Ventricular Arrhythmias in Patients With COPD Are Associated With QT Dispersion*

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**Study objective:** QT dispersion (QTd) and late potentials derived from signal-averaged ECG (SAECG) have been proposed as noninvasive predictors of cardiac arrhythmias that occur in patients with COPD. In this study, we aimed to investigate QTd and SAECG in patients with COPD.

**Design:** Cross-sectional study.

**Setting:** Teaching chest disease hospital and cardiology center in a university hospital.

**Patients:** Thirty patients with COPD (28 men and 2 women; mean ± SD age, 60 ± 9 years) and 31 age- and sex-matched control subjects (28 men and 3 women; mean age, 57 ± 7 years) were included.

**Measurements and results:** Respiratory function tests, arterial blood gas analyses, echocardiographic examinations, rhythm Holter recordings, and heart rate variability (HRV) analyses were performed in addition to the measurements of QT intervals and SAECG. Patients with COPD had higher rate of ventricular premature beats (VPBs) as compared to control subjects (924 ± 493 beats vs 35 ± 23 beats, p = 0.009). Eight patients with COPD (27%) had nonsustained runs of ventricular tachycardia (VT). QTd rates were significantly increased in patients with COPD as compared to control subjects (57.7 ± 9.9 ms vs 37.5 ± 8.2 ms, p < 0.001). On comparing patients with COPD with and without runs of VT, patients with VT had longer QTd (67 ± 10 ms vs 55 ± 8 ms, p = 0.001). However no difference in any HRV and late potential parameters were found between patients with COPD with and without runs of VT. VPB rates were strongly correlated with QTd in patients with COPD (r = 0.61, p < 0.001). On SAECG analysis, patients with COPD had significantly increased total QRS duration as compared to control subjects. Nine of the 30 patients with COPD (30%) had positive late potentials. However, QTd and VPB rates were also similar between patients with COPD with and without late potentials.

**Conclusions:** The development of ventricular arrhythmia in patients with COPD was associated with increased QTd. Increased QTd may be associated with autonomic changes seen in patients with COPD.

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**Key words:** cardiac arrhythmia; COPD; late potentials; QT dispersion

**Abbreviations:** dQRS = QRS duration; E/A = early peak transmural flow velocity/late peak systolic velocity; EF = ejection fraction; FS = fractional shortening; HF = high-frequency spectral power; HRV = heart rate variability; IVRT = isovolumetric relaxation time; IVSd = interventricular septum thickness in diastole; LAS40 = low-amplitude signal in the terminal portion of the QRS; LF = low-frequency spectral power; LVMI = left ventricular mass index; LVWd = left ventricular posterior wall thickness in diastole; NS = not significant; pNN50 = proportion of consecutive beats with R-R intervals showing >50-ms difference; QTd = QT dispersion; QTmax = maximum difference in QT intervals; QTmin = minimum difference in QT intervals; rMSSD = root mean square differences between consecutive R-R intervals of the entire recording; RMS40 = root mean square voltage of the last 40 ms; SAECG = signal-averaged ECG; SDANN = SD of all 5-min R-R interval means; SDNN = SD of all R-R intervals; SND = mean of all 5-min SDs of R-R intervals; TP = total spectral power; VC = vital capacity; VPB = ventricular premature beat; VT = ventricular tachycardia

Cardiac arrhythmia and increased risk of sudden death are known in patients with COPD.1–3 QT dispersion (QTd) and late potentials derived from signal-averaged ECG (SAECG) have been proposed as noninvasive ECG parameters, which may predict increased risk of malignant arrhythmias.4–7 QTd, the interlead variability of the QT intervals in 12-lead ECG, reflects the heterogeneity of repolarization of the myocardium.4,5 Ventricular late potentials are high-frequency, low-amplitude signals in the terminal portion of the QRS wave, which can be filtered, amplified, and shown by SAECG. Late potentials reflect delayed ventricular depolarization, are markers of reentrant ventricular tachycardia (VT), and...
denote increased risk of malignant ventricular arrhythmias and sudden death in patients with ischemic heart disease and congestive heart failure. 

Recently, increased QTd has been reported in patients with COPD.1,8–10 However, there are scarce data on SAECG in patients with COPD. The aim of the study was to investigate QTd and SAECG as predictors of cardiac arrhythmia and their relation to heart rate variability (HRV), respiratory function test parameters, and numbers of daily ventricular premature beats (VPBs) and VT in patients with COPD.

**Materials and Methods**

**Study Groups**

Thirty patients with COPD (28 men and 2 women; mean ± SD age, 60 ± 9 years) and 31 healthy control subjects (28 men and 3 women; mean age, 57 ± 7 years) were included. Patients with hypertension, amyloidosis, diabetes mellitus, valvular heart disease, atrial fibrillation, and age > 65 years were excluded. The presence of ischemic heart disease was assessed with history, chest radiography, ECG, echocardiogram, and exercise testing when necessary. Patients with positive findings for ischemia were excluded. Patients who were receiving any antiarrhythmic drugs, which may influence QT intervals, were also excluded. Other cardiovascular drugs such as β-blockers and xanthine derivatives were stopped 48 h before study. The mean duration of symptoms was 12 ± 7 years in the patients with COPD. All patients had a history of smoking, and the mean smoking load was 54 ± 29 pack-years. Eighteen of the patients (60%) were ex-smokers. COPD was diagnosed according to criteria by American Thoracic Society.11

**Pulmonary Function Testing**

Pulmonary function tests were performed (SensorMedics model 2400; SensorMedics; Yorba Linda, CA). Vital capacity (VC), FVC, FEV1, forced expiratory flow at 25 to 75% of FVC, forced expiratory volume in 1 second (FEV1), and peak expiratory flow rate were measured. Results were given as percentage of the predicted values calculated from the reference values reported by European Community for Coal and Steel. Arterial blood gases were also obtained simultaneously, and PaO2, PaCO2, pH, HCO3, and oxygen saturation were analyzed.

**Echocardiographic Examination**

Echocardiographic examination was done with an echocardiographic system equipped with 2.5- and 3.5-MHz transducers (Sonos 1000; Hewlett-Packard; Andover, MA). M-mode and two-dimensional measurements were done in accordance with methods recommended by American Society of Echocardiography.11,14 Systolic and diastolic dysfunction were diagnosed with the measurements of fractional shortening (FS) [< 0.25] and early peak transmitral flow velocity/late peak systolic velocity (E/A) ratios (< 1), isovolumetric relaxation time (IVRT) > 100 ms.

Criteria for left ventricular hypertrophy was left ventricular mass index (LVMI) > 134 g/m² for male subjects and > 110 g/m² for female subjects. The cardiac mass was calculated by the formula derived by Reichek and Devereux:16

\[\text{LVMI} = 1.04 \times [(LVIDd + IVSd + LVPWd)^2 - LVIDd^2] - 13.6,\]

where LVIDd = left ventricular internal diameter in diastole (centimeters), IVSd = interventricular septum thickness in diastole (centimeters), LVPWd = left ventricular posterior wall thickness in diastole (centimeters), and LVIDs = left ventricular internal diameter in systole (centimeters).

Standardized cardiac mass was calculated by dividing it to body surface area, which was derived from Du Bois formula: body surface area = (weight1.425 × height0.725) × 0.007184.

**Rhythm Holter Recordings and HRV Analysis**

Twenty-four-hour ambulatory ECG recordings were obtained with a solid-state recorder (SEER; Marquette Electronics; Milwaukee, WI). The recordings were downloaded to a Marquette Laser SXP Holter system (Marquette Electronics). Cardiac rhythms were screened for VPBs. Nonsustained runs of VT of three to five consecutive impulses were defined as salvos, whereas six impulses or more lasting < 30 s were defined as VT. The recordings were reviewed to confirm 18 h of clear recording and the beat classifications were manually checked, corrected, and readied for HRV analysis. After all of the artifacts and misclassified beats were corrected and a minimum of 18 h of recording was confirmed, time-domain and frequency-domain analyses were carried out using the software package present in the system. In time-domain analysis, the mean of all 5-min SDs of R-R intervals (SDN), the SD of all R-R intervals (SDNN), the SD of all the 5-min R-R interval means (SDANN), the root mean square differences between consecutive R-R intervals of the entire recording (rMSSD), and the proportion of consecutive beats with R-R intervals showing > 50-ms difference (pNN50) were measured. In frequency-domain analysis, total spectral power (TP) [the area under the curve between 0.01 Hz and 1.00 Hz], low-frequency spectral power (LF) [the area under the curve between 0.04 Hz and 0.15 Hz], high-frequency spectral power (HF) [the area under the curve between 0.15 Hz and 0.40 Hz], and LF/HF ratio were measured.

In time-domain analysis, SDNN and SNDD were accepted as equivalent to TP, SDANN to ultra-low frequency not measured by our system, and rMSSD and pNN50 to HF. In frequency-domain analysis, LF was accepted as equivalent to the sympathetic-plus-parasympathetic components of autonomic function, HF was accepted as representing the parasympathetic component of autonomic function, and LF/HF as depicting the sympathovagal balance of the autonomic function.17

**Measurement of QT Intervals**

QT parameters were measured from the 12-lead ECG recording. ECGs were recorded by means of a 12-channel ECG recorder (model 1709-A; Hewlett-Packard) at a paper speed of 50 mm/s (gain, 10 mV/millimeter). Before measurement of QT parameters, ECGs were enlarged on the same photocopier by a factor of three. The QT interval was measured from the onset of QRS complex to the end of T wave. When T waves were inverted, the end was taken at the point where the trace returned to the baseline between the T wave and the P wave. In the presence of U wave, the end of the T wave was taken as the lowest point between the T wave and the U wave. If the end of the T wave was unclear, then it was excluded from analysis. A minimum of nine leads was studied in each patient. Minimum duration of the QT interval (QTmin), maximum duration of the QT interval (QTm), and their difference (QTd) were measured. Each QT interval was corrected for patient heart rate according to Bazett’s formula15: QTc = QT/√(R-R interval), where QT and R-R interval are expressed in seconds.
SAECG Measurements

SAECG measurement was performed on Marquette Centra electrocardiographic system (Marquette Electronics). For time-domain analysis, signals obtained from three bipolar orthogonal leads were amplified, filtered with double-pass Butterworth filters between 40 Hz and 250 Hz, and combined into a vector magnitude. Total QRS duration (dQRS), duration of high-frequency, low-amplitude signals < 40 µV, and root mean square voltage (40 ms) were measured. Recordings were used in the analysis if the noise level was < 1.0 µV. dQRS > 115 ms, duration of the low-amplitude signal > 38 ms, and root mean square voltage of the last 40 ms (RMS40) < 25 were accepted as abnormal. Late potentials were considered positive when at least two of the parameters above were accepted as abnormal.10

Reproducibility

One observer blindly performed all measures of QT intervals for each lead. In order to determine intraobserver variability of QT intervals, all ECG strips were measured twice. Intraobserver variability for QTd measurements was 12% (coefficient of variation).

Statistical Analysis

Statistical analyses were performed with Statistical Package Program for Social Sciences (SPSS for Windows 10.0; SPSS; Chicago, IL). Values were given as mean ± SD. Comparisons between groups were made by paired and unpaired t tests. Data were log-transformed when appropriate. Bonferroni corrections for multiple comparisons were made. Correlations between numeric parameters were analyzed with Spearman’s ρ test. All p values < 0.05 were accepted as significant.

Table 1—Results of Respiratory Function Tests, Arterial Blood Gas Analyses, and Echocardiographic Examinations

<table>
<thead>
<tr>
<th>Variables</th>
<th>COPD (n = 30)</th>
<th>Control (n = 31)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary function tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VC, %</td>
<td>62 ± 16</td>
<td>100 ± 12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FVC, %</td>
<td>59 ± 17</td>
<td>102 ± 14</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV1, %</td>
<td>41 ± 17</td>
<td>104 ± 15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>69 ± 16</td>
<td>80 ± 7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Arterial blood gas analysis</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.40 ± 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO2, mm Hg</td>
<td>67 ± 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCO2, mm Hg</td>
<td>46 ± 9</td>
<td></td>
<td></td>
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<tr>
<td>HCO3, mmol/L</td>
<td>26 ± 3</td>
<td></td>
<td></td>
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<tr>
<td>Echocardiographic measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>82 ± 12</td>
<td>76 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>IVSd, cm</td>
<td>1.12 ± 0.18</td>
<td>0.98 ± 0.09</td>
<td>0.003</td>
</tr>
<tr>
<td>LVWd, cm</td>
<td>1.03 ± 0.13</td>
<td>1.06 ± 0.19</td>
<td>NS</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>123 ± 28</td>
<td>118 ± 25</td>
<td>NS</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>94 ± 13</td>
<td>80 ± 15</td>
<td>0.004</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.83 ± 0.23</td>
<td>1.10 ± 0.31</td>
<td>0.003</td>
</tr>
<tr>
<td>EF, %</td>
<td>62 ± 8</td>
<td>71 ± 4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FS, %</td>
<td>34 ± 6</td>
<td>41 ± 3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LA diameter, cm</td>
<td>3.88 ± 0.42</td>
<td>3.90 ± 0.39</td>
<td>NS</td>
</tr>
<tr>
<td>RA diameter, cm</td>
<td>4.04 ± 0.48</td>
<td>3.70 ± 0.45</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>RV wall thickness, cm</td>
<td>1.19 ± 0.15</td>
<td>0.80 ± 0.25</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RV diameter, cm</td>
<td>3.43 ± 0.35</td>
<td>2.28 ± 0.54</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Results

In our study, there was no difference in age and sex distribution between patients with COPD and control groups. The results of the respiratory function tests, arterial blood gas analyses, and echocardiographic examinations are given in Table 1.

Echocardiographic Findings

Patients with COPD had increased interventricular wall thickness, right atrial diameter, right ventricular internal dimension, and right ventricular free-wall thickness. They also had lower ejection fraction (EF) and FS compared to control subjects (Table 1). However, none of the patients with COPD had systolic dysfunction (EF < 50% and/or FS < 25%). Left ventricular posterior wall thickness, internal diameter (diastolic), mass index, left atrial diameter, and heart rate were similar between patients with COPD and control subjects. Decreased E/A ratio (0.83 ± 0.23 vs 1.10 ± 0.31, p = 0.003), and increased IVRT (94 ± 13 ms vs 80 ± 15 ms, p = 0.004) were found in patients with COPD as compared to control subjects. Diastolic dysfunction (E/A ratio < 1 and IVRT > 100 ms) was found in 11 of the 30 patients with COPD (36%). Right ventricular internal diameter and wall thickness were not correlated with QTd (r = 0.14, p = 0.49, and r = 0.04, p = 0.85, respectively) or with VPB frequencies (r = -0.03, p = 0.89, and r = 0.03, p = 0.88, respectively.)

HRV Findings

Patients with COPD had decreased SDANN and SDNN in time-domain parameters, and decreased LF in frequency-domain parameters. However, no significant difference in SND, rMSSD, pNN50, TP, and HF was found between study groups. The LF/HF ratio, which represents sympathovagal balance, was also significantly decreased compared to control subjects (Table 2). FEV1 values were significantly correlated with SDANN (r = 0.45, p = 0.01), SND (r = 0.77, p < 0.01), SDNN (r = 0.54, p = 0.003), and mean normal-to-normal intervals between adjacent QRS complexes (r = 0.57, p = 0.001) in time-domain analysis of HRV; and LF (r = 0.74, p < 0.001), HF (r = 0.40, p = 0.03), and LF/HF ratio (r = 0.54, p = 0.003) in frequency-domain analysis of HRV.
Twenty-Four-Hour Holter Recordings

Patients with COPD had higher VPB frequency as compared to control subjects (924 ± 493 beats vs 35 ± 23 beats, mean ± SE; p = 0.009). Eight patients with COPD (27%) had nonsustained runs of VT. On comparing patients with COPD with and without runs of VT, QTmax (455 ± 35 ms vs 433 ± 24 ms, p = 0.03) and QTd (67 ± 10 ms vs 55 ± 8 ms, p = 0.001) were significantly prolonged in patients with VT. No other difference in any HRV and late potential parameters were found between patients with COPD with and without runs of tachycardia.

QTd Analysis

All QT intervals including QTmax, QTmin, and QTd were significantly increased in patients with COPD as compared to control subjects (Table 2). No correlation was found between QTd respiratory function tests, echocardiographic and HRV parameters, and arterial blood gas levels. Patients with COPD were classified into two groups according to presence or absence of QTd > 60 ms. Thirteen patients (43%) had QTd > 60 ms, and the remaining 17 patients (57%) had QTd < 60 ms. No difference in any respiratory function tests, arterial blood gas analyses, and echocardiographic and SAECG parameters was found between patients with COPD with higher and lower QTd. Patients with QTd > 60 ms had higher rMSSD and HF values in analysis of the HRV as compared to patients with QTd < 60 ms, but the differences were not significant (NS) [Table 3]. No difference was found in LF and LF/HF ratio between study groups.

SAECG Analysis

On SAECG analysis, patients with COPD had significantly increased total dQRS as compared to control subjects. However, the low-amplitude signal in the terminal portion of the QRS (LAS40) and RMS40 parameters were found to be no different from those in control subjects.

Nineteen of the 30 patients with COPD (63%) had positive late potentials according to criteria de-
scribed previously. On comparing the patients with and without late potentials, no difference was found in any respiratory function tests, arterial blood gas analyses, and echocardiographic and HRV parameters between study groups. All QT intervals, including QTd and VPB rates on rhythm Holter analysis, were also similar between patients with COPD with and without late potentials.

**DISCUSSION**

Cardiac arrhythmia and sudden death are common and important causes of mortality in patients with COPD. Several factors such as hypoxemia, hypercapnia, acid-base disturbances, autonomic dysfunction, and medications may contribute to the development of arrhythmias in these patients.1–3 We investigated the effect of severity of bronchial obstruction, changes in autonomic function, and echocardiographic changes in the heart with noninvasive markers of cardiac arrhythmia in patients with COPD.

**Echocardiographic Findings**

In our study, patients with COPD had increased IVSd and decreased left ventricular EF without causing overt systolic left ventricular dysfunction. These findings were consistent with previous reports.20–22 The increase in IVSd and right ventricular free-wall thickness without concomitant increase in left ventricular mass could be related to increased pulmonary pressure in patients with COPD. As previously reported,23 we found diastolic dysfunction in a significant percentage of our patients with COPD (36%). However, changes in left and right ventricular parameters in patients with COPD were not associated with changes in QTd, late potentials, and daily VPB frequency. These findings suggest that increased QTd or daily VPB frequency may not be related to structural changes, which could be detectable by echocardiographic examination, in this group of patients.

**Autonomic Nervous System and HRV**

Autonomic disturbances have been described in patients with COPD, which might also contribute to the development of cardiac arrhythmias. Mixed sympathetic and parasympathetic deterioration were reported by HRV studies.24,25 In a study with short-term HRV, blunted response to sympathetic and vagal stimulus was reported.26 In our study, patients with COPD had lower time-domain (SDANN and SDNN) and frequency-domain (LF and LF/HF ratio) HRV parameters compared to control subjects, which implies that the sympathetic component...
of HRV was compromised. The severity of the bronchial obstruction was correlated with changes in autonomic function in our study groups. Stein et al previously reported similar correlations in patients with COPD in PIz α1-antitripsin deficiency. However, none of the HRV parameters were associated with increased daily VPB frequency, VT, or late potentials in our patients, which implies that a link between decreased HRV and presence of arrhythmias may not be direct.

**QTd, Respiratory Function Tests, and Arterial Blood Gas Analyses**

Patients with COPD also had significantly prolonged QTd, which reflects inhomogeneity of the ventricular depolarization as compared to control subjects. Sarubbi et al reported that increased QTd in patients with COPD could be reduced after partial correction of hypoxemia. In addition, Kiely et al reported that acute hypercapnia increased QTd in healthy subjects. These findings suggested that changes in blood gas levels might be implicated for increased QTd in patients with COPD. However, Smith et al reported no effect of exercise-induced hypoxemia on QTd in patients with COPD. We also did not find any correlation between QTd and arterial blood gas analyses and respiratory function test parameters in our cross-sectional study.

**Relation of QTd, VT, and Daily VPB Rates**

In our study, daily VPB rates were correlated with QTd in patients with COPD (Fig 1). Daily VPB rates were significantly higher in patients with prolonged QTd (≥ 60 ms) as compared to patients with shorter QTd intervals (<60 ms) [Table 3]. Patients with runs of VT had longer QTd compared to patients without VT. It was previously reported that QTd was associated with increased risk of death and malignant tachyarrhythmia in patients with heart failure, and in patients awaiting cardiac transplantation. Biernecki et al reported that QTd was correlated with numbers of VPB in patients with COPD. These findings suggested that increased QTd was associated with increased risk of malignant cardiac arrhythmia and may be clinically important in patients with COPD. However, although patients with COPD with QTd <60 ms had longer QTd compared to control subjects, VPB frequency and runs of VT were not statistically different. This finding implies that the predictive value of QTd may become apparent only after reaching a certain threshold level.

**Relation of QTd With HRV**

Patients with COPD who had longer QTd had increased rMSSD and HF values as compared to other group (Table 3). Though these findings did not reach statistical significance, they might be interpreted to suggest that changes in autonomic function, especially the parasympathetic component, might have a role in increased QTd. There is only one study that analyzed the relation of QT prolongation to autonomic function in patients with COPD; Stewart et al reported that QT prolongation was associated with presence of autonomic neuropathy and mortality. However, there is no study investigating the relationship between QTd and HRV parameters in patients with COPD. Our findings imply that the deterioration in HRV might be associated with prolonged QTd in patients with COPD.

**SAECG**

There are scarce data on late potentials in patients with COPD. In our study, 9 of the 30 patients (30% of the patients with COPD) had positive late potentials by way of criteria described previously. On comparing the patients with and without late potentials, no difference was found in any respiratory function tests, arterial blood gas analyses, and echocardiographic and HRV parameters between study groups. All QT intervals, including QTd and VPB rates on rhythm Holter analysis, were also similar between patients with COPD with and without late potentials. These findings suggest that QTd might be superior to SAECG for predicting cardiac arrhythmia, and that QTd and late potentials may reflect different mechanisms of arrhythmias in patients with COPD. Superiority of QTd over SAECG for predicting cardiac arrhythmia was previously reported for other patient groups.

**CONCLUSION**

The development of ventricular arrhythmia in patients with COPD was associated with increased QTd, which is a noninvasive marker of arrhythmogenicity, but not with respiratory function parameters, severity of hypoxemia/hypercapnia, or late potentials. Parasympathetic components of HRV seemed to be associated with increased QTd, and the link to cardiac arrhythmias may be mediated by this. Increased QTd could be related to autonomic changes seen in patients with COPD. Although our major findings reached strong statistical significance, only 61 patients were included in the analysis (30 patients with COPD and 31 patients without COPD). Additional studies with larger numbers of patients would be desirable to confirm our findings and to evaluate clinical outcome.
REFERENCES


