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Hoarseness as a Predictor for Pulmonary Arterial Aneurysm and Extrinsic Left Main Coronary Artery Compression in Patients with Severe Pulmonary Hypertension

Ses Kısıklığının Ciddi Pulmoner Hipertansiyonu Olan Hastalarda Pulmoner Arter Anevrizması ve Sol Ana Koroner Artere Dıştan Basıyı Göstermedeki Rolü

ABSTRACT

Objective: Pulmonary artery (PA) enlargement is a common finding in patients with severe pulmonary hypertension (PH) and may be associated with extrinsic compression of the left main coronary artery (LMCA-Co) and/or compression of the left recurrent laryngeal nerve resulting in hoarseness named as Ortner syndrome (OS). In this study, we evaluated the diagnostic impact of OS in predicting the PA aneurysm and significant LMCA-Co in patients with PH.

Methods: Our study population comprised retrospectively evaluated 865 with PH confirmed with the right heart catheterization between 2006 and 2022. Patients underwent coronary angiography due to several indications, including the presence of a PA aneurysm on echocardiography, angina symptoms, or the incidental discovery of LMCA-Co on multidetector computed tomography. The LMCA-Co is defined as diameter stenosis ³ 50% in reference distal LMCA segment on two consecutive angiographic planes.

Results: The LMCA-Co and hoarseness were documented in 3.8% and 4.3% of patients with PH, respectively. Increasing PA diameter was significantly associated with worse clinical, hemodynamic, laboratory, and echocardiographic parameters. The receiver operating curves revealed that the PA diameter >41 mm was cutoff for hoarseness (AUC: 0.834; sensitivity 69%, specificity 84%, and negative predictive value 98%), and PA diameter >35 mm was cutoff for LMCA-Co >50% (AUC: 0.794; sensitivity 89%, specificity 58 %, and negative predictive value 99%). An odds ratio of hoarseness for LMCA-Co was 83.3 (95% confidence interval; 36.5–190, $P < 0.001$) with 3.2% sensitivity, 98.7% specificity, and 59% positive and 98% negative predictive values.

Conclusion: In this study, a close relationship was found between the presence of hoarseness and the probability of extrinsic LMCA-Co by enlarged PA in patients with severe PH. Therefore, the risk of LMCA-Co should be taken into account in patients with PH suffering from hoarseness.

Keywords: Euphrates, hoarseness, left main coronary artery, pulmonary hypertension

ÖZET

Amaç: Pulmoner arter (PA) genişlemesi, şiddetli pulmoner hipertansiyonu (PH) olan hastalarda sık görülen bir bulgu olup Ortner sendromu (OS) adını alarak sol ana koroner arterin (LMCA) dıştan basısı ve/veya sol rekürren laringeal sinirin basısı ile sonuçlanarak ses kısıklığına neden olabilir. Bu çalışmada OS'nin PH hastalarında PA anevrizmasını ve anlamlı LMCA basısını öngördürmede tanısal etkisini değerlendirmeyi amaçladık.

Yöntem: Çalışma popülasyonu, 2006 ve 2022 yılları arasında sağ kalp kateterizasyonu ile doğrulanan PH ile retrospektif olarak değerlendirilen 865 hastayı içermektedir. Hastalara, ekokardiyografide PA anevrizmasının varlığı, anjina semptomları veya çok kesitli bilgisayarlı tomografide tesadüfen LMCA basısı saptanması gibi endikasyonlarla invaziv koroner anjiyografi yapılmıştır. LMCA basısı, ardışık iki anjiyografik düzlemde referans distal LMCA segmentinde %50'nin üzerinde çap darlığı olarak tanımlanmıştır.

Bulgular: LMCA basısı ve ses kısıklığı PH hastalarının sırasıyla %3.8 ve %4.3'ünde gösterilmiştir. Artan PA çapı daha kötü klinik, hemodinamik, laboratuvar ve ekokardiyografik parametrelerle anlamlı şekilde ilişkili bulundu. ROC eğrileri, 41 mm ve üzerindeki PA çap artışının ses kısıklığı için sınır değer olduğunu ortaya çıkardı (EAA: 0,834; duyarlılık %69, özgüllük %84, negatif öngörü değeri %98) ve PA çapının 35 mm ve üzerinde olması ise LMCA basısı için sınır değer

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olarak bulundu (EAA: 0,794; duyarlılık %89, özgüllük %58, negatif öngörü değeri %99). LMCA basısı için ses kısıklığının Odds oranı, %53,2 duyarlılık, %98,7 özgüllük, %59 pozitif ve %98 negatif öngörü değerleri ile 83,3 (%95 Güven Aralığı; 36,5 -190, $P < 0,001$) bulundu.

Sonuç: Bu çalışmada şiddetli PH'lı hastalarda ses kısıklığının varlığı ile genişlemiş PA ile dıştan LMCA basısı olasılığı arasında yakın bir ilişki bulundu. Bu nedenle, ses kısıklığı şikayeti olan PH hastalarında LMCA basısı riski dikkate alınmalıdır.

Anahtar Kelimeler: Euphrates, pulmoner hipertansiyon, ses kısıklığı, sol ana koroner arter basısı

Pulmonary hypertension (PH) is a progressive disease characterized by an increase in pulmonary vascular resistance (PVR) resulting in right ventricular pressure overload, dilatation or aneurysm in the pulmonary artery (PA), and right-sided heart failure.[1-4] Approximately 89% of reported PA aneurysms are typically found in the main PA, with a higher likelihood of extension toward the left PA compared to the right PA.[5-8] Congenital heart disease has been found to be associated with over 50% of PA aneurysms in patients diagnosed with pulmonary arterial hypertension (PAH).[5-10] The development of PA aneurysms has been attributed to various mechanisms, including cystic medial necrosis caused by structural changes resulting from increased PA tension, turbulent flow through stenotic or abnormally opening pulmonary valves, and shear stress resulting from systemic to pulmonary shunt lesions. These factors are believed to contribute to the transformation into PA aneurysms.[5-8] In addition to the typical symptoms of PAH such as dyspnea, exercise intolerance, cyanosis, palpitations, syncope, and refractory edema, chest pain resembling angina pectoris has been documented in 7–29% of PAH patients.[5-20] Chest pain in patients with PAH can be attributed not only to the imbalanced metabolic demand of the hypertrophied right ventricle but also to the external compression of the left main coronary artery (LMCA-Co) caused by the dilation of the main trunk of the PA.[5-20] Hoarseness due to compression of the left recurrent laryngeal nerve (LRLN) by aneurysmal dilated PA may also be another symptom in patients with PAH, as in the presence of thoracic aortic aneurysm or giant left atrium in severe mitral stenosis named as Ortner syndrome (OS).[21-30]

However, the frequency of OS in patients with PH and its clinical value as a complication of PA aneurysm has remained to be evaluated.[21-30] The objective of this study was to assess the diagnostic significance of hoarseness in predicting the PA aneurysm and its life-threatening complication, significant LMCA-Co in patients with PH.

ABBREVIATIONS

CHD	Congenital heart disease
ERS	European Respiratory Society
ESC	European Society of Cardiology
EUPHRATES	Evaluation of Pulmonary Hypertension Risk factors Associated with Survival
LMCA-Co	Left main coronary artery
LRLN	Left recurrent laryngeal nerve
MDCT	Multidetector computed tomography
OS	Ortner syndrome
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance

Materials and Methods

Our study population included a retrospective evaluation of 865 patients (female 555–64.16%, mean 53.7 ± 18.15 years of age) with PH confirmed with the right heart catheterization between 2006 and 2022 who were enrolled into the single-center, prospective, and observational Evaluation of Pulmonary Hypertension Risk factors Associated with Survival (EUPHRATES) study, and evaluated in accordance with the recommendations of the European Society of Cardiology (ESC)/European Respiratory Society (ERS) 2015 PH guidelines.[1] Moreover, updated criteria of ESC/ERS 2022 PH Guidelines have been used for hemodynamic definitions of PH and pre-capillary PH. Pulmonary arterial systolic and mean pressures (PASP and PAMP) and PVR were assessed in all right heart catheterization procedures.[2] The PAMP >20 mm Hg cutoff value has been utilized as diagnostic criteria for PH, while PAWP ≤ 15 mm Hg and PVR > 2 Wood units criteria have been included in the pre-capillary PH definition.[2-31]

During periodic assessments, functional class assessment,[1,2] 6-min walk distance,[1,2] and Doppler echocardiography[32,33] have been consistently conducted. In cases of clinical worsening episodes caused by PH, repeat right heart catheterization has been performed. For measurements of main PA diameter, parasternal short-axis planes were used on echocardiographic evaluation while axial planes were preferred for multidetector computed tomography (MDCT) measurements of PA diameter.[1-10,32,33] The PA aneurysm was defined as the presence of PA diameter >30 mm on echocardiography and/or MDCT.[1-10,32,33] The demographic, clinical and laboratory characteristics, echocardiographic, MDCT, selective coronary angiography, and RHC data of the patients were obtained from the hospital database. The patients with missing files were excluded from the study. Patients underwent coronary angiography due to several indications, including the presence of a PA aneurysm on echocardiography, angina symptoms, or the incidental discovery of LMCA-Co on MDCT. The optimal planes to visualize the external compression and narrowing of proximal LMCA have been investigated, and the LMCA-Co was defined as the presence of diameter stenosis ³50% in reference distal LMCA segment on two consecutive angiographic planes, and the angle of take-off of the proximal LMCA segment in relation to the left sinus of Valsalva was also assessed.[8-10] Extrinsic compression of LMCA by PA aneurysm was diagnosed with selective coronary angiography, and 45° left anterior oblique planes with or without 30° cranial angulation were preferred for evaluation of LMCA-Co.[8-10] The LMCA-Co and the necessity for stenting were initially evaluated based on recorded images by two experienced interventional cardiologists who were independently blinded to the clinical status of the patients. A final consensus for the optimal

management strategy was achieved for all patients. Hoarseness was defined as a subjective symptom of altered voice quality reported by patients. Patients with hoarseness lasting longer than 4 weeks (persistent) are included to avoid common temporary causes such as acute upper respiratory tract infections. All of the patients reported being non-smoker. Otorhinolaryngological confirmation of the left vocal cord paralysis was also aimed in case of uncertainties for hoarseness.

Written informed consent was obtained from each participant as required and the study protocol was approved by the local Institutional Ethics Committee.

Statistical Analysis

Patients were subclassified into three tertiles according to the PA diameters. Continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR 1–3). Categorical variables were expressed as a percentage and absolute number. To compare continuous variables between the groups with and without LMCA-Co, Student's t-test or Mann–Whitney U test was used. Fisher's exact test or Chi-square test was used to compare categorical variables between these two groups. The estimated probability for LMCA-Co and hoarseness was determined based on PA diameter. Moreover, a plot of the estimated probability of LMCA-Co and hoarseness according to PA diameter was made. The associations between predictors and response variables were presented by odds ratio (OR) with a 95% of confidence interval (CI). Receiver operating characteristic (ROC) curve analysis was employed to illustrate the association between variables and both LMCA-Co and hoarseness, to define the best cutoff value for the development of LMCA-Co and hoarseness. In all analyses, a significance threshold was set at *P*-value of 0.05. Statistical analyses were performed with the use of R 4.2 software (Vienna, Austria).

Results

LMCA-Co ≥ 50% and hoarseness were documented in 5.43% and 4.16%, of patients with PH, respectively. General characteristics of patients according to the tertiles of PA diameters are summarized in Table 1. Increased PA diameter was significantly associated with the increasing frequency of Group

Table 1. Patients' characteristics according to pulmonary artery diameter tertiles

	First (n = 288)	Second (n = 288)	Third (n = 289)	*P*
Age	53.5 ± 18	56 ± 17.7	52.5 ± 18.3	0.054
Sex (female)	185 (64.2%)	177 (61.5%)	193 (66.8)	0.41
IPAH	84 (29.2%)	70 (24.3%)	69 (23.9%)	0.52
APAH-CHD	57 (19.8%)	60 (20.8%)	106 (36.7%)	<0.001
Group 1	163 (56.6%)	151 (52.4%)	186 (64.4%)	0.01
APAH-CTD	18 (6.3%)	18 (6.3%)	7 (2.4%)	0.055
Eisenmenger	30 (10.4%)	35 (12.2 %)	58 (20.1%)	0.002
Large defect	8 (2.8%)	6 (2.1%)	13 (4.5%)	0.23
Small defect	1 (0.3%)	5 (1.7%)	5 (1.7%)	0.23
Post-defect closure	19 (6.6%)	16 (5.6%)	31 (10.7%)	0.045
Group 2	5 (1.7%)	12 (4.2%)	8 (2.8%)	0.22
Group 3	27 (9.4%)	28 (9.7%)	18 (6.2%)	0.25
Group 4	85 (29.5%)	92 (31.9%)	75 (26%)	0.28
6MWD (m)	238 ± 153	219 ± 149	232 ± 140	0.307
ASD VSD PDA Segmental complex	18 (6.5%) 25 (9%) 5 (1.8%) 13 (5%)	21 (7.4%) 22 (7.8%) 8 (2.8%) 7 (2.6%)	44 (15.7%) 40 (14.2%) 21 (7.4%) 13 (5.1%)	<0.001 0.027 <0.001 0.28
Saturation (%)	92 ± 7.6	90 ± 8.9	89 ± 8.2	0.003
HR	89 ± 15.8	88 ± 215.7	89 ± 215.6	0.28
Hgb (g/dL)	13.2 ± 2.3	13.4 ± 2.6	13.8 ± 2.8	0.006
ProBNP (pg/mL)	419 (140–1599)	565 (173–1981)	602 (213–1803)	0.02
Follow-up (day)	400 (59–1326)	348 (82–1136)	537 (108–1307)	0.12
Mortality	116 (40.3%)	117 (40.6%)	127 (43.9%)	0.61
Hoarseness	1 (0.3%)	6 (2.1%)	29 (10%)	<0.001
WHO FC I II III IV	4 (1.4%) 41 (14.2%) 148 (51.4%) 95 (33%)	1 (0.3%) 27 (9.4%) 150 (52.1%) 110 (38.2%)	2 (0.7%) 18 (6.2%) 171 (59.2%) 98 (33.9%)	0.02

Table 1. Patients' characteristics according to pulmonary artery diameter tertiles (continued)

	First (n = 288)	Second (n = 288)	Third (n = 289)	*P*
LMCA	2 (0.7%)	10 (3.5%)	35 (12.1%)	<0.001
SBP (mm Hg)	137 ± 27.5	132 ± 24.9	132 ± 23.8	0.07
DBP (mm Hg)	72 ± 13.8	72 ± 14.4	71.7 ± 13	0.85
LVEDP (mm Hg)	12.9 ± 7.5	12.5 ± 4.8	12.5 ± 6.8	0.70
PAPs (mm Hg)	77.7 ± 30.3	79.2 ± 24.8	86.6 ± 28	<0.001
PAPm (mm Hg)	46.4 ± 20.5	48.1 ± 17.4	54.1 ± 19.7	<0.001
PVR (Wood units)	8.1 ± 6	8.1 ± 5.3	10 ± 7.4	0.002
SVR (Wood units)	21.8 ± 8.2	20.9 ± 6.9	21.3 ± 7.9	0.45
Qp/Qs	1.13 ± 0.52	1.10 ± 0.45	1.21 ± 0.6	0.008
CO (mL/min)	4.3 ± 1.21	4.4 ± 1.3	4.3 ± 1.2	0.30
CI (mL/min/m^2)	2.5 ± 0.8	2.5 ± 0.7	2.4 ± 0.6	0.30
PA diameter (mm)	27.5 ± 2.8	33.5 ± 1.6	43.7 ± 7.5	-
Aortic diameter (mm)	31.4 ± 4.9	32.1 ± 5.2	32.7 ± 5.9	0.13
PA/Ao ratio	0.91 ± 0.16	1.07 ± 0.18	1.38 ± 0.35	<0.001
TAPSE (cm)	1.95 ± 0.5	1.81 ± 0.5	1.82 ± 0.5	<0.001
RA area (cm^2)	20.3 ± 8.5	24.9 ± 10.9	25.7 ± 8.7	<0.001
REVEAL	8.9 ± 2.1	9.3 ± 2.2	9.1 ± 1.9	0.09
REVEAL 2.0	8.6 ± 3	9.1 ± 3.2	9.2 ± 2.8	0.02
REVEAL Lite	8 ± 2.6	8.5 ± 2	8.6 ± 2.4	0.02
COMPERA	1.8 ± 0.6	1.9 ± 0.7	1.9 ± 0.5	0.005
SPAHR	1.6 ± 0.5	1.8 ± 0.56	1.8 ± 0.50	0.007
FPHN 0 1 2 3	144 (50%) 108 (37.5%) 24 (8.3%) 12 (4.2%)	163 (56.6%) 99 (34.4%) 19 (6.6%) 7 (2.4%)	167 (57.8%) 108 (37.4%) 10 (3.5%) 4 (1.4%)	0.06
St (cm/s)	12.3 ± 3.1	11.6 ± 3	11.5 ± 3.2	0.004
LVEF (%)	63 ± 5.4	62 ± 7.2	63 ± 5.6	0.62
TR Vmax (m/s)	4 ± 0.8	4.1 ± 0.7	4.2 ± 0.8	0.003

Continuous variables given as median and interquartile range. IPAH, idiopathic pulmonary arterial hypertension; APAH-CHD, pulmonary arterial hypertension and congenital heart disease; APAH-CTD, pulmonary arterial hypertension and connective tissue disease; 6MWD, 6-minute walking distance; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; HR, heart rate; Hgb, hemoglobin; proBNP, Pro-brain natriuretic peptide; WHO FC, World Heart Organization functional class; LMCA, left main coronary artery; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEDP, left ventricle end diastolic pressure; PAPs, pulmonary artery systolic pressure; PAPm, pulmonary artery mean pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; CO, cardiac output; CI, cardiac index; TAPSE, tricuspid annular systolic excursion rate; RA, area: Right atrial area; REVEAL, registry to evaluate early and long-term PAH disease management; COMPERA, comparative, prospective registry of newly initiated therapies for pulmonary hypertension; SPAHR, Swedish pulmonary arterial hypertension registry; FPHN, French pulmonary hypertension network; LVEF, Left ventricular ejection fraction; TR, Vmax: Tricuspid regurgitation maximum velocity.

1 PH, specifically APAH-CHD due to patent ductus arteriosus, atrial or ventricular septal defect, Eisenmenger syndrome, PAH following the shunt defect repair, and higher levels of NT-pro-brain natriuretic peptide and hemoglobin, PA systolic and mean pressures, PVR, Qp/Qs ratio, PA/aortic diameter ratio; and decreasing pulse oximetric % saturation, tricuspid annular systolic excursion rate and tissue Doppler of the tricuspid lateral annulus (St) and higher Registry to Evaluate Early and Long-Term PAH Disease Management 2.0 (REVEAL 2.0), REVEAL 2.0 lite, Swedish Pulmonary Arterial Hypertension Registry, and Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension risk scores. In Figure 1, ROC curves revealed that the PA diameter ≥ 41 mm was cutoff for hoarseness (AUC: 0.834; sensitivity 69%, specificity 84%, and negative predictive value 98%), and PA diameter ≥ 35 mm was cutoff for LMCA-Co ≥ 50% (AUC: 0.794; sensitivity 89%, specificity 58%, and negative predictive value 99%). For PA diameters (mean −1 SD) of 26.7 mm and (mean +1 SD) 43.1 mm, probabilities of hoarseness were 0.8 % and 6.3%, and probabilities of LMCA-Co ≥ 50% were 1.8% and 8.4%, respectively (Table 2a and b).

Three models were utilized to test the relationship among PA diameter, hoarseness, and LMCA-Co ≥ 50% (Table 3). Response variables were LMCA-Co > 50% in Model 1 and hoarseness in Model 2, and the predictor was PA diameter in both models.

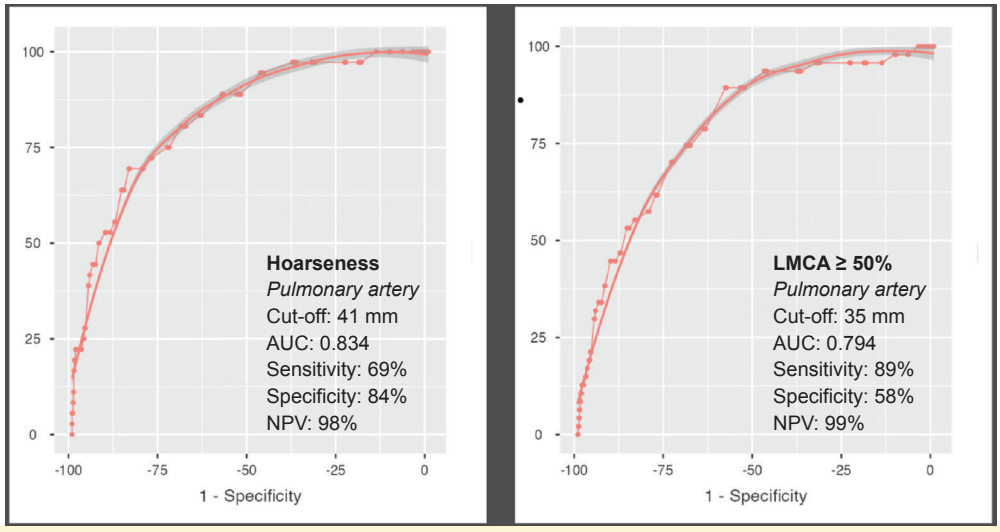

Figure 1. Pulmonary artery diameter cut-off value for prediction of hoarseness and extrinsic compression of the left main coronary artery. LMCA, Left main coronary artery; mm, milimeter; AUC, Area under curve; NPV, Negative predictive value.

Table 2. Probability of LMCA Compression and Hoarseness According to Pulmonary Artery Diameter

	a. Hoarseness		b. LMCA compression	
	Pulmonary artery diameter cm	Probability of LMCA ≥50% compression	Pulmonary artery diameter cm	Probability of Hoarseness
Mean−1 SD	26.7	1.8%	26.7	0.8%
Mean	34.9	4.0%	34.9	2.3%
Mean+1 SD	43.1	8.4%	43.1	6.3%

LMCA, left main coronary artery; SD, standard deviation.

Table 3. Predictive Ability of Pulmonary Artery Diameter, and Hoarseness for Predicting LMCA ≥50% Compression and Hoarseness with Different Logistic Regression Models

	Odds ratio	Confidence interval	*P*
Model-1	1.10	1.07–1.13	<0.001
Model-2	1.13	1.10–1.17	<0.001
Model-3	83.3	36.5–190	<0.001

Model-1, Response variable LMCA compression ≥50% predictor pulmonary artery diameter; Model-2, Response variable hoarseness, predictor pulmonary artery diameter; Model-3, Response variable LMCA compression, predictor hoarseness; LMCA, left main coronary artery.

In Model 3, the response variable was LMCA-Co > 50%, and the predictor was hoarseness. OR values were 1.10 (95% CI; 1.07–1.13, $P < 0.001$) in Model 1, 1.13 (95% CI; 1.10–1.17, $P < 0.001$) in Model 2 whereas 83.3 (95% CI; 36.5–190, $P < 0.001$) in Model 3 (Table 3). The sensitivity, specificity, and positive and negative predictive values of hoarseness for LMCA-Co ≥ 50% were 53.2%, 98.7%, and 59% and 98%, respectively.

Discussion

In this single-center PH study, angiographically proven LMCA-Co ≥ 50% and hoarseness were documented in 5.43% and 4.16%, of patients with PH, respectively. The presence of hoarseness due to LRLN nerve compression by enlarged PA was found to predict significant LMCA-Co in this setting. The compressions by the upper and lower borders of the PA aneurysm seem to result in OS and extrinsic LMCA-Co concomitantly. The OR of hoarseness for LMCA-Co > 50% was 83.3 (95% CI; 36.5–190, $P < 0.001$) with 53.2% sensitivity, 98.7% specificity, and 59% positive and 98% negative predictive value.

Excessive enlargement of the PA can result in external compression on vital structures in close proximity, such as the LMCA, LRLN, and tracheobronchial tree.[9-30] Anatomically, at the level of the aortic arch, the left vagus nerve gives rise to the LRLN. The LRLN loops posteriorly under the aortic arch and courses toward the neck within the groove between the esophagus and trachea. Its function is to provide innervation to the intrinsic muscles of the larynx, specifically controlling the movement of the left vocal cord.[21-23] Due to the short distance at the level of the aortic window, as small as 0.4 cm, and relatively long course of the LRLN, a cardiovocal syndrome caused by compression of the LRLN between the enlarged PA and aorta is not rare in patients with severe PH.[21-23] Ortner first described the cardiovocal syndrome

in 1897, based on observations made in two patients diagnosed with mitral valve stenosis and vocal cord paralysis.[21] Thereafter, this syndrome was also reported in patients with idiopathic PAH, PH associated with congenital heart disease (APAH-CHD) and chronic thromboembolic PH, and in some cases, the hoarseness was reported to improve after reducing the PA pressure with PAH-specific therapies.[22-30] Indirect laryngoscopy is crucial to confirm diagnosis and to rule out other causes of the left vocal cord palsy.[22-30] To investigate the site of compression on the LRLN, it is necessary to obtain computed tomography and/or magnetic resonance imaging of the neck and chest.[22-23] Idiopathic PAH and APAH-CHD have been the two most frequent etiologies of PH in cases of LRLN compression.[22-30]

The majority of the data regarding proximal LMCA-Co by a PA aneurysm have been derived from case reports or small series.[8-20] In the largest series conducted by Galie et al.[9], which focused on evaluating LMCA deformation patterns and management strategies, 15.8% of patients with PAH underwent MDCT due to angina or angina-like symptoms.[9] The MDCT evaluation showed LMCA-Co, LMCA dislocation (a take-off angle 1 mm), and close proximity patterns in 28.9%, 40.5%, and 8.3% of the patients, respectively.[9] Main PA diameter > 40 mm as assessed by MDCT was found to predict LMCA-Co ≥ 50%, and angiographic LMCA-Co ≥ 50% were diagnosed in 10%, 30, 6%, and 91, 4% of the proximity, dislocation, and compression patterns of MDCT, respectively.[9] In our series, we previously reported an 8.2% rate of LMCA-Co ≥ 50% in patients who underwent coronary angiography, and 4.4% in overall PH patients.[10] We also reported that the LMCA takeoff angle in reference to the left sinus of Valsalva was lower than 30° in all patients with LMCA-Co.[10] While LMCA-Co has been found to be associated with PA diameter and PA diameter/aortic diameter ratio, but not with the severity of PAH in two large PAH series, our findings indicated that the risk of LMCA-Co was predicted not only by PA diameter and PA diameter/aortic diameter ratio but also by the clinical etiology of patent ductus arteriosus, a younger age, and the hemodynamic severity of PAH.[10]

In this present study, increased PA diameter was significantly associated with the higher frequency of Group 1 PH, specifically APAH-CHD including Eisenmenger syndrome and precapillary PH following the shunt defect repair, and with worse clinical, hemodynamic, laboratory, and echocardiographic parameters as assessed by multiparametric risk scores. The increasing PA diameter showed a relation with the higher probabilities of hoarseness and LMCA-Co ≥ 50%. For PA diameters (mean-1 SD) of 26.7 mm and (mean +1 SD) 43.1 mm, the probability of hoarseness was 0.8% and 6.3%, and the probability of LMCA-Co ≥ 50% was 1.8% and 8.4%, respectively.

At present, there is no standardized optimal treatment for PA aneurysm or management strategy for LMCA-Co.[5-20] In adults, surgical repair of PA aneurysms has been considered for individuals with the following indications: Main PA diameter <5.5 cm, an increase in PA aneurysm diameter of more than 5 mm within 6 months, presence of clinical symptoms, severe coexisting valvular pathologies or shunt flow, verification of LMCA-Co or adjacent structures, and thrombus formation in the PA.[5-8,20] Furthermore, patients with PH who have a high surgical risk may require a heart-lung transplantation.[5-8,20] LMCA stenting has emerged as the preferred revascularization strategy, demonstrating favorable angiographic outcomes and satisfactory short-term clinical results, and compression of the ostial or proximal part of this artery, sparing the LMCA bifurcation permits a single stent placement.[9,10,18,19] In the comprehensive series conducted by Galie et al.[9], it was observed that 85.4% of patients with LMCA stenosis > 50% of underwent LMCA stenting, whereas both the rate of LMCA-Co and the LMCA stenting were lower in our study group. Furthermore, unlike the 48.9% rate of drug-eluting stent placement reported in the series by Galie et al.[9], our study exclusively employed bare metal stents for LMCA-Co. Among our patients, bare-metal stents were implanted in 54.5% of cases, and one patient underwent reconstructive PA surgery, along with at ASD repair.[10] The benefit of using drug-eluting stents in this setting has yet to be established due to the large diameters of the LMCA, whereas durability of radial force against extrinsic compression poses a significant challenge in this context. The long-term follow-up data of patients who underwent LMCA stenting indicate a favorable clinical outcome, despite a trend toward statistically significant renarrowing of the LMCA after the stenting procedure.[9,10-19] Except one in-hospital death possibly related to underlying heart failure, we documented no death during the follow-up of period.[10] The choice of optimal methods for adjunctive periprocedural imaging and physiological assessment represents another crucial aspect to consider. Intravascular ultrasound, with or without a pressure wire, can be utilized to assess LMCA-Co, as well as to evaluate optimal stent sizing, deployment, and apposition during the stenting procedure.[9,10,20]

Limitations

This study suffered from retrospectively nature of single-center patient data. Another limitation is although all of the patients reported to be non-smoker after initial diagnosis of PH; we could not obtain data on smoking history before the diagnosis. Therefore, this could potentially have an effect on hoarseness condition. Moreover, the absence of detailed laryngoscopy evaluation confirming the left vocal cord paralysis in all patients with hoarseness might be a limitation even in the presence of PA aneurysm.

Conclusions

In this single-center study, 1st time, we demonstrated a close relationship between the presence of hoarseness, due to LRLN compression and probability of extrinsic LMCA compression by enlarged PA in patients with severe PAH. The risk of LMCA-co should be taken into account in patients with PAH suffering from hoarseness.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of Koşuyolu High Specialization Training and Research Hospital (Approval Number: 2013.3/4, Date: 12.07.2013).

Informed Consent: Written informed consent was obtained from each participant.

Peer-review: Externally peer-reviewed.

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References

1. Galiè N, Humbert M, Vachiery JL, et al.; ESC Scientific Document Group. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2016;37(1):67–119. [CrossRef]
2. Humbert M, Kovacs G, Hoeper MM, et al.; ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2022;43(38):3618–3731. Erratum in: *Eur Heart J.* 2023;44(15):1312. [CrossRef]
3. Kaymaz C, Mutlu B, Küçükoğlu MS, et al. Preliminary results from a nationwide adult cardiology perspective for pulmonary hypertension: RegiStry on clInical outcoMe and sUrvival in pulmonaRy hypertension Groups (SIMURG). *Anatol J Cardiol*. 2017;18(4):242–250. [CrossRef]
4. Kücükoglu SM, Kaymaz C, Alehan D, et al.; THALES Registry Investigators. Pulmonary arterial hypertension associated with congenital heart disease: lessons learnt from the large Turkish Nationwide Registry (THALES). *Pulm Circ.* 2021;11(3):20458940211024206. [CrossRef]
5. Kreibich M, Siepe M, Kroll J, Höhn R, Grohmann J, Beyersdorf F. Aneurysms of the pulmonary artery. *Circulation*. 2015 Jan 20;131(3):310–316. [CrossRef]
6. Veldtman GR, Dearani JA, Warnes CA. Low pressure giant pulmonary artery aneurysms in the adult: natural history and management strategies. *Heart.* 2003;89(9):1067–1070. [CrossRef]
7. Sakuma M, Demachi J, Suzuki J, Nawata J, Takahashi T, Shirato K. Proximal pulmonary artery aneurysms in patients with pulmonary artery hypertension: complicated cases. *Intern Med.* 2007;46(21):1789–1793. [CrossRef]
8. Lee SE, An HY, Im JH, et al. Screening of mechanical complications of dilated pulmonary artery related to the risk for sudden cardiac death in patients with pulmonary arterial hypertension by transthoracic echocardiography. *J Am Soc Echocardiogr.* 2016;29(6):561–566. [CrossRef]
9. Galiè N, Saia F, Palazzini M, et al. Left main coronary artery compression in patients with pulmonary arterial hypertension and angina. *J Am Coll Cardiol.* 2017;69(23):2808–2817. [CrossRef]
10. Akbal OY, Kaymaz C, Tanboga IH, et al. Extrinsic compression of left main coronary artery by aneurysmal pulmonary artery in severe pulmonary hypertension: Its correlates, clinical impact, and management strategies. *Eur Heart J Cardiovasc Imaging.* 2018;19(11):1302–1308. [CrossRef]
11. Mesquita SM, Castro CR, Ikari NM, Oliveira SA, Lopes AA. Likelihood of left main coronary artery compression based on pulmonary trunk diameter in patients with pulmonary hypertension. *Am J Med.* 2004;116(6):369–374. [CrossRef]
12. Dubois CL, Dymarkowski S, Van Cleemput J. Compression of the left main pulmonary artery in a patient with the Eisenmenger syndrome. *Eur Heart J.* 2007;28:1945. [CrossRef]
13. Vaseghi M, Lee JS, Currier JW. Acute myocardial infarction secondary to left main coronary artery compression by pulmonary artery aneurysm in pulmonary arterial hypertension. *J Invasive Cardiol.* 2007;19(12):E375–E377.
14. Kajita LJ, Martinez EE, Ambrose JA, et al. Extrinsic compression of the left main coronary artery by a dilated pulmonary artery: clinical, angiographic, and hemodynamic determinants. *Catheter Cardiovasc Interv*. 2001;52(1):49–54. [CrossRef]
15. de Jesus Perez VA, Haddad F, Vagelos RH, Fearon W, Feinstein J, Zamanian RT. Angina associated with left main coronary artery compression in pulmonary hypertension. *J Heart Lung Transplant.* 2009;28(5):527–530. [CrossRef]
16. Yeh DD, Ghoshhajra B, Inglessis-Azuaje I, MacGillivray T, Liberthson R, Bhatt AB. Massive pulmonary artery aneurysm causing left main coronary artery compression in the absence of pulmonary hypertension. *Tex Heart Inst J.* 2015;42(5):465–467. [CrossRef]
17. Ihdayhid AR, Asrar Ul Haq M, Dembo L, Yong G. Simultaneous coronary and pulmonary angiography to diagnose critical left main coronary artery stenosis secondary to dilated pulmonary artery. *JACC Cardiovasc Interv.* 2016;9(11):1193–1194. [CrossRef]
18. Alfonso F, Rivero F. Left main coronary artery compression in patients with pulmonary arterial hypertension. *J Am Coll Cardiol*. 2017;69(23):2818–2820. [CrossRef]
19. Rich S, McLaughlin VV, O'Neill W. Stenting to reverse left ventricular ischemia due to left main coronary artery compression in primary pulmonary hypertension. *Chest*. 2001;120(4):1412–1415. [CrossRef]
20. Lee MS, Oyama J, Bhatia R, Kim YH, Park SJ. Left main coronary artery compression from pulmonary artery enlargement due to pulmonary hypertension: a contemporary review and argument for percutaneous revascularization. *Catheter Cardiovasc Interv.* 2010;76(4):543–550. [CrossRef]
21. Ortner N. Recurrenslahmung bei mitral stenose. *Wien Klin Wochenschr.* 1897;10:753e755.
22. Wilmshurst PT, Webb-Peploe MM, Corker RJ. Left recurrent laryngeal nerve palsy associated with primary pulmonary hypertension and recurrent pulmonary embolism. *Br Heart J*. 1983;49(2):141–143. [CrossRef]
23. Paquette CM, Manos DC, Psooy BJ. Unilateral vocal cord paralysis: A review of CT findings, mediastinal causes, and the course of the recurrent laryngeal nerves. *Radiographics*. 2012;32(3):721–740. Erratum in: *Radiographics.* 2012;32(7):2166. [CrossRef]
24. Subramaniam V, Herle A, Mohammed N, Thahir M. Ortner's syndrome: Case series and literature review. *Braz J Otorhinolaryngol.* 2011;77(5):559–562. [CrossRef]
25. Garg R, Singh A, Sawlani KK, Mishra AK. Hoarseness of voice as presenting complaint of idiopathic pulmonary arterial hypertension. *Lung India.* 2017;34(2):212–214. [CrossRef]
26. Wilmshurst PT, Webb-Peploe MM, Corker RJ. Left recurrent laryngeal nerve palsy associated with primary pulmonary hypertension and recurrent pulmonary embolism. *Br Heart J*. 1983;49(2):141–143. [CrossRef]
27. Andjelkovic K, Kalimanovska-Ostric D, Djukic M, et al. Two rare conditions in an Eisenmenger patient: Left main coronary artery compression and Ortner's syndrome due to pulmonary artery dilatation. *Heart & Lung*. 2013;42(5):382e–386e. [CrossRef]
28. Nakao M, Sawayama T, Samukawa M, et al. Left recurrent laryngeal nerve palsy associated with primary pulmonary hypertension and patent ductus arteriosus. *J Am Coll Cardiol*. 1985;5(3):788–792. [CrossRef]
29. Nakahira M, Nakatani H, Takeda T. Left vocal cord paralysis associated with long-standing patent ductus arteriosus. *AJNR Am J Neuroradiol*. 2001;22(4):759–761.
30. Kaya Ö, Yoldaş T, Karademir S, Örün UA, Sarı E. A pediatric case of Ortner`s syndrome caused by heritable pulmonary arterial hypertension and review of the literature. *Turk J Pediatr*. 2019;61(6):963–966. [CrossRef]
31. Tanyeri S, Akbal OY, Keskin B, et al. Impact of the updated hemodynamic definitions on diagnosis rates of pulmonary hypertension. *Pulm Circ*. 2020;10(3):2045894020931299. [CrossRef]
32. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr.* 2010;23(7):685–713; quiz 786–8.
33. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;28(1):1–39.e14. [CrossRef]

Hoarseness as a Predictor for Pulmonary Arterial Aneurysm and Extrinsic Left Main Coronary Artery Compression in Patients with Severe Pulmonary Hypertension

865 pts
w/ Pulmonary Hypertension

- The LMCA-Co* were documented in 3.8% of patients.
- Hoarseness were documented in 4.3% of patients.

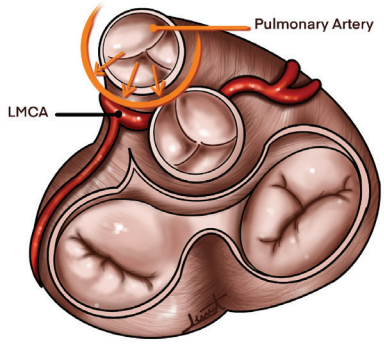

Illustration of external compression of the LMCA with PA dilation.

- PA diameter >41 mm was cutoff for hoarseness.
- PA diameter >35 mm was cutoff for LMCA-Co >50%.
- The OR of hoarseness for LMCA-Co > 50% was 83.3 (95% CI; 36.5–190, P < 0.001).

A close relationship was found between the presence of hoarseness and the probability of extrinsic LMCA-Co by enlarged PA in patients with severe PH.

*LMCA-Co: Compression of the Left Main Coronary Artery

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