Response to reviewer

We would like to thank the reviewer for the evaluation of our manuscript and the notification that our current manuscript is a complete review of the diagnosis, mechanisms, pathogenesis and treatment options of the PH associated with HHT. We are happy to completely address the comments raised.

Comment #1: First paragraph: "....is an autosomal dominant inherited disorder with late onset penetrance (nearly 97% at the age of 60 years) characterized...."
Reply #1: We agree with the reviewer and add the proposed sentence to the first line of the manuscript.

Comment #2: Genetics and pathogenesis:
Rewrite the first paragraph: BMPR-II mutations did not found in the PH-HHT, but mutations of other genes encoding endothelial surface protein components of the TGF-beta receptor, as the endoglin (ENG) gene on chromosome 9 causing HHT type 1 and the activin receptor-like kinase (ACVRL1) gene on chromosome 12 causing HHT type 2[5,6]
Reply #2: We thank the reviewer for the comment, however we think that this paragraph is more suitable for the paragraph on "Pathophysiology and genetics of PAH". The addition of the sentence on BMPR-II is of additional value for the manuscript. We re-wrote the above sentence and added the text on page 8 of the manuscript.

Comment #3: Add in the second paragraph: "The exact pathogenesis of HHT is still unclear." However, hypoxia or local hemodynamic changes could act as a possible triggers promoting tissue inflammation or endothelial cell injury[2].
Reply #3: We thank the reviewer for the comment and added the sentence with the correct references [Circo et al. Curr Opin Pulm Med 2014 and Abdalla et al. J Med Genet 2006] on page 3 of the manuscript.

Comment #4: Diagnosis. "The positive predictive value for a definite clinical diagnosis and the negative predictive value for an unlikely diagnosis are excellent (100% and 97.7%, respectively)", when compared with DNA testing.
"Therefore, genetic testing has emerged as an important tool to help make the diagnosis in paediatric patients and younger adults with a 'possible' clinical diagnosis"
Reply #4: We thank the reviewer for the comments, and added both sentences to page 4 of the manuscript.

Comment #5: Although pulmonary vascular resistance (PVR) should not be part of the general definition of PH, PVR should be included in the hemodynamic characterization of patients with precapillary PH (5° WSPH Niza). So we recommend to add after "Depending.....post capillary PH." Patients with pre-capillary PH are characterized by a mPAP ≥ 25 mm Hg, PAWP ≤ 15 mm Hg, and elevated PVR (>3 Wood units).[Hoeper MM. et al JACC 2013]
Reply #5: We agree with the reviewer and added the sentence to the manuscript on page 4 including the reference.

Comment #6: Remove the secondary title: "Pulmonary hypertension and hereditary haemorrhagic telangiectasia"
Reply #6: Following the guidelines for manuscript submission a secondary "running/short" title was required. However, we now removed this secondary title.

Comment #7: Replace: "PH may be categorised into two distinct types in patients with HHT" by PH-HHT can occur by several mechanisms. Most often, post-capillary PH may develop as a consequence of a hyperkinetic state resulting in heart failure associated with high cardiac output (CO) due to hepatic arteriovenous malformations (HAVMs) (figure 2) while less frequently, precapillary PH can be related to PAH characterised by remodeling of small pulmonary arteries with broadly similar histologic lesions than observed in idiopathic PAH.

Reply #7: We agree with the reviewer that the above sentence contributes more to the manuscript and therefore we replaced the sentence on page 5 of the manuscript.

Comment #8: Move the paragraph "High-output PH versus PAH" before "High output PH" and remove the title. "RHC is the gold standard for making the diagnosis.....". Remove "and shows characteristic differences (table 2)". Put (table 2) at the end of the paragraph and update it in accordance to recent WSPH of Niza: [Simmoneau G et al JACC 2013;62].

Reply #8: We thank the reviewer for the comment, however we think that the reviewer means to change table 1 of the manuscript. We changed this table according the article of Simmoneau et al. [Simmoneau et al. JACC 2013] We moved the paragraph and removed the title. We moved the table to the end of the paragraph.

Comment #9: PAH. Pathophysiology and genetics of PAH.

Add in last sentence "..... in patients with both HHT and PAH, suggesting a less potent association between endoglin and PAH.[15,16]

Reply #9: We thank the reviewer for the comment and we added the above sentence to the manuscript on page 8 of the manuscript.

Comment #10: Prognosis. Add after the paragraph: It is noteworthy that ACVRL1 mutation carriers may develop severe PAH without any clinical evidence of HHT because of the early development of PAH in these patients and the late-onset penetrance of ACVRL1 mutation for HHT manifestations.[32]

Reply #10: We thank the reviewer for the comment and we added the above sentence to the manuscript. It highlights the importance of PH in HHT.

Comment #11: Pulmonary arteriovenous malformations in PH

Add before the first paragraph: The coexistence of PH and PAVMs has specific clinical and therapeutic implications.

"..... as a stroke or brain abscess.[1,38] Contrast echocardiography is the screening test of choice (sensitivity up to 98.6%), with a direct relationship between shunt grade and prevalence of cerebral manifestations in patients screened for HHT.[38]

Rewrite the second sentence of the second paragraph: Measuring the pulmonary pressure before and after embolization of PAVMs in 43 patients, Shovlin et al. found no significant....."

In the last paragraph, finish the first sentence "..... with severe PAH.", and rewrite the last sentence: "Although patients with severe PH were excluded from the above studies, it would be prudent to consider that the higher the mean PAP and PVR at baseline and the larger the PAVM, the greater likelihood of worsening PH after embolization.

Reply #11: We agree with all comments and changed the sentences on page 10 of the manuscript.