Original Article

Assessing the correlation between the degree of tricuspid regurgitation and pulmonary hypertension

A comprehensive study

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ABSTRACT

الأهداف: تقييم العلاقة بين شدة قلس ثلاثي الشرفات (TR) وارتفاع ضغط الدم الرئوي.

المنهجية: أجريت دراسة مقطعية على 118 مريضاً يعانون من ارتفاع ضغط الدم الرئوي في مركز واحد في جدة، المملكة العربية السعودية، بين عامي 2018-2021. قمنا باستبعاد المرضى الذين يعانون من أمراض عضوية في الصمامات الرئوية أو ثلاثية الشرفات، أو خضعوا سابقًا لعمليات جراحية في الصمامات ثلاثية الشرفات أو الصمامات الرئوية، أو لديهم أجهزة تنظيم ضربات القلب الدائمة أو يعانون من أمراض خطيرة.

النتائج: كانت نسبة عالية من المرضى من النساء (n=100, 85%) والسمنة (n=57, 48%). كان لدى المرضى الذين يعانون من TR أكثر من خفيف ضغط الشريان الرئوي الانقباضي (sPAP) أعلى من أولئك الذين يعانون من قلس تافه أو خفيف (p<0.001). كان هناك ارتباط كبير بين شدة TR p<0.001 وحجم الغرف اليمنى (p=0.001). وعلاوة على ذلك، كان ضغط الشريان الرئوي (PAP) أعلى بكثير في المرضى الذين يعانون من ضعف خفيف في البطين الأيمن (p=0.001).

الخلاصة: الزيادة في درجة TR وحجم الأذين الأيمن كانت تنبئ بارتفاع sPAP. تسلط النتائج التي توصلنا إليها الضوء على التفاعل بين TR وحجم القلب الأيمن ووظيفة البطين وPAP. يمكن أن يساعد فهم هذه الارتباطات في تقسيم المخاطر، ومراقبة تطور المرض، وتوجيه العلاج لدى هؤلاء المرضى.

Objectives: To evaluate the relationship between severity of tricuspid regurgitation (TR) and pulmonary hypertension.

Methods: Cross-sectional study of 118 patients with pulmonary hypertension was carried out at a single center in Jeddah, Saudi Arabia, between 2018-2021. Patients who had pulmonary or tricuspid valves organic diseases, previously undergone tricuspid or pulmonary valve surgeries, had permanent pacemakers or critically ill were excluded.

Results: A high proportion of patients were women (n=100, 85%) and obese (n=57, 48%). Patients with more than mild TR had higher systolic pulmonary artery pressure (sPAP) than those with trivial or mild regurgitation (p<0.001). There was a significant association between severity of TR (p<0.001) and right chambers size (p=0.001). Furthermore, pulmonary artery pressure (PAP) was significantly higher in patients with mild right ventricular impairment (p=0.001).

Conclusion: Increase in degree of TR and right atrial size were predictors of elevated sPAP. Our findings highlight the interplay among TR, right heart size, ventricular function, and PAP. Understanding these associations can aid in risk stratification, monitoring disease progression, and potentially guiding treatment in those patients.

Keywords: pulmonary hypertension, tricuspid regurgitation, right ventricular dilatation, right ventricular dysfunction, right atrial dilatation

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Pulmonary arterial hypertension (PAH) occurs because of the narrowing and thickening of the small pulmonary arteries, leading to changes in the pulmonary vasculature and sustained vasoconstriction. Additionally, remodeling of the pulmonary vasculature, inflammation, and thrombosis can occur in the small pulmonary arteries and arterioles, thus contributing to increased resistance of the pulmonary vasculature.[1,2] In patients with PAH, the main vasoconstrictor is endothelin-1, which is found excessively within the plasma and is inversely proportional to cardiac output and pulmonary blood flow.[2] Pulmonary arterial hypertension predominantly affects women in the age group of 30-60 years, and its incidence is 1.8 times higher in women than in men.[1] Pulmonary hypertension is defined as a mean pulmonary artery pressure (mPAP) of >25 mmHg.[2] Pulmonary arterial hypertension is usually associated with moderate to severe tricuspid regurgitation (TR), whose severity is determined by other factors, including the distortion of right heart geometric cavities.[3,4] More than moderate TR could lead to right-sided remodeling of the heart. Hence, the right ventricular myocardium may be irreversibly injured in patients with chronic TR.[5]

Functional tricuspid regurgitation (FTR) is one of the most common complications in patients with PAH who have a systolic pulmonary artery pressure (sPAP) of >50 mmHg. Functional tricuspid regurgitation is characterized by an anatomically normal tricuspid valve (TV) structure.[6-8] The mechanism of FTR begins when the right ventricle (RV) afterload increases owing to PAH and eventually leads to RV remodeling, TR, and RV failure.[8-10] Several factors, such as pregnancy and smoking, worsen the outcomes of PAH.[11,12] Therefore, these 2 factors should be considered during the investigation of PAH. A study has previously reported that TR severity can be determined by measuring sPAP. Nevertheless, not all patients with pulmonary hypertension exhibit significant TR.[3] At the same time, another study observed that increased severity of TR is correlated with increased severity of pulmonary hypertension and adverse remodeling of the RV and TV apparatus.[13]

According to previous studies, echocardiographic parameters, such as continuous-wave Doppler, which is used to measure the difference in pressure between the right atrium (RA) and RV, can be used to evaluate the peak TR velocity. A peak TR velocity of <2.8 m/s is regarded as normal.[3,14] Therefore, our study aimed to evaluate the relationship between severity of TR and pulmonary hypertension using echocardiography.

Methods. This study is a cross-sectional retrospective study in which electronic files of patients who visited PAH clinics in King Abdulaziz Medical City "King Faisal Cardiac Center", Jeddah, Saudi Arabia, from November 2018 to March 2021 were reviewed.

All patients over the age of 18 years with sPAP of ≥50 mmHg or mPAP of 30 mmHg were included in the study. Patients who had previously undergone tricuspid/pulmonary valve surgeries; those with pulmonary stenosis, TV diseases, or permanent pacemakers; ventilated patients; and New York Heart Association Class IV patients were excluded. The total study sample size was 118 patients, and 82 patients were excluded. These patients' files were reviewed using the electronic BestCare system via medical file numbers.

Approval was obtained from institutional review board of King Abdullah International Medical Research Center, Jeddah, Saudi Arabia (study no.: SP21J/079/03).

The variables of interest were the patient's demographics (including age, gender, body mass index, and marital status), smoking status, pregnancy in case of women, ischemic heart disease (IHD), chronic obstructive pulmonary disease, hypertension, and diabetes mellitus.

Echocardiographic parameters included mPAP and sPAP, TR (trivial, mild, moderate, severe, massive, and torrential), pulmonary valve regurgitation (PR; none, trace, mild, moderate, and severe), RA dilatation (normal, mildly dilated, moderately dilated, and severely dilated), RV dilatation (normal, mildly dilated, moderately dilated, and severely dilated), RV function (normal, mildly impaired, moderately impaired, and severely impaired), left ventricular ejection fraction (LVEF), mitral stenosis, mitral regurgitation, right ventricular systolic velocity (cm/s), tricuspid annular plane systolic excursion (cm), and LV filling pressure (E/e').[5,8]

Statistical analysis. A Microsoft Excel sheet was used to collect variables of interest in rows and columns (rows of each patient and columns including the variables of interest). The data were analyzed using Stata 18 (Stata Corp, College Station, TX, USA). Continuous variables are presented as mean and standard deviation (SD) and categorical variables as frequencies and percentages (%). Continuous variables were compared using analysis of variance for variables of equal variance or the Kruskal-Wallis test in case of unequal variance. A post-hoc analysis was carried out using Bonferroni or Dunn's test. Categorical data were compared using Fisher's exact test. Factors affecting PAH were assessed using a stepwise linear regression, and a *p*-value of ≤0.05 was required to retain the variable in the final

model. Residual vs. fitted plots were used to test linear regression assumptions. A *p*-value of <0.05 was considered significant.

Results. The mean age of the study sample was 59.73±18.86 years, with the majority being women (85%). A high proportion of the population was obese (48.3%), whereas 3.4% were underweight. Moreover, 82% of the patients had mitral regurgitation, and 14.4% had IHD. Most patients 72.88% had a normal LV function with EF of >55% (Table 1).

Patients with TR severity more than mild had higher sPAP than those with trivial and mild TR (p<0.001). Similarly, there were significant differences between PR and TR severity. Thus, of the patients with moderate PR, had more than severe TR (p=0.025, Table 2).

In the torrential TR group, 30% of the patients had severely dilated RVs, whereas 10% had moderately dilated RVs. Similarly, the percentage of patients with severe TR and a moderately dilated RV was approximately 35%. Likewise, RV function was mildly impaired in patients with torrential TR, of which 50% had mildly impaired RV function and 20% had moderately impaired RV function. However, only 4% had severely impaired RV function. Most RV functions were normal in patients with mild TR (Table 2). There was a significant association between TR degree (p=0.001) and RV size and function (p<0.001).

Table 1 - Demographic and clinical characteristics of adult patients with pulmonary hypertension (N=118).

Patient's characteristics	n (%)
Age (years), mean±SD	59.73±18.86
Female	100 (84.7)
Body mass index	
Underweight	4 (3.4)
Normal	27 (22.9)
Overweight	30 (25.4)
Obese	57 (48.3)
Marital status	
Single	19 (16.1)
Married	99 (83.9)
Ischemic heart disease	17 (14.4)
Mitral stenosis	7 (5.9)
Mitral regurgitation	97 (82.2)
Ejection fraction >55%	86 (72.9)
Chronic obstructive pulmonary disease	9 (7.6)
Diabetes mellitus	50 (42.4)
Hypertension	66 (55.9)

Values are presented as numbers and percentages (%) or mean ± standard deviation (SD).

Right ventricular size and function were affected by the increase in sPAP, which was significantly higher in patients with mild (p=0.01), moderate (p<0.001), and severe (p=0.002) RV dilatation than in those with normal RV size. Similarly, mPAP was significantly higher in patients with mild (p=0.005), moderate (p<0.001), and severe (p=0.046) RV dilatation than in those with normal RV size. Pulmonary artery pressure (PAP) was significantly higher in patients with RV function impairment than in those with normal RV (p=0.001, Table 3).

Right ventricular dilatation and PR were associated with increased mPAP. Tricuspid regurgitation and RA dilatation were associated with increased sPAP (Table 4).

Discussion. This study examined the relationship between the degree of TR and PAH by considering various factors. The findings revealed several significant associations that contributed to an in-depth understanding of this relationship. A high prevalence of the female gender and obesity was observed in the patient population, which is aligned with known risk factors for TR and pulmonary hypertension.[3] This study demonstrated a progressive relationship in which greater TR severity corresponds to increased PAH. Furthermore, there is a significant association between the severity of TR and the enlargement of the RA and RV. Another main finding was that patients with RV dilatation, RV function impairment, severity of TR or RA dilatation had significantly higher sPAP than those with normal findings. Besides, RV dilatation and PR were positively linked to elevated mPAP. Previous studies have reported that PAH and RV dysfunction are significantly correlated, as RV dysfunction starts with RV wall thickening in response to pressure overload, and subsequently, RV is dilated.[15,16]

According to this study, only a few patients with PAH and severe sPAP had severely impaired RV function. This result supports the findings of Mutlak et al.[3] Another study has reported that FTR is associated with annular dilatation of the TV as a result of RA and RV enlargement or increase in the RV afterload. Similarly, RV and annular dilatation has been shown to affect TV leaflet coaptation and displace the closure line of the leaflet.[17]

Although TR is routinely assessed via echocardiography, it is important to determine its severity in the presence of pulmonary hypertension. As the severity of TR increases, morbidity and mortality increase and survival declines remarkably.[18,19] Consequently, elevated RV systolic pressure and RV dilation and dysfunction are associated with increased TR severity, as reported previously.[18,20] On the contrary,

Table 2 - Clinical and echocardiographic data according to the degree of tricuspid regurgitation.

Variables	Trivial TR (n=14)	Mild TR (n=41)	Moderate TR (n=25)	Severe TR (n=26)	Massive TR (n=2)	Torrential TR (n=10)	*P*-values
Age (years), mean±SD	61.29±15.70	58.44±20.40	62.92±19.46	61.62±17.63	32.50±2.12	55.40±17.53	0.314
sPAP(mmHg), mean±SD	45.99±22.80	52.44±12.63	61.45±16.91	67.08±14.87	82.80±10.04	69.41±25.64	<0.001
mPAP(mmHg), mean±SD	36.09±6.69	33.42±11.63	34.48±12.18	35.52±9.29	59.00±6.65	33.30±13.39	0.029
PR							
None	8 (57.1)	14 (34.1)	11 (44.0)	3 (11.5)	-	3 (30.0)	0.025
Trace	2 (14.3)	15 (36.6)	7 (28.0)	6 (23.1)	-	1 (10.0)	
Mild	2 (14.3)	10 (24.4)	7 (28.0)	14 (53.8)	1 (50.0)	4 (40.0)	
Moderate	2 (14.3)	2 (4.9)	-	3 (11.5)	1 (50.0)	2 (20.0)	
RA size							
Normal	11 (78.6)	28 (68.3)	17 (68.0)	5 (19.2)	-	2 (20.0)	<0.001
Mildly dilated	3 (21.4)	10 (24.4)	5 (20.0)	8 (30.8)	1 (50.0)	1 (10.0)	
Moderately dilated	-	3 (7.3)	3 (12.0)	7 (26.9)	-	3 (30.0)	
Severely dilated	-	-	-	6 (23.1)	1 (50.0)	4 (40.0)	
RV size							
Normal	8 (57.1)	32 (78.0)	17 (68.0)	9 (34.6)	-	3 (30.0)	0.001
Mildly dilated	4 (28.6)	5 (12.2)	5 (20.0)	5 (19.2)	1 (50.0)	3 (30.0)	
Moderately dilated	1 (7.1)	4 (9.8)	3 (12.0)	9 (34.6)	-	1 (10.0)	
Severely dilated	1 (7.1)	-	-	3 (11.5)	1 (50.0)	3 (30.0)	
RV function							
Normal	12 (85.7)	39 (95.1)	21 (84.0)	12 (46.1)	1 (50.0)	3 (30.0)	<0.001
Mildly impaired	1 (7.1)	2 (4.9)	2 (8.0)	6 (23.1)	1 (50.0)	5 (50.0)	
Moderately impaired	1 (7.1)	-	2 (8.0)	7 (26.9)	-	2 (20.0)	
Severely impaired	-	-	-	1 (3.8)	-	-	
EF%							
40-55%	3 (21.4)	10 (24.4)	3 (12.0)	15 (57.7)	-	1 (10.0)	0.005
>55%	11 (78.6)	31 (75.6)	22 (88.0)	11 (42.3)	2 (100.0)	9 (90.0)	
RVs' (cm/s), mean±SD	12.28±3.20	12.14±2.69	11.35±2.29	9.90±2.38	12.75±3.18	9.20±2.45	0.002
TAPSE (cm), mean±SD	1.98±0.47	1.97±0.37	1.85±0.26	1.77±0.55	1.60±0.42	1.64±0.41	0.063
E/e', mean±SD	13.63±19.76	12.19±6.25	11.70±6.25	14.00±9.77	7.90±3.68	13.10±13.18	0.548

Values are presented as numbers and percentages (%) or mean ± standard deviation (SD). TR: tricuspid regurgitation, sPAP: systolic pulmonary arterial pressure, mPAP: mean pulmonary arterial pressure, PR: pulmonary regurgitation, RA: right atrium, RV: right ventricle, EF: ejection fraction, RV's: right ventricular systolic velocity, TAPSE: tricuspid annular plane systolic excursion, E/e': left atrium filling pressure

Table 3 - Systolic and mean pulmonary artery pressure in patients with different grades of right ventricular dilatation and hypofunction.

RV size	Normal RV size (n=69)	Mild RV dilatation (n=23)	Moderate RV dilatation (n=18)	Severe RV dilatation (n=8)	*P*-values
sPAP (mmHg)	52±13	64±21	68±21	73±34	<0.001
mPAP (mmHg)	28±12	38±13	39±10	36±17	0.002
RV function	**Normal RV function (n=88)**	**Mildly impaired (n=17)**	**Moderately impaired (n=12)**	**Severely impaired (n=1)**	***P*-values**
sPAP (mmHg)	55±18	70±21	62±22	72	0.015
mPAP (mmHg)	31±14	39±12	32±7	35	0.193

Values are presented as mean ± standard deviation (SD). mPAP: mean pulmonary artery pressure, RV: right ventricle, sPAP: systolic pulmonary artery pressure

RV could adapt its function normally even with the progression of PAH.[21] In most patients in our sample, RV function was normal based on the severity of sPAP, but it was severely impaired in patients with severe sPAP. Moreover, RA size was severely affected by the increasing severity of TR, and there was a significant association between the 2. Furthermore, most of our findings were in women, and as the severity of TR increased in addition to severe PAH, the mean age decreased slightly, which agrees with previous research.[22,23] The groups for the severity of TR were classified into 2 categories which included severe and less than severe.

Table 4 - Factors associated with systolic and mean pulmonary artery pressure.

Variables	β (95% CI)	*P*-values
Mean pulmonary artery pressure		
Right ventricle dilatation	3.55 (1.09-6.03)	0.005
Pulmonary valve regurgitation	2.67 (0.24-5.11)	0.031
Systolic pulmonary artery pressure		
Tricuspid regurgitation	4.14 (1.49-6.78)	0.002
Right atrial dilatation	5.51 (1.97-9.05)	0.003

Values are presented as beta and 95% confidence interval (CI).

Study strengths & limitations. Although the findings should be interpreted with caution, this study has several strengths. The main strength is the exclusion criteria, which were developed to exclude patients with confounding diseases that may interfere with the accuracy of the results. Moreover, the data were collected from electronic medical records reviewed by experienced echocardiographers as part of routine clinical practice to minimize measurement errors. This research included the updated echocardiographic scoring system for TR severity and RV function assessment in addition to a comprehensive examination of the most common clinical manifestations pertaining to the development of both PAH and TR, such as RV size, RV function, and RA size.

Nonetheless, this study also has several potential methodological limitations. First, the study is limited by the inability to estimate sPAP owing to the lack of this information in patients who had neither TR nor PR jet in echocardiography as its estimation depends on the presence of these 2 parameters. Therefore, these patients were not included in the study. Second, another source of uncertainty is associated with alterations in the values of the variables based on the presence of several echocardiographic examinations during the period of the study. Third, the method of estimating mPAP using the acceleration time could have affected the validity of the study as any small change in the measurement might affect the mPAP value and the class of PAH severity. Finally, the generalizability of these findings is limited by the sample size of the study. It would have been more beneficial if more methods had been used to measure the variables concisely, including pressure value estimation from cardiac catheterization, which could be considered in future studies.

In conclusion, increase in the degree of TR and right atrial size were predictors of increased sPAP. On the contrary, RV dilatation and PR affected mPAP. These findings highlight the interplay among TR, right heart chamber size, ventricular function, and PAP. Comprehending these associations can aid in risk stratification, monitoring disease progression, and potentially guiding treatment decisions for patients with TR and pulmonary hypertension. However, further investigations with larger prospective cohorts are warranted to validate and expand upon these findings. Overall, our study has provided valuable insights into the complex relationship between TR and pulmonary hypertension, serving as a foundation for future research and clinical management strategies.

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