Peer Review File

Article Information: https://dx.doi.org/10.21037/cdt-21-515

Reviewer A:

When this study is proposed, there must be some hypothesis or mathematical calculations regarding possibility of some effect of 1.5 ml balloon inflation on pressures at various sites. For example, what is the diameter of 1.5ml balloon, what is the pulmonary artery diameter, what is the possible stenosis ratio, how many % of pulmonary vascular bed would be stenosed, what is the effect of blood flow to the contralateral lung and what would be the effect on pulmonary pressures? Please clarify these points and if there is indeed a possibility of changing pressures by 1.5ml balloon, then show the results.

Reply for Reviewer A: the reviewer brings up important points to improve the manuscript. The diameter of a fully inflated PAC balloon is 1.3 cm (area: 1.3 cm^2), while the main pulmonary artery diameter in healthy individual and patient with PH is 2.5 cm (area: 4.9 cm^2) and 3 cm (area: 7.1 cm^2), respectively (1, 2). Therefore, a PAC balloon inflation represents reduction in effective vascular area of 27% in healthy and 18% in subjects with PH. These important data have been added to the introduction of the manuscript. Given this reduction in area we expect effects on pressure, but without testing, it is difficult to determine without using sophisticated hemodynamic models that take into account vascular compliance, length and diameter of distal vessels, condition of the contralateral lung, etc. This study answers what is the effect in pressure and flow of a PAC balloon inflation in the pulmonary artery.

Reviewer B:

The manuscript is clear and interesting. The Authors hypothesized that:

1) short-term balloon inflation has a minimal effect on pulmonary hemodynamics in most PH patients but

2) may have a more relevant impact in those with severe PH.

The issue of the increase in pulmonary circulation resistance due to the inflation of the Swan-Ganz catheter balloon is of great importance for the correct interpretation of the results of hemodynamic measurements performed during right heart catheterization. The hypothetical increase in pulmonary resistance caused by the temporary closure of one of the pulmonary arteries by the catheter balloon may overestimate the results of PVR measurements, which in turn leads to over-recognition of pulmonary hypertension and worsens the prognostic parameters of both PAH and CTEPH, like mRAP or CO.

The total number of 210 patients participated in the study, end-expiratory mPAP was measured in 209 patients, and CO in 63. Ultimately, TPR was calculated for 62 patients who had measurement performed twice: with inflated and deflated balloon. The authors proved that the changes in sPAP, mPAP, dPAP, CO and TPR

values caused by the inflation of the catheter balloon are minimal and - as it can be assumed - have no clinical significance. The study confirms the reliability of the results obtained during catheterization with the use of the Swan-Ganz catheter. Moreover, the results of the study do not indicate that balloon inflation poses a risk to the patient due to a temporary deterioration in hemodynamics.

I appreciate the reviewer's evaluation of our manuscript.

I have two main comments:
1. The presented results apply to the entire study population, without specifying patients with severe PH. The study does not answer the question whether balloon inflation does not affect the hemodynamics of patients with very high PAP and PVR values. In the cohort of PAH patients, the mean value of PVR was 7.3 +/-5.2 Wood units, which suggests that both patients with PVR> 10 Wood units and <3 Wood units were studied. A sub-analysis comparing the effect of balloon inflation on patients with PVR above and below the median of PVR would be useful.

We agree with the reviewer and we have performed a new analysis in patients with PVR above and below the median (6 Wood units). We added the following sentence in the discussion: "When patients with PAH were divided in 2 groups based on the median PVR, i.e. PVR < 6 and PVR ≥ 6 Wood units, we noted no significant difference in the change between balloon up minus down, both in the end-expiration mean PAP (PVR<6 Wood units: 0.43 ± 1.9 mmHg (n=36) vs PVR ≥ 6 Wood units: 0.03 ± 1.7 mmHg (n=32), p=0.37), and TPR (PVR<6 Wood units: -0.06 ± 1.1 Wood units (n=18) vs PVR ≥ 6 Wood units: -0.83 ± 1.7 Wood units (n=13), p=0.14). "

2. The methodology for measuring CO during balloon inflation is not clear.

I have some questions to the Authors.
1. Why TPR=mPAP/CO was calculated for 62 patients only (Table 1) whereas results of PVR=(mPAP-PAWP)/CO were presented for 183 patients (Table 2).

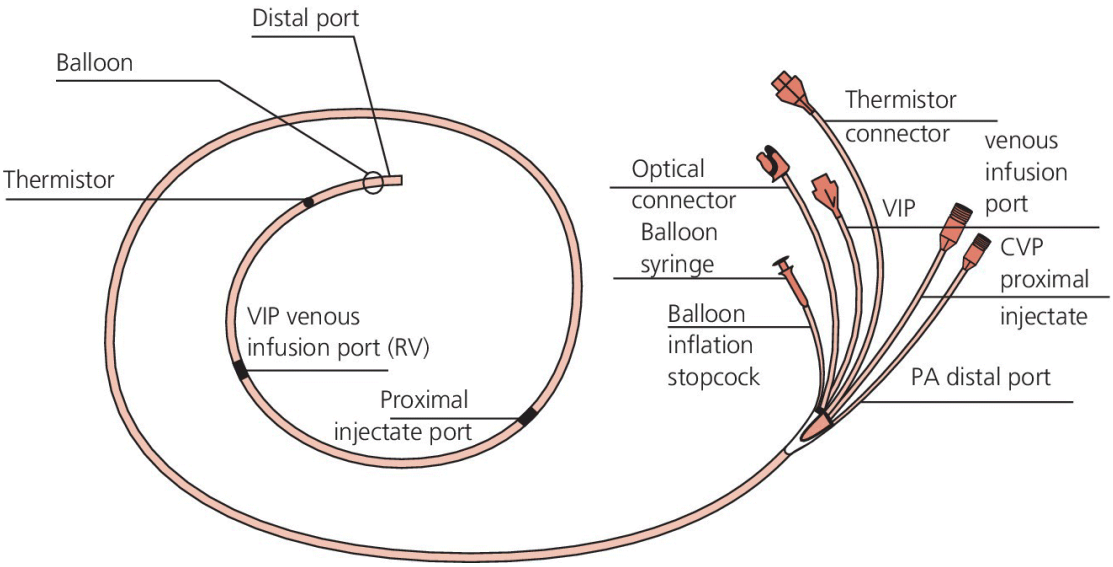
When the PAC balloon is up in the main pulmonary artery, we cannot measure PAWP, therefore, only TPR and not PVR can be compared between balloon up and down conditions. We presented the TPR (mPAP/CO) in patients in whom this value was able to be calculated, since we determined CO with PAC with balloon up only in a fraction of patients (n=62). The PVR presented in table 2, is the was determined before balloon inflation (n=210). In table 2 we added the ¶ symbol to communicate this: "¶ TPR only reported for subjects who also had TPR measured with balloon up". We also added in table 2 whether hemodynamic determinations were done with balloon up or down, to avoid confusion.

2. Why did you analyze the impact of balloon inflation for TPR instead of PVR? (see: Introduction, row 59-60).

This is an important question. When we inflate the PAC balloon in the main pulmonary artery, we measure the pulmonary artery pressure, but not the Wedge pressure since the balloon is not wedged, but free floating in the pulmonary artery. We can measure CO because the thermistor is located before the balloon. Therefore, only TPR can be compared and not PVR, given the lack of PAWP determination when the balloon of the PAC is free floating in the pulmonary artery. We added this sentence in the methods section to explain the above: "Only TPR was compared between the two conditions, since only PAP but not PAWP (a value needed to calculated PVR) could be determined when the PAC balloon was inflated but free floating in the pulmonary artery."

3. Cardiac output (CO) was measured using the thermodilution method. Thermodilution measurement requires the injection of a bolus of cold fluid into proximal lumen of PAC and recording of the blood temperature by thermistor at the catheter tip, which is located distally to the balloon. The measurement may be performed with the deflated balloon only. Inflation of the balloon closes the pulmonary artery, making measurement impossible as the flow in the artery stops. So my question is: how did you calculate presented in the Table 1 "balloon-up" cardiac output?

The distal thermistor of the PAC is located before the balloon, so it does not affect the measurements by thermodilution (this was added to the manuscript" "(the distal thermistor is located before the PAC balloon, not affecting thermodilution measurements when the balloon is inflated)"



I also suggest correction of some editorial errors:
- Table 2: "TPR (Wood units)" should be instead of "TPR (Wood units) &".
- line 88: "Patients" instead of "Patient"
- line 53: The subtitle "Introduction" is misleading because both the introduction and the rest of the manuscript appear below.

Reply: We apologize for these errors and we have now fixed them. We changed the & symbol to ¶, to facilitate the understanding.