

Evaluation of Right Ventricular Diastolic Function in Patients with Chronic Obstructive Pulmonary Disease Using Pulsed Doppler Tissue Imaging

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Abstract

Objective: To evaluate the global and segmental diastolic function of right ventricle (RV) using pulsed tissue Doppler imaging (TDI) in patients with clinically stable chronic obstructive pulmonary disease (COPD) without pulmonary hypertension.

Methods: Twenty **consenting** stable patients with COPD (mean age 61.4 ± 8.6 , 16 males) with normal **pulmonary** artery pressure (group I), and 20 age-matched normal subjects (mean age 57.8 ± 4.0 , 11 males, Group II) were enrolled. All participants underwent conventional echocardiography. TDI of the RV was performed from 4 different segments; myocardial early (Em) and late (Am) diastolic peak velocities, systolic peak velocity (Sm), and early diastolic velocity deceleration time (eDTm), duration of S wave, isovolumetric relaxation (IVRTm) and contraction (IVCTm) times were measured.

Results: The conventional echocardiographic measurements of the two groups were similar. However, specific TDI parameters differed between groups: anterior wall Em was lower, duration of anterior S wave and IVRTm measurements from all segments of RV from apical 4-chamber (A4C) view were longer and eDTm measured from apex was shorter in COPD patients (parasternal Em $p=0.003$; duration of anterior wall S wave $p=0.02$; A4C apical IVRTm $p=0.02$; A4C middle IVRTm $p=0.001$; A4C basal IVRTm $p=0.01$; A4C apical eDTm $p=0.05$).

Conclusion: TDI is more sensitive than conventional echocardiography in evaluation of diastolic function in patients with COPD. In COPD patients with an unlikely diagnosis of pulmonary hypertension, diastolic functions of RV seem to show some **deterioration** but this difference fails to reach a **statistically** significant level. The basal segment of RV free wall represents global RV diastolic functions.

Keywords: *Chronic Obstructive Pulmonary Disease; Diastole; Echocardiography; Pulmonary Heart Disease; Ventricular Dysfunction, Right Ventricle*

Abbreviations

A:	Late diastolic peak velocity
A4C:	Apical 4-chamber
Am:	Myocardial late diastolic peak velocity
COPD:	Chronic obstructive pulmonary disease
DT:	Early diastolic wave deceleration time
eDTm:	Myocardial early diastolic velocity deceleration time
E:	Early diastolic peak velocity
Em:	Myocardial early diastolic peak velocity
FEV ₁ :	Forced expiratory volume in first second
FVC:	Forced vital capacity
IVRT:	Isovolumetric relaxation time
IVRTm:	Myocardial isovolumetric relaxation time
IVCT:	Isovolumetric contraction time
IVCTm:	Myocardial isovolumetric contraction time
NS:	Not significant
PAP:	Pulmonary artery pressure
pO ₂ :	Partial arterial oxygen pressure
pCO ₂ :	Partial carbon dioxide pressure
PHT:	Pulmonary hypertension
RV:	Right ventricular
Sm:	Myocardial systolic peak velocity
TDI:	Tissue Doppler imaging

Introduction

Right ventricular (RV) function can be altered in several diseases involving lungs and heart. In patients with chronic obstructive pulmonary disease (COPD) alveolar hypoxia may lead to **increased** pulmonary artery pressure (PAP), subsequently resulting in the development of right ventricular hypertrophy, dilatation, dysfunction and finally failure ¹⁻³. The diastolic abnormalities are one of the earliest manifestations of cardiac dysfunction in patients with COPD and can be as a **consequence** of impaired myocardial relaxation.

Transthoracic echocardiography has become the primary tool in the assessment of RV functions because right heart catheterization, magnetic resonance imaging or radionuclide ventriculography are not feasible for daily practice and are not acceptable for screening RV functions due to cost and the risk of complications. Conventional Doppler has been used in estimating PAP⁴. Doppler echocardiography allows estimation of PAP by means of measuring tricuspid regurgitation velocity, pulmonary regurgitation velocity, and right ventricular outflow tract flow acceleration time. In clinical practice, the most commonly used method involves incorporating peak TR velocity into modified Bernoulli equation to derive the transtricuspid gradient and adding the mean right atrial pressure to estimate PASP⁴. However, this measurement depends on a good tricuspid regurgitation signal, which is not present in all patients.

Evaluation of the right ventricle functions with echocardiography has limitations due to the complex geometry of right ventricle ^{5,6}. Pulsed tissue Doppler imaging (TDI) is a rapid and non-invasive method for the evaluation of myocardial functions by measuring regional velocities and time intervals ⁷. Several studies have investigated TDI in assessing the RV functions in several diseases involving lungs ⁸⁻²⁰; whereas the number of studies using TDI in evaluation of RV segmental diastolic function in COPD patients without pulmonary hypertension (PHT) is limited ^{9,12, 15, 19, 20}.

The aim of our study is to compare the global and segmental RV diastolic function by using pulsed TDI in patients with stable COPD without PHT based on echocardiography findings to normal control subjects. We also aimed to determine the differences in TDI measurements between different segments of RV wall in order to find out the most affected part of RV in patients with COPD.

Material and Methods

We enrolled 20 stable patients with COPD defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) Consensus Report (mean age 61.4 ± 8.6 , 16 males) with normal pulmonary artery pressure (group I) ²¹. Control group (group II) consisted of 20 consecutive age matched normal subjects (mean age 57.8 ± 4.0 , 11 males) shown to have no pulmonary disease with pulmonary function testing and saturation measurements. The study protocol was approved by the local Ethics Committee. All patients provided written informed consent prior to participation in the study.

Patients with COPD acute attack, systemic arterial hypertension, atrial fibrillation, significant valvular disease, coronary artery disease, left ventricular heart failure and poor echocardiographic image quality were excluded. Additionally patients were excluded if they had PHT according to echocardiographic parameters, such as pulmonary artery ejection flow analysis: acceleration time, acceleration time/RVET ; pulmonary regurgitant flow derived parameters-mean PAP, diastolic PAP; indirect 2D and M mode signs of pulmonary hypertension.

History, physical examination and pulmonary function testing of patients were reviewed for COPD classification. Medications such as inhaled β_2 agonists, anticholinergics, steroids, theophylline and oxygen were continued. The control subjects were normal volunteers with no systemic diseases and were not taking any medications.

Spirometric measurements of all patients were done (Sensor Medics V-max 229 Spectra, Bithoven, The Netherlands) according to the standards of the American Thoracic Society ²². Forced expiratory volume in first second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC values were recorded. Saturation values were recorded for all patients. Arterial blood was taken for measurements of pH, partial arterial oxygen pressure (pO_2) and partial carbon dioxide pressure (pCO_2) from patients whose oxygen saturation was < 92 %.

Echocardiographic examinations were performed using a commercially available ultrasound machine (Acuson Sequoia C 256, Acuson Siemens, Mountain View, California) equipped with a 3.5 MHz transducer. Parasternal and apical views were obtained according to the recommendations of American Society of Echocardiography⁴. Recordings were made with a simultaneous superimposed ECG; separate

measurements were made for each subject with 2D, TDI. Left ventricular ejection fraction was derived from Simpson's modified single plane method using the apical 4- chamber view.

The systolic pulmonary artery pressure (sPAP) was assessed by measuring the gradient between the right ventricle and the right atrium using the peak velocity ($V_{\max}$) of the tricuspid regurgitation by using a modified Bernoulli equation and then adding the mean right atrial pressure ($\text{sPAP} = 4V_{\text{TR}}^2 + \text{right atrial max pressure}$). The right atrial pressure was estimated according to the respiratory variation in the inferior vena cava diameter at its entrance into the right atrium. The inferior vena cava size was measured during quiet respiration and forced inspiration in the subcostal view. The right atrial pressure was estimated as follows: 5 mmHg if IVC size is <1.5 cm and collapses with inspiration; 10 mmHg if IVC size is 1.5-2.5 cm and diameter decreases >50% with inspiration; 15 mmHg if IVC size is over 2.5 cm and diameter decreases 50% by inspiration; and 20 mmHg if IVC is dilated and diameter is not changed by inspiration²³. ESC criteria for detecting the presence of PHT, based on tricuspid regurgitation peak velocity and Doppler-calculated sPAP at rest (assuming a normal right atrial pressure of 5 mmHg) and additional echocardiographic variables suggestive of PHT were used to determine the sPAP^{24,25}. In summary, PHT was unlikely if $\text{sPAP} \leq 36$ mmHg with no additional echocardiographic variables suggestive of PHT. Diagnosis of PHT was possible if sPAP was 37-50 mmHg or if $\text{sPAP} \leq 36$ mmHg with additional echocardiographic variables suggestive of PHT. Diagnosis of PHT was likely if $\text{sPAP} > 50$ mmHg.

For TDI recordings, a 5-mm sample volume was placed at four different segments including the basal, mid and apical segments of the RV free wall from the A4C view and basal anterior wall from the parasternal long axis view. Myocardial early (Em) and late (Am) diastolic peak velocities, systolic peak velocity (Sm), and early diastolic velocity deceleration time (eDTm), duration of S wave, isovolumetric relaxation time (IVRTm) and isovolumetric contraction time (IVCTm) were measured. IVRTm was measured from end of Sm to onset of Em. IVCTm was measured from end of Am to onset of Sm. Right ventricular myocardial performance index (MPI) and E/Em ratio were also calculated. MPI index was calculated as the sum of IVRTm and IVCTm divided by duration of Sm. Tissue Doppler images were recorded at a sweep speed of 100 m/sn, and all measurements were calculated as the mean of 3 consecutive cardiac cycles. Doppler and 2D echocardiography and TDI examinations were recorded on

VHS videotape. All the echocardiographic examinations were done and analyzed by the same investigator unaware of the subjects' clinical status.

Statistical Analysis: SPSS v.9.0 software (Statistical Package for the Social Sciences, SPSS Inc, Chicago, Ill, USA) was used for statistical analyses. Continuous variables are expressed as means $\pm$ standard deviation. All continuous variables checked with Kolmogorov-Smirnov normality test to show their distributions. Continuous variables with normal distributions were compared using the unpaired Student *t* test. Continuous variables with abnormal distributions were compared using the Mann-Whitney U test. For categorical variables, the chi-square test was used. Values for *P* less than 0.05 were considered statistically significant.

Results

Forty subjects, 27 men, with a mean age of 59.6 ± 13.3 years were included into the study. Demographic findings of patients are shown in Table 1. Smoking rates were similar in both groups. In patients with COPD; cough (75%), sputum (70%) and shortness of breath (55%) were the most frequent symptoms. The other symptoms in this group of patients were wheezing (20%), chest tightness (25%) and edema (20%). All patients were in sinus rhythm. Mean heart rate was 82.2 ± 15.2 bpm in group I and 79.8 ± 13.6 bpm in group II ($p > 0.05$).

Table 1: Demographic and Pulmonary Function Test Findings of Study Population

	Group I	Group II	P value
Age, year	61.4 ± 8.6	57.8 ± 4.0	NS
Gender (n)	16 M, 4 F	11 M, 9 F	NS
Weight (kg)	73.95 ± 12.1	72.1 ± 8.2	NS
Height (cm)	169.0 ± 10.3	163.2 ± 8.4	NS
Smoking, n (%)	17 (85.0)	16 (80.0)	NS
FEV ₁ (% of predicted value)	56.4 ± 21.6	91.7 ± 12.8	<0.001
FVC (% of predicted value)	67.1 ± 20.3	88.3 ± 8.4	<0.005
FEV ₁ /FVC	57.9 ± 10.0	76.1 ± 5.3	<0.001
Oxygen Saturation (%)	91.7 ± 2.2	94.36 ± 2.1	<0.005

F: Female, FEV₁: Forced expiratory volume in first second, FVC: Forced vital capacity, M: Male, NS: Not significant.

Mean FEV₁, mean FVC and FEV₁/FVC values were significantly lower in group I than group II (Table 1). When classified according to GOLD Consensus Report; 4 patients (20%) had mild, 8 patients (40%) had moderate, 5 patients (25%) had severe and 3 patients (15%) had very severe COPD. Besides, saturation values were also significantly lower in COPD group. Arterial blood gas was analyzed for 15 patients in group I with oxygen saturation less than 92%; mean pO₂ was 62.6 ± 9.5 mmHg while pCO₂ was 43.2 ± 6.9 mmHg. Oxygen saturation of all other patients was higher than 92%.

The segmental and global systolic function of left ventricle was normal in both groups. There was no significant difference between 2D and Doppler echocardiographic examination results of patients of two

groups ($p>0.05$) (Table 2). Tricuspid regurgitation was determined in 14 patients with COPD, and mean sPAP was calculated as 29.0 ± 5.3 mmHg. There were no patients with more than mild tricuspid regurgitation in group II, and sPAP values were all below 30 mmHg.

Table 2: Echocardiographic Parameters of COPD Patients and Control Group.

	Group I	Group II	P value
Left atrium diameters, (cm)	3.2 ± 0.3	3.3 ± 0.4	NS
Left ventricle diameters, end systole (cm)	2.6 ± 0.6	2.7 ± 0.4	NS
Left ventricle diameters, end diastole (cm)	4.2 ± 0.6	4.3 ± 0.5	NS
Right ventricle diameters (cm)	3.2 ± 0.6	3.0 ± 0.4	NS
Right atrium diameters (cm)	3.4 ± 0.5	3.3 ± 0.3	NS
Posterior wall thickness (cm), end diastole	1.2 ± 0.2	1.2 ± 0.2	NS
Interventricular septum thickness (cm), end diastole	1.2 ± 0.2	1.2 ± 0.2	NS
Fractional shortening (%)	37.7 ± 5.7	37.3 ± 5.9	NS
Ejection fraction (%)	55.6 ± 5.5	57.3 ± 3.3	NS
Pulmonary flow velocity (cm/sec)	90.2 ± 24.5	90.3 ± 20.5	NS
Mitral E wave velocity (cm/sec)	61.8 ± 12.1	64.9 ± 10.2	NS
Mitral A wave velocity (cm/sec)	78.6 ± 18.2	77.8 ± 16.0	NS
Tricuspid E wave velocity (cm/sec)	57.5 ± 13.8	55.8 ± 5.0	NS
Tricuspid A wave velocity (cm/sec)	57.5 ± 15.5	51.1 ± 8.1	NS
Tricuspid DT (msec)	236.9 ± 51.8	219.2 ± 44.8	NS
IVRT (msec)	103.0 ± 20.0	103.0 ± 12.5	NS

A: Late diastolic peak velocity, DT: Early diastolic wave deceleration time, E: Early diastolic peak velocity, IVRT: Isovolumetric relaxation time, NS: Not significant.

Two-dimensional Doppler measurements from tricuspid valve revealed a similar E/A ratio in both groups ($p=0.293$). TDI parameters obtained from anterior wall of RV in the parasternal long axis view and at tricuspid basal, mid, and apical segments of the RV free wall in the A4C view are presented on Table 3-6. IVRTm was longer in all segments of A4C view in group I than in group II. In addition to this, eDTm was shorter in group I at A4C apical level. There was no significant difference for other parameters from A4C view. From RV parasternal long axis view, patients in group I had lower tricuspid Em (13.8 ± 4.6 cm/sec; $p=0.003$) and shorter S wave duration (215.1 ± 57.3 msec; $p=0.02$) than patients in group II; while other parameters were similar between two groups. Also, TDI Sm values were compared from all segments and no difference was detected. When we compared the E/Em ratios of the groups, we found the E/Em ratio of the anterior RV wall was significantly higher in the COPD group while the other segments were not

different (Table 7). The global function of the right ventricle was evaluated by myocardial performance index (MPI), and no difference was detected (Table 7).

Table 3: Apical 4-Chamber Basal Segment TDI Findings

	Group I	Group II	P value
Sm (cm/sec)	23.6 ± 9.2	22.3 ± 4.9	NS
Em (cm/sec)	19.4 ± 6.9	20.4 ± 3.5	NS
Am (cm/sec)	26.5 ± 6.9	28.1 ± 8.4	NS
Duration of S wave (msec)	229.9 ± 41.1	239.8 ± 46.0	NS
IVRTm (msec)	131.1 ± 31.9	104.5 ± 22.9	<0.01
IVCTm (msec)	79.3 ± 26.7	70.6 ± 16.6	NS
eDTm (msec)	130.3 ± 39.6	149.0 ± 37.7	NS

Am: Myocardial late diastolic peak velocity, eDTm: Myocardial early diastolic velocity deceleration time, Em: Myocardial early diastolic peak velocity, IVCTm: Myocardial isovolumetric contraction time, IVRTm: Myocardial isovolumetric relaxation time, NS: Not significant, Sm: Myocardial systolic peak velocity.

Table 4: Apical 4-Chamber Mid-Segment TDI Findings

	Group I	Group II	P value
Sm (cm/sec)	20.4 ± 5.8	18.3 ± 4.2	NS
Em (cm/sec)	17.0 ± 5.6	17.9 ± 5.2	NS
Am (cm/sec)	24.6 ± 7.7	23.2 ± 7.7	NS
Duration of S wave (msec)	206.1 ± 43.8	315.7 ± 30.8	NS
IVRTm (msec)	148.9 ± 52.4	97.8 ± 15.8	0.001
IVCTm (msec)	79.8 ± 35.4	67.8 ± 13.0	NS
eDTm (msec)	110.9 ± 34.2	139.9 ± 49.6	NS

Abbreviations as in Table 3.

Table 5: Apical 4-Chamber Apical Segment TDI Findings

	Group I	Group II	P value
Sm (cm/sec)	15.8 ± 5.3	14.9 ± 4.9	NS
Em (cm/sec)	13.6 ± 5.7	11.8 ± 3.8	NS
Am (cm/sec)	17.9 ± 7.8	16.1 ± 6.0	NS
Duration of S wave (msec)	173.8 ± 83.6	211.2 ± 51.6	NS
IVRTm (msec)	172.1 ± 60.5	132.8 ± 26.2	0.02
IVCTm (msec)	85.6 ± 59.0	73.3 ± 8.1	NS
eDTm (msec)	86.0 ± 24.8	106.6 ± 28.0	0.05

Abbreviations as in Table 3.

Table 6: Parasternal Long Axis Right Ventricle Anterior Wall TDI Findings

	Group I	Group II	P value
Sm (cm/sn)	15.9 ± 3.1	15.0 ± 3.5	NS
Em cm/sn)	13.8 ± 4.6	18.7 ± 3.4	0.003
Am (cm/sn)	17.1 ± 5.6	22.1 ± 14.1	NS
Duration of S wave (msn)	215.1 ± 57.3	259.4 ± 34.5	0.02
IVRTm (msn)	137.1 ± 58.2	110.1 ± 30.5	NS
IVCTm (msn)	86.3 ± 33.9	70.6 ± 18.3	NS
eDTm (msn)	101.0 ± 37.5	100.8 ± 21.2	NS

Abbreviations as in Table 3.

Table 7: E/Em ratios from different segments of right ventricle and myocardial performance index calculated from the basal lateral tricuspid wall TDI measurements.

	Group I	Group II	P value
Tricuspid E/paras Em	4.6±1.9	3.2±0.8	0.018
Tricuspid E/apex Em	5.0±2.5	5.0±1.3	0.953
Tricuspid E/basal Em	3.6±2.0	2.7±0.5	0.099
Tricuspid E/mid Em	3.7±1.6	3.4±0.9	0.580
MPI basal	0.47±0.15	0.54±0.15	0.277

E: Early diastolic peak velocity, Em: Myocardial early diastolic peak velocity, MPI: myocardial performance index, NS:

Not significant, paras: parasternal

Discussion

The evaluation of RV function is clinically useful in patients with COPD because the presence of RV failure has prognostic implications²⁶. However, there are very few studies in literature evaluating segmental diastolic functions of right ventricle and none of them are on patients with COPD^{27,28}. In this first study on segmental diastolic functions of right ventricle in COPD patients, we found that in the clinically stable COPD patients without PHT, although Doppler echocardiographic measurements were normal TDI parameters, especially IVRTm, were able to detect RV diastolic dysfunction. Segmental analysis of RV with TDI does not seem to provide any additional information regarding the diastolic functions; as the measurements from the lateral basal segment represent the whole ventricle sufficiently.

The gold standard for the diagnosis of PHT is right heart catheterization. However, because this procedure is expensive, and potentially risky, the transthoracic echocardiography is the most commonly used diagnostic tool for estimation of PAP since it is an inexpensive, easy, reliable and reproducible technique. For the last two decades, the most commonly used method is composed of incorporating TR velocity into a modified Bernoulli equation to estimate sPAP. However, sPAP can be determined by echocardiography in less than half of patients with COPD. The limitations are absence of adequate TR velocity, suboptimal echocardiographic images because of hyperinflation of the lungs, expansion of the thoracic cage²⁹. Moreover, right heart catheterization, magnetic resonance imaging or radionuclide ventriculography are not acceptable for screening RV functions for daily practice transthoracic echocardiography and TDI is used in evaluation of RV functions. TDI has been used in the assessment of RV systolic and diastolic functions in addition to estimation of LV function; and it was suggested that TDI might be more sensitive than standard echocardiography^{16,30-33}. The advantage of using TDI to assess RV function is that measurement is independent of geometric assumptions and endocardial border tracing. There are few studies with contradictory results in the literature assessing the RV diastolic function with conventional Doppler in patients with COPD without PHT^{14,18,34,35}. In our study, no significant difference in RV diastolic function was detected by conventional echocardiography between the two groups. In evaluation of diastolic function, sample volume was placed only at tricuspid annular level in these studies. We have evaluated RV functions with TDI at four different segments. No difference

was detected by segmental measurements compared to measurement from tricuspid annular level only. The measurement from basal segment might be sufficient to evaluate RV diastolic function.

In the current study, a statistically significant difference was observed in all segmental IVRTm measurements in apical-4 chamber view in COPD patients compared to controls. Although this parameter was longer in COPD group than controls also in parasternal long axis view, the difference was not statistically significant. In the study of Caso et al., there was a significant positive correlation between the tricuspid annulus IVRTm and sPAP ($r=0.76$); IVRTm derived by TDI was the only parameter distinguishing patients with COPD with and without PHT and control group¹⁴. Moreover it was shown that, after excluding patients with elevated mean RAP, the correlation between IVRT and sPAP was improved^{36,37}. In our study we found IVRTm being longer in COPD patients without PHT than controls. Given that the pulsed Doppler measurements in our study didn't demonstrate any difference between groups, the diastolic dysfunction pointed out with this difference in IVRTm could be considered as an early subclinical manifestation of myocardial diastolic derangement. Moreover, we observed that RV Sm decreased whereas IVRTm increased from tricuspid annulus towards apex. This can be due to geometry of RV myocardium and is consistent with the literature^{8,37}. The decrease in Em and the shortening of duration of Sm, obtained in our study by TDI from parasternal long axis view, were thought to be secondary to myocardial relaxation defect due to COPD.

There are potential limitations in this study. An invasive PAP measurement was not used. The right heart catheterization might be able to clarify the relation between IVRTm and systolic PAP. The incidence of tricuspid regurgitation in patients with COPD is between 24-66%, which might limit estimation of PHT with Doppler echocardiography^{38,39}. Despite technical difficulty, Doppler-measured tricuspid regurgitation is widely used in clinical setting for PHT estimation. Pulmonary acceleration time, which shows better correlation with mean pulmonary arterial pressure measurements in cardiac catheterization, was not performed. There may be some load dependence to TDI. TDI is preload dependent in cases of normal diastolic function⁴⁰. Another important issue is the small sample size.

Conclusion

RV diastolic dysfunction, which may not be detected by conventional echocardiography techniques including M-mode, two-dimensional and spectral Doppler, can be determined by TDI from different segmental levels in patients with COPD even in the absence of PHT. We observed that measurement from basal RV free wall reflects the segmental measurements adequately. The findings of the present study may have some serious clinical implications. TDI-derived indexes for RV diastolic function obtained from different segmental levels of the RV free wall are usually easily measurable and can reflect the global function. IVRTm can be the most reliable parameter to detect RV diastolic dysfunction in this group of patients. In conclusion, it might be suggested that TDI derived IVRTm can be used as a follow up diagnostic tool in COPD patients for early diagnosis of RV diastolic dysfunction even before development of PHT so that with prompt treatment, the right heart failure might be prevented. Finally, further studies evaluating RV diastolic function longitudinally in patients with COPD and investigating its relation to bronchodilator, long-term oxygen, or vasodilator treatment are required.

Competing interests

Authors have declared that no competing interests exist.

Authors' Contributions

Drs. A. Ozsancak Ugurlu, A.İ. Atar and İ. Atar designed the study, collected data, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Drs. A. Ozsancak Ugurlu, A. İ. Atar and O. Gulmez wrote the final draft of the manuscript. Dr. S. Savas Bozbas collected data. Drs. H. Muderrisoglu and F. Oner Eyuboglu designed the study. All authors read and approved the final manuscript.

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