative in this review. A detailed legend is needed

Response 3: Image 3 has been modified according to the reviewer's suggestions.

Comments 4: In paragraph “3. NOS Regulation”, there is no description of the regulation of nNOS, which is involved in cardiovascular disease, and which the authors discuss in paragraph 5.

Response 4: Paragraph 3 has been improved as suggested.

Comments 5: Line 107 to 112: this passage needs to be revised because it describes the same idea twice: it should be written more clearly.

Response 5: The passage has been revised.

Comments 6: Paragraphs "4. NOS downstream signaling" and "5. Effects of NO signaling on CV system" deal with the same topic. There is no different information in these 2 paragraphs, which leads to repetition. A new single paragraph should be written, with a hierarchy.

Response 6: The two paragraphs have been revised and merged.

Comments 7: References should be checked carefully, examples of errors identified: line 194, Fegal et al are not the authors of papers 34 and 35; line 220, reference 43 does not correspond to the idea expressed; Ref 54 is Rubin et al, not Ghofrani et al

Response 7: References have been checked as suggested.

Comments 8: Paragraph “7. Modulation of pulmonary vascular NO in PAH”: this paragraph is descriptive and would merit a final synthesis assessing the benefits and limitations of PDE5 inhibitors. Probably also to be considered at the end of paragraph 8.

Response 8: Both paragraphs have been improved as suggested.

Minor comments:

Comments 9: Line 103, “The principal intracellular receptor for NO…”: The term "receptor" is generally used in receptor-ligand processes, but in this case it's more a "target" than a "receptor"

Response 9: the term has been changed.

Comments 10: Line 108 and 112, in the same way, “members” is inappropriate, as is “cell species”

Response 10: these lines have been revised.

Comments 11: There are many errors in the text, so it needs to be proof-read carefully. Here are some of the mistakes found:
Line 56, “guano- sine”
Line 58, “ pathway in many physiological systems”
Line 61, “NO exerts its action”
Line 83, “regulated mainly by »
Line 86, “the ability to of”
Line 87, “and coordinates
Line 100, “activity is is calcium-independent”
Line 127, “and vascular smooth muscle cells (VSMC)”
Line 131, “localized in in the sarcoplasmic”
Line 171, “eNOS espression”
Line 188, “et all.” Line 190, “ha only few effects”
Line 236, “ed last”
Line 238, “sex minutes”
Line 240, “e +14.7% in 80 mg-group”
Line 289, “it directly stimulates sGC independent of NO levels”
Lines 368-369, “PDF5i” Line 372, “decreased by 347±1235 pg·mL-1” => really?
Line 394, “sGC Riociguat” =>sGC activator (Riociguat)
Line 400, “An initial tiral”
Line 413, “Heart Failure with reduced ejection fraction (HFrEF)” => uppercase - In the term Ca2+, "2+" must be superscripted. To be reviewed in the text (lines 136, 138, 154, 158, 159 etc…) - “six minutes walking distance”: this is written a number of times before 6MWD,
line 299, and 6- MWD,
line 304, appear, and then the abbreviations is not used systematically. Use the abbreviation the first time the expression is used and then use it systematically

- Figure 2: “mitochondrial respiration “ in the legend but there is no reference to this point in the figure. Either the figure needs to be completed, or this point needs to be removed from the legend
- For some terms and clinical trials, abbreviations are not indicated: lines 298 to 303: ERA, PC, PVR, WHO, TID (which is sometimes in lower case, sometimes in upper case); Lines 348 to 375: TAPSE, RIVER, RESPITE, REPLACE
- Table 2: the formatting of the table needs to be reviewed, particularly the "Sample" column. In addition to the authors, the name of the clinical trial would be interesting. The meaning of abbreviations should be indicated in the legend
- Lines 381 to 384: “23 (20%) of 113 patients” it would be clearer like this "23 of 113 patients (20%)”. It's the same in the next 3 lines

Response 11: The text has been revised according to suggestion.