Reviewer A:
Manek et al present an interesting review of various hemodynamic indices with prognostic and therapeutic implications in patients with PH. The detailed informations on calculations and background are largely correct. Their presentation is comprehensive and concise, and provides a good overview.
However, I want to make some comments:

We truly appreciate the constructive comments provided the reviewer.

Comment 1
I propose to give some more informations about PH classification in the introduction for those readers who are not familiar with PH. Especially the different forms of group 2 PH (Ipc-PH and Cpc-PH) should be introduced early for better understanding

Reply 1- We agree with the reviewer, and we have now expanded the information on PH classification and group 2 PH subtypes.
Changes in text: We added the following sentences: "Group 1 PH or pulmonary arterial hypertension (PAH) is characterized by precapillary PH [pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and pulmonary vascular resistance (PVR) ≥ 3 Wood units (WU)] that can lead to right heart failure and death (2). Group 2 PH or PH resulting from left heart disease is characterized by postcapillary PH (PAWP > 15 mmHg) and can be divided in 2 hemodynamic subgroups, isolated postcapillary PH (IpcPH) in which the PVR is < 3 WU and combined pre- and postcapillary PH (CpcPH) in which the PVR is ≥ 3 WU." (See Page 4, Line 84-90)

Comment 2
- The sentence "Cardiac index (CI) is reflective of the global function of the RV (in patients with normal left ventricular function) …" may be misinterpreted; I would recommend to name systolic and diastolic LV function as a potential cause of a diminished CI and to discuss some pathophysiologic background

Reply 2- We agree with the reviewer that a pathophysiological explanation would be interesting; but after writing this new paragraph we realized that it markedly increased the length of the CI section and it felt that the information was over the scope of our paper.
Changes in Text: We have now added systolic and diastolic LV function. The sentence now reads" "Cardiac index (CI) is reflective of the global function of the RV (in patients with normal systolic and diastolic left ventricular function) and forms an integral component to assess the functionality of the cardiopulmonary unit." (See Page 5, Line 128)

Comment 3
- The Fick method of CO measurement is called the gold standard; however, citing from current PH guidelines "Thermodilution measured in triplicate is the preferred method because it can provide reliable measurements even in patients with low CO and/or severe tricuspid regurgitation". Furthermore, there are two variants of the Fick method (direct and indirect), which should be emphasized and explained.

Reply 3: We have optimized the following paragraph following the reviewer's recommendations.

Changes in Text: "The gold standard is the direct Fick method that requires the determination of resting oxygen consumption (VO2) and analysis of arterial and mixed venous blood to measure the oxygen saturation and hemoglobin, which are necessary for calculation of oxygen content. The use of pulse oxygenation and prior hemoglobin determination introduces potential sources of error (16). Thermodilution is recommended by the 6th WSPH when direct Fick methodology is not available because it can provide reliable measurements even in patients with low CO and/or severe tricuspid regurgitation; however, the wide limits of agreement (±1.96 SD of the differences) of up to 1 L/min/m2 between methods, impacts the risk group allocation proposed by ESC/ERS given the narrow CI band (2–2.5 L/min/m2) (17). Indirect Fick methodology, which estimatesVO2 based on a variety of formulae is not reliable and not recommended for routine CI determination (3,17)." (See Page 6-7, Line 154-170)

Comment 4
- Stroke volume: the authors state "it removes the compensatory heart rate (HR) response when CO is inappropriate to meet the body demands …" Although you can imagine what that should mean, the authors should clarify their thoughts and explain, why SV should be a better measure for RV function than CI. The statement about the Fick method should be revised as named above

Reply 4: We agree with the reviewer, and we have now clarified the sentence as noted below.
Changes in Text: "As PAH progresses the SV decreases; however, this is initially counterbalanced by an increase in heart rate; a compensatory mechanism that regulates the CI. Hence in early stages the CI may be numerically normal even when the SV is reduced." (See Page 7, Line 178-180)
The Fick methodology was clarified as part of the reply to comment 3. (See Page 6-7, Line 154-179)

Comment 5
- The statement about SSc-PAH "hemodynamic indices like RAP, CI, and PVR had limited utility in predicting survival" is based on one study published 2009. Please discuss the current guidelines recommending these parameters for all

patients with group 1 PH including SSc-PAH

Reply 5: We agree with the reviewer and based on the previous comment we optimized the following sentences as below.
Changes in Text: "SVI is a particularly useful prognostic indicator in patients with systemic sclerosis (SSc) associated PAH (SSc-PAH), in whom traditional hemodynamic indices like RAP, CI, and PVR showed limited utility in predicting survival in one study (39). Despite these results, the 6th WSPH recommends RAP and CI for prognostication in PAH, including patients with SSC-PAH." (See Page 9, Line 225-228)

Comment 6
- "TPG was removed in favor of PVR" – here it would be useful to mention the formula for PVR calculation and thus underline the strong dependency of PVR on TPG

Reply 6: We agree with the reviewer and necessary changes have been made as noted below.
Changes in Text: "Due to these limitations TPG was removed, in favor of PVR (TPG/CO), as a tool to establish the different hemodynamic types of PH due to left heart disease (PH-LHD)" (See Page 9, Line 238-239)

Comment 7
- "heart transplantation guidelines recommend regular assessment of pulmonary hemodynamics with vasodilators … to assess reversibility of the precapillary PH" – PH in HTx candidates is usually post-capillary, and a part of them has combined PH (Cpc-PH). I would prefer to use the term "reversibility of the pre-capillary component, if Cpc-PH is present" here

Reply 7: This was modified as noted below
Changes in Text: "Given the increased morbidity-mortality of a high TPG (TPG $\geq$ 15 mmHg) or PVR $\geq$ 3 WU, heart transplantation guidelines recommend regular assessment of hemodynamics with pulmonary vasodilators (e.g., intravenous nitrates or inhaled nitric oxide) and inotropic agents (e.g., milrinone), to assess reversibility of the precapillary component in patients with CpcPH." (See Page 10, Line 260-264)

Comment 8
- DPG: one more argument against DPG would be that calculating a "gradient" between a mean pressure (PAWP) and a single-point measured pressure (dPAP) is not correct from a physiological point of view

Reply 8: Based on this comment the following sentence was modified as noted below.
Changes in Text: "These negative results could in part be explained by the negative numeric values of DPG observed in some studies that reflect inconsistent pressure

measurements across different parts of the respiratory cycle (e.g., dPAP averaged across the respiratory cycles while PAWP measured at end-expiration)," (See Page 11, Line 307-309)

Comment 9
- PVR: in the setting of HTx candidate evaluation, PVR is as important as TPG to assess "PH reversibility", and vasoreactivity testing is recommended if PVR is > 3 WU (2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation) – this should be mentioned

Reply 9: This was optimized based on the comment as noted below.
Changes in Text: "Given the increased morbidity-mortality of a high TPG (TPG $\geq$ 15 mmHg) or PVR $\geq$ 3 WU, heart transplantation guidelines recommend regular assessment of hemodynamics with pulmonary vasodilators (e.g., intravenous nitrates or inhaled nitric oxide) and inotropic agents (e.g., milrinone), to assess reversibility of the precapillary component in patients with CpcPH." (See Page 10, Line 260-264)

Comment 10
- PVRI: "A PVRI value of $\geq$ 30 WU.m2 was a predictor of three-year survival in patients with PAH" – please correct the PVRI unit (the cited paper used "mm Hg/liter/min/m2")

Reply 10: The units are equivalent, and we have made changes as noted below to reflect both units.
Changes in Text: We showed both in the sentence WU.m^2 to maintain consistency with units used in PVR: "A PVRI value of $\geq$ 30 WU.m2 (or mmHg/L/min/m2) was a predictor of three-year survival in patients with PAH (76)" (See Page 12, Line 385)

Comment 11
- Ea: there is a ongoing debate on how Ea should be calculated correctly (10.1161/CIRCHEARTFAILURE.120.007081; 10.1164/rccm.201802-0283LE); I would propose to mention at least the alternate formula using mPAP instead of sPAP

Reply 11: We agree with the reviewer and added the following sentence as noted below
Changes in Text: "In PH, as the RV pressure rises throughout ejection with peaking at or near end-systole, the end systolic pressure is better approximated by systolic PAP and not mPAP. In the absence of direct end-systolic pressure measurement, one can cautiously estimate it by the equation ESP $= 1.65 \times$ mPAP $- 7.79$." (See Page 17, Line 586-589)

Comment 12
- The RAP/PAWP ratio plays an important role in the context of LVAD implantation

Reply 12: We agree with the reviewer a short paragraph to describe the utility of the ratio in LHF and LVAD implantation has been added

Changes in Text: "An increase RAP/PAWP ratio was associated with higher PVR, reduced RV function and worse outcomes in patients with advanced systolic left heart failure. Similarly, a higher RAP/PAWP was associated with renal failure and mortality in acute decompensated systolic heart failure. In addition, RA/PAWP ratio may help to identify patients at high risk of developing right ventricular failure and mortality after the implantation of a left ventricular assist device. RAP/PAWP ratio increased immediately following LVAD implantation, then decreased for a short period followed by a gradual increase in the long-term that may represent change in the RV function over time." (See Page 15, Line 509-516)

Comment 13
- PAPi: the sentence "Therefore, PAPP component in PAPi is increased by increased in SV …" seems incorrect

Reply 13: This is correct based on the PAC formula. We optimized the following sentence to clarify this.

Changes in Text: "As previously described PAC = SV/(sPAP – dPAP); and by rearranging the terms, PAPP=SV/PAC. Based on this formula, the PAPP component in PAPi is affected by changes in SV and/or PVR (which has a hyperbolic relationship with PAC)." (See Page 15, Line 522-523)

Comment 14
- PV loops: please consider the TAPSE/PASP ratio (e.g. 10.1016/j.ijcard.2018.01.053) to be included as an important noninvasive method for estimation of RV-PA coupling

Reply 14: We agree with the reviewer and we have now added the following sentences

Changes in Text: "The ratio of echocardiography-derived tricuspid annular plane systolic excursion (TAPSE) and pulmonary arterial systolic pressure (PASP) may provide a noninvasive estimation of the RV-arterial coupling in PAH. A low TAPSE/PASP ratio (<0.19 mm/mmHg) is associated with overall mortality in patients with PAH, even when adjusted by clinical covariates and traditional echocardiographic and hemodynamic indicators." (See Page 18, Line 605-610)

Comment 15
Table 2:
- CI / SV /SVI are measures of RV and! LV function, and more information is needed to allocate such global parameters to one of the ventricles

Reply 15: We agree with the reviewer. Hence, we have mentioned in the manuscript

that CI is a measure of RV function in the presence of normal systolic and diastolic LV function and also changed the table.

Changes in Text: This was changed in the table 2.

Reviewer B:
The research concept was very good, and it must have taken a lot of time to analyze this data.

However, it is very sorry that new contents or new parameters that could be helpful in clinical practice were not presented, and the conclusion was rather regressive from the hypothesis of the introduction of the study.

Reply:
We appreciate the reviewer's comments. We tried our best to include all hemodynamic indices that have been studied in pulmonary hypertension with at least one published study in Pubmed. We would be happy to include any indices that the reviewer recommends. We narrowed our hypothesis to avoid a regression as it regards to the conclusion. Importantly, up to date there are not review papers that present the value of a large variety of hemodynamic indices in patients with PAH. Although there may be other indices, these are usually obtained by using MRI, echocardiography, endovascular ultrasound / intravascular doppler; which are outside the scope of the present manuscript.

Changes in Text: Deleted "We also attempt to describe where these indices are positioned today and envision future clinical applications and potential measurement by non-invasive methods" (Page 5)

Reviewer C:
This is a review article of hemodynamic parameters in pulmonary hypertension. The concept of the work and data presentation are very useful and can help not only to systematize knowledge about right heart catheterization but also bring a comprehensive source of parameters helpful in better assessment of patients with pulmonary hypertension. The article needs some minor revision, as suggested below.

We truly appreciate the reviewer's comments and recommendations to improve our manuscript.

1. Slight grammatical correction is necessary, please pay special attention to the use of a comma before the word "and" depending on the context of the sentence.

Reply 1: We apologize for these mistakes, and we have now proofread the article and made necessary corrections.

2. In the following part:
47 characteristics and therapeutic management (1). Group 1 PH or pulmonary arterial
48 hypertension (PAH) is characterized by precapillary PH [pulmonary artery wedge
49 pressure (PAWP) ≤ 15 mmHg and pulmonary vascular resistance (PVR) ≥ 3 Wood units
50 (WU)] that can lead to right heart failure and death (2).
Presentation of the hemodynamic criteria for the classification of all the groups of pulmonary hypertension, not only PH-1, will allow for a better systematization of the data, taking into account that the article concerns the whole group of pulmonary hypertension, not only PH-1.

Reply 2: As per your recommendations, we have now added a paragraph in the introduction outlining the different forms of PH
Changes in Text: "Group 1 PH or pulmonary arterial hypertension (PAH) is characterized by precapillary PH [pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and pulmonary vascular resistance (PVR) ≥ 3 Wood units (WU)] that can lead to right heart failure and death (2). Group 2 PH or PH resulting from left heart disease is characterized by postcapillary PH (PAWP > 15 mmHg) and can be divided in 2 hemodynamic subgroups, isolated postcapillary PH (IpcPH) in which the PVR is < 3 WU and combined pre- and postcapillary PH (CpcPH) in which the PVR is ≥3 WU." (See Page 4, Line 84-90)

3. In the following part:
182 transplantation in patients with preoperative TPG >15 mmHg (51). Given the morbidity-
183 mortality of a high TPG, heart transplantation guidelines recommend regular assessment
184 of pulmonary hemodynamics with vasodilators (e.g. intravenous nitrates or inhaled nitric
185 oxide) and inotropic agents (e.g. milrinone or dobutamine) to assess reversibility of the
186 precapillary PH (52).
It should be noted that, according to the recommendations, the possibility of performing the RHC reversibility test with milrinone applies only to patients with RCM.
There are no recommendations for the use of dobutamine in vasodilator challenge.

Reply 3: We apologize for the confusion. Dobutamine was removed.
Changes in Text: We modified the sentence to read: "Given the increased morbidity-

mortality of a high TPG (TPG ≥ 15 mmHg) or PVR ≥ 3 WU, heart transplantation guidelines recommend regular assessment of hemodynamics with pulmonary vasodilators (e.g., intravenous nitrates or inhaled nitric oxide) and inotropic agents (e.g., milrinone), to assess reversibility of the precapillary component in patients with CpcPH. (See Page 10, Line 260-264)

4. Reference 47 and 70 are the same:
Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53(1):1801913.

Reply 4: We have removed the duplicate references, added new references, and renumbered the references appropriately (Pages 21-31)

5. Reference 5 and 9 are the same:
Benza RL, Gomberg-Maitland M, et al. Predicting Survival in Patients With Pulmonary Arterial Hypertension: The REVEAL Risk Score Calculator 2.0 and Comparison With ESC/ERS-Based Risk Assessment Strategies. Chest 2019;156(2):323–37.

Reply 5: We have removed the duplicate references, added new references, and renumbered the references appropriately (Pages 21-31)

6. Reference 46 and 58 are the same:
Naeije R, Vachiery J-L, Yerly P, et al. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease Eur Respir J 2013;41(1):217–23.

Reply 6: We have removed the duplicate references, added new references, and renumbered the references appropriately (Pages 21-31)

7. Please use the same way of showing numbers of references:
Different methods are used to determine the RV-arterial coupling including
378 invasive methods (single beat or multiple beat measurements of Ees) as well as
379 noninvasive methods (magnetic resonance imaging analysis) (119–122).

Patients with PAH and CTEPH have a decreased Ees/Ea ratio when compared with
382 controls (120,121,123,124).

Reply 7: We have removed the duplicate references, added new references, and renumbered the references appropriately (Pages 21-31)

Reviewer D:
This is a very detailed and exhaustive review on hemodynamic indices in pulmonary hypertension. The authors include routine parameters (CI, SV, PVR) as well as additional (more sophisticated) parameters (PA elastance, PA pulsatility, PV loops).

We sincerely appreciate the reviewer's comments.

Comments:
1. Especially for the physician treating children with pulmonary hypertension, it would be interesting to read an additional chapter on the changes of specific parameters during vasoreactivity testing and their implications on prognosis.

Reply 1: The reviewer brings a good point. The scope of the study was to describe various hemodynamic indices, including their description, normal values, use and limitations as they apply to improving both the pathophysiological understanding and prognostic assessment in PH. The authors have a particular interest in the hemodynamic changes that occur during inhaled nitric oxide (PMID: 31894408, 23662172, 20004088); however, limited data exits on the impact of inhaled nitric oxide on most of the indices described. We are currently planning a prospective research study that is comparing most of these indices before and during inhaled nitric oxide administration and its impact on prognosis and response to PH therapies.

2. The authors may also want to add the assessment of Pulmonary Flow Reserve which can contribute to prognostication, especially in children with PH (Assessment of pulmonary endothelial function during invasive testing in children and adolescents with idiopathic pulmonary arterial hypertension. J Am Coll Cardiol. 2012 Jul 10;60(2):157-64. doi: 10.1016/j.jacc.2012.04.010).

Reply 2- We agree with the reviewer that this is an interesting topic that was not presented. We have not included any indices that require tools not regularly available during RHC. The pulmonary flow reserve requires intravascular Doppler flow measurement, a tool that is not regularly available during routine RHC. We have added the following sentences in the methods portion of the manuscript to clarify this
Changes in Text: "All the indices presented can be obtained during a regular right catheterization. We chose to include pulmonary artery pressure-volume loops since there are methods to estimate the RV-arterial coupling using the hemodynamic data acquired during right heart catheterization (e.g., single beat method that uses a nonlinear extrapolation of early and late isovolumic portions of the RV pressure curve). The impact of provocative maneuvers (i.e., exhaled nitric oxide, fluids, and exercise) on these indices is beyond the scope of the manuscript." (See Page 5, Line 117-123)

3. I guess adding 2-3 images would be instructive and could improve reading comprehension.

Reply 3- We agree with the reviewer, and we have now created a figure summarizing all our indices (figure 1), in addition to our tables.

4. Some typos:
Line 83: well known
Line 219: could (2x)
Line 374: Ees/Ea ratio

Reply 4- Thank you for pointing these out. These typos were fixed.