

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-22-1793>

Reviewer A

This is a study titled – “Ultrasonographic features and Influencing factors of pulmonary hypertension of total anomalous pulmonary venous connection in adults” by Ghao et al.

Overall, it is a well-written paper about a rather rare clinical condition that has limited data.

Thank you for the time taken to review the manuscript.

Comment 1: The focus of this paper appears to be echocardiographic associates / potential predictors of PASP >60. From the tables provided, the only significant factor is an RV size >52mm. Were other factors such as an Aorta / PA ratio or a lower LV size at all significant? Was RA size measured?

Interestingly – ASD size did not seem to be associated with differences in PASP. Would expand on this further.

Reply: Thank you for your suggestions. We have added echocardiographic parameters such as aorta / PA ratio, RA transverse diameter and longitudinal diameter to the results section. All echocardiographic parameters were standardized by body surface area (BSA). We found that the LA and aorta/PA ratio and RVd and RA were significant parameters related to PASP, whereas ASD size was not. We have also added a scatter diagram (Figure 6) of PASP and ASD/BSA. PASP was also affected by individual differences in pulmonary vessels of patients. One of the limitations of our study was the small number of patients; therefore, we will continue the study and include more patients in the future.

Changes in the text: Results (Lines 175-178), Table 2, Figure 6.

Comment 2: Would patients with ASD have served as a better control group rather than normal controls? Given that the main question at hand is how the TAPVC influences echo changes?

Reply: Thank you for your suggestion. We enrolled patients diagnosed only with secundum ASD to serve as a control group. The ASD diameters of the secundum ASD patients were matched with that of the TAPVC patients.

The results showed that the left atrium and the AO/PA ratio were significantly smaller in the TPVC group than in the ASD group, additionally, patients with TAPVC had larger RVds and RAs than those with only ASD. The reason for this was that the volume overload was severe in the TAPVC group compared with that in the ASD group since the blood flow of pulmonary veins direct back into the right atrium.

Changes in the text: Methods (Lines 107-109), Results (Lines 175-178), and Table 2.

Comment 3: The term gestation which is frequently used in this paper is slightly confusing and I would think this would refer to patients who are currently pregnant. If the authors are referring to a prior history of pregnancy as a significant association – would rephrase it accordingly throughout the paper to avoid confusion.

Reply: Thank you for your suggestion. Indeed, we did not express this term clearly – we were referring to a prior history of pregnancy and currently pregnant status. We have added that seven patients had a history of pregnancy and were 3-10 years postpartum, of which three patients were pregnant for a second or third time at the time of the diagnosis.

Changes in the text: Results section (Lines 205-207).

Comment 4: Along the same line – how far out from pregnancy are these patients? Could a recent pregnancy with its associated hemodynamic changes perhaps explain the higher PASP in these patients? Would have to mention this if you are making a claim that past history of pregnancy is associated with higher PASP.

Reply: Thank you for your suggestion. Seven patients had a history of pregnancy and were 3-10 years postpartum: we have now included this information in the Results section (Lines 205-207).

Increased blood volume and hemodynamic changes during pregnancy including prior history of pregnancy or currently pregnant status can lead to increased pulmonary capillary blood volume and lead to higher PASP in these patients. We have added this explanation in the Discussion section (Lines 288-291).

Changes in the text: Results (Lines 205-207) and Discussion (Lines 288-291).

Comment 5: Table 1 – please clarify “60 mmHg > PASP ≥ 50 mmHg”

Reply: Thank you for your suggestion, we have modified Table 1 accordingly.

Changes in the text: Results section (Table 1).

Reviewer B

This study is investigating the echocardiographic features of an adult patient with TAPVC. As it is rare to see adult patients with TAPVC nowadays, this study is important and reminds the clinicians to be aware of TAPVC when seeing the patients with enlarged right ventricle and pulmonary hypertension. This paper is well written, however, there are issues the authors must think about.

Major points

Comment 1: As the main differential diagnosis is secundum ASD, the echocardiographic comparison should be designed with the adult patients with secundum ASD.

Reply: Thank you for your suggestion. We have added that patients diagnosed with

only secundum ASD served as the control group. The ASD diameters in secundum ASD patients were matched with the ASD diameters in TAPVC patients.
Changes in the text: Results (Lines 175-178) and Table 2.

Comment 2: Why pulmonary hypertension was divided at 60mmHg?

Reply: Thank you for your question. According to the “2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension”, when the peak TR velocity is $> 3.4\text{m/s}$ (PASP is approximately 60 mmHg), further intervention is needed; therefore, we divided pulmonary hypertension at 60 mmHg.

Changes in the text: Methods (Lines 152-155).

Comment 3: Are there any hemodynamic data before surgery?

Reply: Thank you for your suggestion. We did not find other significant hemodynamic data.

Comment 4: There should be some patients who underwent “treatment and repair” strategy, which means treating pulmonary hypertension with medication first before surgical repair. How many patients have had “treatment and repair”?

Reply: Thank you for your suggestion. Thirteen patients underwent repair operation, of which three patients had “treatment and repair” because of severe pulmonary hypertension.

Changes in the text: Results (Lines 204-205).

Comment 5: The size of cardiac structure is mainly dependent on the body size. Therefore, the comparison of body size is necessary in comparing the cardiac structural size.

Reply: Thank you for your suggestion. All echocardiographic parameters were standardized by body surface area (BSA).

Minor points

Comment 6: The representative images of chest x-ray or cardiac CT should be provided.

Reply: Thank you. We have added a representative image of cardiac CT as Figure 5.

Changes in the text: Figure 5.

Reviewer C

【General comments】

In this manuscript, the authors reported that the ultrasonographic features of pulmonary

hypertension of unrepaired total anomalous pulmonary venous connection (TAPVC) in adult. Because it is relatively rare to see the survived TAPVC patients to the adults in these days due to the oxygen saturation monitoring for newborn, this report might be helpful to know the prognosis of these patients. However, it is not clear that the evaluation of the factor to affect pulmonary hypertension in these patients. Therefore, there are several concerns need to be resolved in this study.

【Specific comments】

Methods

Comment 1: Although the patients with pulmonary hypertension were divided into two groups with $PASP \geq 60$ mmHg, TR velocity is not clear to decide the PASP.

Reply: Thank you for your suggestion. Not all the PASP of all patients was measured by right cardiac catheterization; the PASP of five patients was measured by right cardiac catheterization, and the PASP of 11 patients was estimated by TR. If there is no obstruction of the RV outflow tract, PASP is equal to the square of TR velocity plus RA pressure. We have added in the Methods section.

Changes in the text: Methods (Lines 143-146).

Results

Comment 2: Although they found that there was a significant association between gestation and PASP, I could not find the details in this manuscript. The details about the gestation and other parameters should be shown.

Reply: Thank you for your suggestion. Due to the limited sample size and according to clinical experience, we chose pregnancy (prior history of pregnancy or currently pregnant status) as a parameter along with age in the Results section.

Changes in the text: Results (Lines 190-192) and Table 5.

Comment 3: They mentioned about the ultrasonographic features about the anatomical details of TAPVR in result. Because they already mentioned about the TAPVC types in table 1 according to the diagnosis of the type of TAPVC, it is better to be mentioned about anatomical features in the methods section.

Reply: Thank you for your suggestion. We have moved the description of anatomical features to the Methods section.

Changes in the text: Methods (Lines 111-119).

Comment 4: In table 2, both mean and median are shown. Either mean or median is fine.

Reply: Thank you for your suggestion. We have deleted this table, and relevant parameters are presented in Table 2.

Changes in the text: Table 2.

Discussion

Comment 5: Does TAPVC type classified as sub-cardiac represent the infracardiac type?

Reply: Thank you for your suggestion. We have added a description in the manuscript that the sub-cardiac classification of TAPVC is the same as the infracardiac type, and used the infracardiac type throughout the paper.

Changes in the text: Methods (Line 115).

Comment 6: In line 203, they mentioned that TAPVC patients who live to adulthood, mild clinical symptoms appear relatively late. However, TAPVC patients have symptoms since they were infants even though they could live to adulthood.

Reply: Thank you for your suggestion. We repeatedly confirmed the clinical manifestations and symptoms of the patients, as described in the Results section (Lines 195-201). Some of the patients had no serious symptoms in infancy and they received surgical repair after diagnosis in adulthood. The lack of serious symptoms may be related to no obstruction of the pulmonary vein and relatively larger ASD diameter.