Factors associated with suggestive of pulmonary hypertension measured by echocardiography in patients with a mediastinal tumor: A single-center study

Running title: Suggestive pulmonary hypertension and mediastinal tumor

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Abstract

Background: Ultrasound techniques are generally not used as a primary tool in the evaluation

of mediastinal tumors and cysts. This study aimed to identify factors associated with pulmonary hypertension (PH) measured by transthoracic echocardiography (TTE) in patients with a mediastinal tumor.

Methods: This retrospective, observational study was performed from January 2015 to December 2020. Fifty-five patients (mean age, 62 ± 13 years; 31 [56%] women) who had a mediastinal tumor and underwent TTE were included. Patients were classified as with PH or without PH. We analyzed clinical factors and echocardiographic parameters.

Results: PH was found in 21 (38%) patients. Twenty-two patients were asymptomatic, and none had symptoms associated with PH. Forty-seven (86%) patients underwent surgery, and 23 (42%) patients were diagnosed with malignant tumors. The presence of PH was not related with malignancy. Patients with PH were older than those without PH (67 ± 10 versus [vs.] 59 ± 14 years, p = 0.017). Small left ventricular (LV) systolic dimension (29.4 ± 3.6 vs. 31.6 ± 3.6 mm, p = 0.040) and dimension (4.2 ± 0.3 vs. 4.5 ± 0.3 mm, p = 0.004) and hyperdynamic LV ejection fraction (EF, 69 ± 6 vs. 65 ± 5%, p = 0.019) were associated with PH. Among them, older age, small LV dimension, and high EF were independently associated with PH.

Conclusion: The presence of PH had no significant effect on patients' clinical manifestation or malignancy.

Key words: mediastinal mass, echocardiography, pulmonary hypertension

Introduction

Ultrasonographic methods have been used to help differentiate solid mediastinal masses (MTs) from cystic MTs and to assist in determining the connection between a mass and adjacent structures; such methods are especially useful in the evaluation of masses associated

with the heart and in vascular abnormalities. In general, given the accuracy and detail provided by computed tomography (CT) images, magnetic resonance imaging, and selected radionuclide scan findings, ultrasound techniques are generally not used as a primary tool in the evaluation of mediastinal tumors and cysts. [1-3]

However, we came across two clinical cases in which transthoracic echocardiography (TTE) detected suggestive of pulmonary hypertension (PH), which was defined as elevated estimated right ventricular systolic pressure (RVSP) by TTE and incidentally found a MT on chest CT performed for the evaluation of pulmonary thromboembolism (PTE). Figure 1A, B provides details of these two cases. Case A was a 75-year-old woman who was admitted because of fainting, and echocardiography showed (A-1) elevated RVSP (60 mmHg). Case B was a 63-year-old woman who presented with atypical chest pain without any coronary risk factors. Her RVSP was 54 mmHg (B-1). On pulmonary angiographic CT performed to discriminate PTE, both cases showed only an anterior MT without other abnormalities (A-2,3, and B-2,3). The figure legend provides more detailed clinical information and echocardiographic parameters. Based on these cases, TTE can be used to not only diagnose and manage patients with PH but to also detect the probability of patients having PH. [4]

Therefore, we retrospectively reviewed the significance of clinical characteristics in patients with suggestive of PH detected by TTE among those with a MT.

Methods

Study design and participants

This retrospective study included 55 patients who were diagnosed with an MT and underwent echocardiography at the Kangnam Sacred Heart Hospital, Hallym University from January 2010 to December 2019. Patients with documented PH who were eligible for the five clinical classifications of PH[4] were excluded from this study. In addition, patients with primary or metastatic lung cancer, systemic cancer, mediastinal lymph node enlargement, pericardial mass were excluded. We investigated the clinical features and prevalence of suggestive of PH in enrolled patients with an MT. Patients were classified into two groups according to the RVSP estimated by echocardiography[5] (patients with suggestive of PH, RVSP ≥35 mmHg, n = 21; patients without PH, RVSP <35 mmHg n=34). We analyzed clinical factors including baseline characteristics, echocardiographic, laboratory parameters, and the results of the pulmonary function test (PFT).

Transthoracic echocardiography

TTE was performed using standard techniques with a 2.5-MHz transducer. Standard two-dimensional and Doppler echocardiography was performed using a commercially available echocardiographic machine (Vivid 7R GE Medical System, Horten, Norway) with the same setup interfaced with a 2.5-MHz phased-array probe. All measurements were performed in accordance with the guideline [6]. With the study participant in the partial left decubitus position and breathing normally, the observer obtained images from the parasternal

long and short axes and from the apical four-chamber, two-chamber, and long-axis views. Depth setting was optimized to display the left ventricle on the screen as large as possible, and the same field depth was kept for both four-chamber and two-chamber apical views. Sector width was reduced to increase spatial and temporal resolutions. The left ventricular end-diastolic dimension (LVEDD), end-diastolic interventricular septal thickness (IVS), and end-diastolic left ventricular (LV) posterior wall thickness (PWT) were measured at end-diastole in accordance with the standards established by the American Society of Echocardiography. And LV end-systolic dimension (LVESD) and LV dimension (LVD) were also measured. Left ventricular ejection fraction (LV EF) was determined using the biplane Simpson method. Maximal left atrial volume was calculated using the Simpson method and indexed to the body surface area. LV mass was calculated using the Devereux formula as follows: $1.04[(\text{LVEDD} + \text{IVSTd} + \text{PWTd})^3 - (\text{LVEDD})^3] - 13.6$, where IVSTd stands for interventricular septal wall thickness and PWTd stands for posterior wall thickness in diastole. Thereafter, the LV mass index was calculated and indexed to body surface area. Diastolic wall strain was calculated as follows using M-mode echocardiography: [(PWTs) – (PWTd)/(PWTs)].

Mitral flow velocities were recorded in the apical four-chamber view. Mitral inflow measurements included the peak early (E) and peak late (A) flow velocities and E/A ratio. Tissue Doppler of mitral annulus movement was also obtained from the apical four-chamber

view. A 1.5-mm sample volume was placed sequentially at the septal annular sites. The analysis was performed for early diastolic (E') and late diastolic (A') peak tissue velocities. As a noninvasive parameter for LV stiffness, the LV filling index (E/E') was calculated by the ratio of transmitral flow velocity to annular velocity. Adequate mitral and tissue Doppler image signals were recorded in all patients.

RVSP was calculated using tricuspid regurgitation (TR) velocity. Peak TR velocity was obtained from the apical four-chamber view or right ventricular (RV) inflow view with continuous wave (CW) Doppler imaging. Then RVSP was calculated using the simplified Bernoulli equation (pressure gradient [PG] of the right atrium [RA] and right ventricle = 4[TRVmax]^2) + right atrial pressure [RAP] using inferior vena cava collapsibility [7]. In addition, we measured RV/LV basal diameter ratio. This was measured from the standard apical four-chamber view without foreshortening at end diastole. A ratio >1 measured at end diastole suggests RV dilatation.[5]

Statistical analysis

All continuous data are expressed as mean ± standard deviation (SD), and all categorical data are presented as a percentage or absolute number. Continuous variables were analyzed using one-way analysis of variance in three independent groups, the Student t-test was used to analyze two independent groups, and chi-square test was used to analyze dichotomous variables. In addition, multivariate analysis (logistic regression, SPSS for Macintosh, version

10.0.7a, IBM Corp., Armonk, NY, USA) was performed. Non-normally distributed variables were analyzed using the Kruskal-Wallis test or Mann-Whitney U test. All variables with a p-value <0.05 were considered statistically significant.

Results

Clinical characteristics of the study population

The clinical characteristics of the patients are shown in Table 1. The study population included 55 patients (55% female; average age, 62 years) who were diagnosed with MT and underwent echocardiography. Twenty-one patients (38%) had echocardiographically assessed suggestive of PH. Most patients were asymptomatic, and the most common symptoms were atypical chest pain, dyspnea, and cough. Nine patients (16%) had myasthenia gravis (MG). Forty-seven patients underwent surgery, and 24 patients had confirmed malignancy. Most tumors were located in the anterior mediastinum (93%).

Comparison of baseline characteristics according to the presence of suggestive of pulmonary hypertension

The comparison of patients' clinical characteristics between the groups is shown in Table 2. Patients with suggestive of PH were significantly older than those without PH (67.2 ± 10.0 versus [vs.] 58.8 ± 13.6, p = 0.017). There were no significant differences in other clinical parameters such as sex and conventional risk factors between the groups. The

presence of symptoms, malignancy, and MG were not related to PH. The cardiac biomarker and lactate dehydrogenase (LDH) also did not differ significantly between the two groups, but a higher average value of the brain natriuretic peptide (BNP) level was observed in patients without PH than in those with suggestive of PH.

Echocardiographic parameters and pulmonary function test results

The echocardiographic parameters of the patients are shown in Table 3. Mean RVSP values were 40.5 ± 7.6 mmHg in patients with suggestive of PH and 26.2 ± 4.8 mmHg in patients without PH. There was no significant difference in echocardiographic parameters in terms of both systolic and diastolic functions. However, compared to patients without PH, those with PH had smaller LV ESD and LVD, which were associated with more dynamic LV EF.

The results of the PFT are also shown in Table 3. There was no significant difference in PFT results between the groups.

Multivariate analyses

We performed multivariate analysis with age, LV ESD, LVD, and EF. All of these variables showed a significant correlation with the presence of PH except LV ESD. Older age (odds ratio [OR]: 1.065, 95% confidence interval [CI]: 1.002-1.133, p = 0.045), small LVD (OR: 0.066, 95% CI: 0.055-0.781; p = 0.031), and dynamic EF (OR: 1.183, 95% CI: 1.002-

1.396, p = 0.048) were independently associated with PH.

Discussion

Major Findings

According to this study's findings, older age was associated with suggestive of PH. However, there was no accompanying deterioration in heart (both systolic and diastolic) or lung function, but rather parameters indicating volume depletion (small LV end-systolic dimension and increased relative wall thickness) were related to suggestive of PH. There were no significant complications after surgery in patients with preoperative PH, and PH did not progress in any case during the follow-up. Although this study was not a prospective study and did not assess prognosis, there were no reports of postoperative complications associated with suggestive of PH after surgery.

Role of echocardiography

The role of echocardiography in screening of PH is pivotal in various clinical settings, including congenital heart disease and connective tissue disease.[8-11] PH is a hemodynamic and pathophysiologic condition defined as an increase in mean pulmonary artery pressure ≥25 mm at rest as assessed by right heart catheterization. It can be found in multiple clinical conditions with distinct pathogenetic and clinical features, such as pulmonary arterial hypertension and left heart, lung, and thromboembolic diseases. [4] Because of the nature of PH, in the early

stages of the disease, symptoms are non-specific, and there are often no significant physical changes. If there are risk factors, it is important to screen for PH before irreversible change occurs. [12] In this regard, TTE, by providing direct and/or indirect signs of elevated pulmonary artery pressure, is an excellent noninvasive screening test for patients with symptoms or risk factors for PH, such as connective tissue disease, anorexigen use, pulmonary embolism, heart failure, and heart murmurs. It may also provide key information on both the etiology and prognosis of PH. [9] A small degree of TR is present in most healthy individuals. [13] TR peak velocity can be analyzed in the inflow view of the parasternal long axis, parasternal short axis view, and apical four-chamber view using CW Doppler imaging. The peak TR velocity reflects the PG between the right ventricle and RA. Using the modified Bernoulli equation, the PG between the RA and right ventricle can be estimated from the peak velocity of TR between the two chambers: peak PG = 4 × (peak TR velocity)^2. [6,7] Thus, RVSP is defined as the sum of RAP and peak PG, and RVSP >37 mmHg is suggestive of PH. [6] Peak TR velocity <2.8-2.9 m/s and peak systolic pressure <35-36 mmHg are normal ranges. [14,15] Therefore, in this study, a patient in whom the RVSP was <35 was considered normal, and patients with RVSP of 35 mmHg were considered to have PH and were compared with those without PH.

Factors associated with elevated RVSP

RVSP increases with age in patients without other pathologies.[16,17] Likewise, patients with

elevated RVSP were older than those with normal RVSP in this study.

According to Wroebl et al.' study, the higher the RVSP estimated by TTE performed before lung transplantation in patients with chronic obstructive pulmonary disease (COPD), the longer the duration of treatment for mechanical ventilator after surgery.[18] However, postoperative cardiac complications were not increased in patients with high RVSP in this study. Cleary, there were no patients with significant COPD or with poor lung function enrolled in this study, and there were no significant differences in PFT results in both patient groups.

Interestingly, small LV size (smaller end-systolic dimension of LV, small LV dimension) and slightly increased LV EF were associated with elevated RVSP, and smaller LVD and higher LV EF were independently associated with elevated RVSP. Small LV size was also associated with poor prognosis in patients with heart failure independent of EF [19], an increased risk of thrombosis in patients with LV assist device,[20] and poor exercise capacity even in patients with normal EF.[21] Several factors affect the standard value for LV dimension including age, sex, and race; among them, aging is related with a small LV chamber size.[5] According to this study's results, aging and elevated RVSP are related, so small LV cavity size, which is associated with elevated RVSP, may also be related to aging. However, since small LV cavity size is also an indicator that reflects volume depletion,[22] it can be inferred whether it is related to an increase in RVSP due to vasoconstriction associated with volume

depletion.[23]

Study Limitations

This study has a few limitations. Firstly, this was a single center study with a small study population, which is a major limitation. Secondly, in this study, it was not confirmed whether patients with PH before surgery improved after surgery. Thirdly, in particular, since this study had a retrospective study design, evaluation of the RV function was not routine. Therefore, an accurate evaluation of the RV function was not performed in patients with PH. However, the patients included in this study had normal right atrial and RV sizes, and no patients showed clinically significant RV failure.

Clinical implications

TTE is widely used to identify cardiac function and causes in patients with various clinical conditions and symptoms, including heart disease. Therefore, even in situations where PH is not suspected (it does not belong to one of the five classifications of PH), RVSP is elevated. If RVSP is elevated without any other abnormalities on TTE that was performed to differentiate the cause of non-specific symptoms, such as dyspnea or chest pain, it is not easy to suspect PH or necessary to conduct an invasive work-up immediately. In this study, studies of PH found in patients with an MT revealed that the elevation of RVSP without other abnormalities was not clinically significant and was not associated with a poor prognosis.

Conclusions

Overall, 38% of patients with an MT showed suggestive of PH, and age, small LV size, and relative dynamic LV EF were associated with PH. However, there was no accompanying deterioration in heart (both systolic and diastolic) or lung function, no significant complications after surgery in patients with preoperative suggestive of PH, and no progression of PH during the follow-up.

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Conflict of interests

The authors do not have any conflicts of interest.

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Table 1. Clinical parameters of the study population

	N=55
Age, years	62.2 ± 12.9
Female gender	31 (56%)
Tumor location	55 (100%)
anterior	51 (93%)
middle	3 (5%)
posterior	1 (2%)
Symptoms	
none	22 (40%)
ptosis	7 (13%)
DOE, chest pain	11 (20%)
Dizziness, general weakness	5 (9%)
cough	7 (13%)
SVC syndrome	2 (4%)
hypotension	1 (2%)
Myasthenia gravis	9 (16%)
Malignant tumor	23 (42%)
Diabetes mellitus	11 (20%)
Hypertension	27 (49%)
Pulmonary disease	13 (23%)
Surgery	47 (86%)
Pulmonary hypertension	21 (38%)

Data are mean ± standard deviation (SD) or or n (%). DOE, dyspnea of exertion; SVC, superior vena cava.

Table 2. Comparison of baseline characteristics of the study population

	PH (n=21)	No PH (n=34)	p
Age (years)	67.3 ± 10.0	58.8 ± 13.6	0.017
Female gender	15 (71%)	16 (47%)	0.098
SBP (mmHg)	121.6 ± 16.1	115.2 ± 11.5	0.127
DBP	71.4 ± 10.9	72.3 ± 8.5	0.738
Heart rate (bpm)	74.4 ± 18.6	70.8 ± 11.5	0.374
BMI (kg/m^2)	24.9 ± 3.5	24.7 ± 2.9	0.766
DM	3 (14.3%)	8 (23.5%)	0.502
Hypertension	10 (47.6%)	17 (50.0%)	1.000
Pulmonary ds	3 (14.3%)	10 (29.4%)	0.328
malignancy	7 (33.3%)	16 (47.1%)	0.403
Sx	11 (52.4%)	22 (64.7%)	0.407
MG	4 (19.0%)	5 (14.7%)	0.719
BNP	44.0 ± 31.5	72.5 ± 157.1	0.528
LDH	225.6 ± 70.1	219.2 ± 55.6	0.707

Data are represented as mean ± SD or n (%). SBP, systolic blood pressure; DBP, diastolic BP; BMI, body mass index; DM, diabetes mellitus; Sx, presence of symptoms; MG, myasthenia gravis; BNP, brain-natriuretic peptide; LDH, lactate dehydrogenase.

Table 3. Echocardiographic parameters and pulmonary function test of the study population

	PH (n=21)	No PH (n=34)	p
LAVI (ml/m^2)	24.9 ± 10.6	22.2 ± 5.7	0.222
LV EDD (mm)	47.9 ± 4.5	48.8 ± 4.3	0.467
LV ESD	29.4 ± 3.6	31.6 ± 3.6	0.040
LVMI (g/m^2)	105.1 ± 19.2	95.1 ± 26.6	0.141
LV EF (%)	68.6 ± 6.1	64.8 ± 5.4	0.019
E (cm/s)	67.2 ± 19.8	64.2 ± 20.6	0.600
A (cm/s)	78.2 ± 16.0	69.2 ± 16.9	0.059
E/A ratio	0.88 ± 0.26	1.00 ± 0.43	0.263
DT (ms)	207.5± 48.1	209.4 ± 39.8	0.877
E' (cm/s)	7.1 ± 1.9	8.0 ± 3.2	0.196
A' (cm/s)	10.4 ± 2.4	9.5 ± 2.0	0.171
E'/A'	0.70 ± 0.22	0.89 ± 0.44	0.249
E/E'	9.8 ± 3.0	8.8 ± 3.2	0.249
S' (cm/s)	8.5 ± 1.6	7.6 ± 1.7	0.057
RVSP	40.5 ± 7.6	26.2 ± 4.8	<0.001
TR Vmax	2.89 ± 0.40	2.29 ± 0.29	<0.001
RVD	3.23 ± 0.52	3.57 ± 0.69	0.061
LVD	4.18 ± 0.31	4.46 ± 0.34	0.004
RV/LV Ratio	0.78 ± 0.12	0.80 ± 0.15	0.639
PFT			
FVC	2.9 ± 0.9	3.3 ± 0.9	0.159
FEV1	2.1 ± 0.7	2.4 ± 0.9	0.184
DLco	15.2 ± 2.8	18.0 ± 4.4	0.123

Data are represented as mean ± SD or n (%). LAVI, left atrial volume index; LVMI, left ventricular mass index; LVEDD and ESD, LV end-diastolic and systolic dimension; EF, ejection fraction; DT, deceleration time; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation, RVD, RV dimension; LVD, LV dimension; PFT, pulmonary function test; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; DLco, diffusion capacity.

Table 4. Uni-and multivariate analysis on the associating factors of elevated RVSP

	Odds ratio	95% CI	p
Univariate analysis			
age	1.061	1.008-1.117	0.024
LVESD	0.846	0.718-0.997	0.046
LVD	0.071	0.010-0.518	0.009
EF	1.130	1.016-1.256	0.024
Multivariate analysis			
age	1.065	1.002-1.133	0.045
LVESD	1.104	0.837-1.456	0.483
LVD	0.066	0.005-0.781	0.031
EF	1.183	1.002-1.396	0.048

LVESD, left ventricular end systolic dimension; LVD, LV dimension; EF, ejection fraction.

Figure legend

Figure 1. Two patients with echocardiographically confirmed pulmonary hypertension who were

diagnosed with a mediastinal tumor later.

A: A 75-year-old female patient with hypertension presented with syncope. A-1, The pressure gradient (PG) of the right atrium (RA) and right ventricle (RV) using tricuspid regurgitation (TR) velocity is 50 mmHg, right atrial pressure is 10 mmHg, and echocardiographic measurement of the right ventricular systolic pressure (RVSP) is 60 mmHg. Her other echocardiographic findings are within normal range (ejection fraction: 64%, E/E': 12). With regard to laboratory findings, the lactate dehydrogenase level is 232 IU/L, and D-dimer level is 1.0 μg/mL. This patient's pulmonary function is also normal, and there is no suspected pulmonary thromboembolism. A-2 and 3, pulmonary angiographic computed tomography (CT) performed to rule out pulmonary thromboembolism reveals a 17-mm poorly enhanced nodular lesion in the anterior mediastinum (white arrow).

B: A 63-year-old female patient without coronary risk factors presented with atypical chest pain. A-1, The PG of RA and RV using TR velocity is 49 mmHg, right atrial pressure is 5 mmHg, and RVSP is 54 mmHg. Her other echocardiographic findings are within normal range (ejection fraction: 72%, E/E': 8). This patient's pulmonary function is also normal, and there is no suspected pulmonary thromboembolism. A-2 and 3, Chest CT shows a 3.8-cm (cranio-caudal diameter), elongated, and lobulated soft tissue attenuation lesion in the left lower anterior mediastinum (white arrow).