Diaphragmatic Central Motor Conduction Changes In Chronic Obstructive Pulmonary Disease

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Short running title: Cortico-diaphragmatic changes in COPD

Abstract

Background and objectives: Respiratory muscles dysfunction has been reported in COPD. Transcranial magnetic stimulation (TMS) is easy non-invasive that has been used for assessing the respiratory corticospinal pathways particularly of diaphragm. We aimed to study the cortico-diaphragmatic motor system changes in COPD using TMS and to correlate the findings with the pulmonary function.

Methods: A case control study recruited 30 stable COPD from the out-patient respiratory clinic of Main Alexandria University hospital- Egypt and 17 healthy control subjects who were subjected to spirometry. Cortical conduction of the diaphragm was performed by TMS to all participants followed by cervical magnetic stimulation of the phrenic nerve roots. Diaphragmatic resting motor threshold (DRMT), cortical motor evoked potential latency (CMEPL), CMEP amplitude (CMEPA), peripheral motor evoked potential latency (PMEPL), PMEP amplitude (PMEPA) and central motor conduction time (CMCT) were measured.

Results: 66.7% of COPD patients had severe and very severe COPD with median age of 59 (55-63) years. There was statistically significant bilateral decrease in DRMT, CMEPA and PMEPA in COPD group versus healthy subjects and significant increase in CMEPL and PMEPL (p <0.01). Left CMCT was significantly prolonged in COPD group versus healthy subjects (p <0.0001) but not right CMCT. Further, there was significant increase in CMEPL and CMCT of left versus right diaphragm in COPD group (p= 0.003 and 0.001 respectively) that inversely correlated with FEV_1% and FVC% predicted.

Conclusion: Central cortico-diaphragmatic motor system is affected in COPD patients with heterogeneity of both sides that is correlated with pulmonary function.

Significance: Coticospinal pathway affection could be a factor for development of diaphragmatic dysfunction in COPD patients accordingly its evaluation could help in personalization of COPD management especially pulmonary rehabilitation programs

Keywords: Transcranial magnetic stimulation, corticospinal pathways, phrenic nerve, pulmonary function

Introduction

Chronic obstructive pulmonary disease (COPD) is mainly presented with dyspnea and exercise limitation secondary to irreversible airflow obstruction; however, nowadays COPD is considered as multi-systemic inflammatory disorder rather than simple respiratory disease.[1] Respiratory muscles dysfunction has been reported in COPD compared to healthy elderly individuals [2] and has been implicated in the development of dyspnea.

Respiratory muscles, particularly the diaphragm which is considered the main inspiratory muscle, are affected in COPD in two main ways. Firstly, change of shape and geometry of the chest wall secondary to air trapping and hyperinflation in COPD leads to chronic reduction of the apposition zone of the diaphragm [3] and shorten of the diaphragm fiber sarcomere. [4] Secondly, local activation of muscle proteases and oxidative stress due to inspiratory loading induce structural muscular injury [5, 6] that is further affected by exposure to systemic inflammatory process associated with COPD. [7]

Transcranial magnetic stimulation (TMS) is easy, non-invasive and painless tool that aimed at measuring neuronal electrical activity. [8] TMS has been used as investigation tool for assessing the respiratory corticospinal pathways and studying of diaphragmatic motor evoked potential (MEP). [8-12] TMS has been used to identify central origin of a diaphragmatic dysfunction in stroke, [13] multiple sclerosis, [14] amyotrophic lateral sclerosis, [15] or spinal cord injury. [16]

Cervical magnetic stimulation of the phrenic nerve roots has been used previously to assess diaphragm weakness in COPD patients. [17] In the last decade, a recent study demonstrated increased excitability of the motor cortex controlling respiratory

muscles in COPD especially diaphragm which could be secondary to increased inspiratory load and subsequent elevated respiratory drive. [18] However, still little research has been conducted in COPD to assess central neural drive to the diaphragm and its possible involvement in physiological derangement in COPD patients. Accordingly, we aimed to study the cortico-diaphragmatic motor system changes in COPD patients using TMS; to correlate the findings with the pulmonary function; and to detect possible cutoff value for corticospinal diaphragmatic pathway affection that could be a reference in this group of patients.

Methods

Study design and ethics

A case control study recruited 30 stable COPD according to updated GOLD guidelines 2017 [1] who attended the out-patient respiratory clinic of Main Alexandria University hospital, Egypt as well as 17 healthy control subjects who were invited to participate in the study. The study has been approved by the scientific committee of faculty of medicine, Alexandria University, Egypt. A written informed consent was obtained from all participants enrolled in this study. The study was conducted over 10 months.

Study population and their characterization

Thirty COPD patients were included in the study. All patients were stable i.e. no COPD exacerbation in last 4 weeks, and has been proved to have airway obstruction using spirometry (post-bronchodilator $FEV_1/FVC < 0.70$) as being accepted by updated GOLD guidelines 2017. [1] All patients who were known to have COPD

93 exacerbation, current oral corticosteroids therapy or within last 30 days, bronchial
94 asthma, interstitial lung diseases, metabolic diseases (mainly diabetes mellitus, uremia
95 and hepatic failure), neurological diseases (as cerebrovascular stroke, epilepsy,
96 peripheral neuropathy and muscle diseases), body mass index (BMI) more than 40
97 kg/mm^2, history of drug abuse, history of any neoplasm, or any contraindications for
98 magnetic stimulation were excluded from the study. Further, 17 healthy control
99 subjects with normal lung function referred for check-up were recruited from other
100 clinics.

101 All the participants underwent detailed history taking that included age, sex, smoking
102 history, respiratory symptoms, current medications; followed by local and general
103 examination, chest X-ray, spirometry for measurement of post- bronchodilator FVC,
104 FEV_1 and FEV_1/FVC ratio. For COPD patients, arterial blood gases (ABG) were
105 assessed for COPD patients, and venous blood sample was taken for measurement of
106 fasting blood glucose, liver function testing, renal function testing, complete blood
107 picture, and serum electrolytes (sodium and potassium). Computed tomography of
108 chest was performed if indicated clinically.
109

110 Diaphragmatic neural function assessment

111 Firstly**,** TMS of the diaphragm was carried out using electrophysiological apparatus
112 with a circular coil (Nihon Kohden MEB-7102K© with peak magnetic field strength
113 of 2 Tesla; Tokyo, Japan). The coil was applied tangentially to the scalp of patient at
114 diaphragmatic motor cortical area, a point of optimal excitability, located 3 cm lateral
115 to midline and 2-3 cm anterior to auricular plane [9] with face A of the coil visible
116 from above for left hemisphere stimulation and face B for right hemisphere
117 stimulation recording cortical MEPs responses. Surface electrodes were placed in the

118 7th and 8th right and left intercostal spaces respectively within the anterior axillary
119 line, and the reference electrode on the corresponding lower rib for recording
120 diaphragmatic cortical MEP response contralateral to the stimulation site. A ground
121 electrode was placed on the manubrium sterni. [19] The recording conditions utilized
122 were: filter setting high at 3K Hz and low at 3Hz, vertical gain 0.2- 2mV/ division,
123 and sweep speed 5 msec/division. The stimulus threshold was determined by
124 increasing the stimulus strength (expressed as the % of the maximum output of the
125 stimulator) until 3 reproducible MEPs responses were obtained, then the stimulus
126 intensity was set at 20% above the threshold value. The angle of the coil around the
127 stimulation site was changed until the highest MEP response during inspiratory phase
128 was recorded. The following parameters were measured from central stimulation:
129 diaphragmatic resting motor threshold (DRMT), cortical motor evoked potential
130 latency (CMEPL) in milliseconds (ms), CMEP amplitude (CMEPA) in microvoltage
131 (μv).
132 Secondly, cervical magnetic stimulation of the phrenic nerve roots in the neck was
133 performed bilaterally. The periphery of the circular coil of the apparatus was placed 2
134 cm lateral to mid-line and 1-2 cm above the 5th cervical spine while the patient head
135 slightly bent forward. The diaphragmatic peripheral motor evoked potential (PMEP)
136 was recorded by using the same recording electrodes setting previously discussed
137 whereas peripheral motor evoked potential latency (PMEPL) and PMEP amplitude
138 (PMEPA) were measured. Central motor conduction time (CMCT) was then
139 calculated as follow: CMCT = CMEPL – PMEPL. [20]
140

141 **Statistical analysis**

Quantitative data were expressed as mean ± standard deviation (SD) or median (interquartile range; 25-75 percentile) according to the normal distribution of data while qualitative data was expressed as number and percentage (%). Mann - Whitney test, Kruskal - Wallis test, student t-test, Chi-square test and Spearman rho correlation were used as appropriate. ROC (receiver operating characteristic) curve and area under the curve (AUC) has been used to detect cutoff values for diaphragmatic CMEPs that could differentiate COPD from healthy individuals. All the analysis has been performed using MedCalc® (version 9.2.1.0, Acacialaan 22, B-8400 Ostend, Belgium) and SPSS package (PASW Statistics for Windows, Version 22.0. Chicago: SPSS Inc.).

Results

Participants' characteristics

All the baselines characteristics of COPD patients and healthy control are shown in table "1". All the recruited patients were males with no statistically significant difference between both groups regarding age, BMI, and smoking status; however smoking index was significantly higher in COPD group ($p < 0.0001$). Baseline FVC%, FEV_1% and FEV_1/FVC were significantly lower in COPD group ($p < 0.0001$) whereas 2 COPD patient (6.7%) had mild airway obstruction, 8 patients (26.7%) had moderate airway obstruction, 12 patients (40%) had severe airway obstruction and 8 patients (26.7%) had very severe airway obstruction according GOLD classification.

Diaphragmatic neural function assessment

Both CMEPs and PMEPs of studied population are illustrated in table "2" with demonstration example in figure "1". There was statistically significant bilateral decrease in DRMT, CMEPA and PMEPA in COPD group versus healthy subjects ($p < 0.0001$ for all and 0.001 for PMEPA on right). Further, there was statistically significant increase in CMEPL and PMEPL bilaterally in COPD group versus healthy subjects ($p < 0.0001$ for all and 0.006 for CMEPL on right side). Left CMCT was significantly prolonged in COPD group vs. healthy subjects ($p < 0.0001$) but not for right CMCT "p= 0.376; table 2". Further, there was significant increase in CMEPL and CMCT of left versus right diaphragm in COPD group "p= 0.003 and 0.001 respectively; table 3" but there was no statistically significant difference in control group.

Correlations

Left diaphragmatic CMEPL and CMCT inversely correlated with different pulmonary function parameters (i.e. FVC% predicted, FEV_1% predicted and FEV_1/FVC) and positively correlated with CMEPA among the studied population "$p < 0.01$; figures 2A-F". However, right diaphragmatic CMCT did not correlate with pulmonary function parameters ($p > 0.05$) while right CMEPL is inversely correlated with FVC% predicted (p= 0.036) but not FEV_1% predicted or FEV_1/FVC ($p > 0.05$) among the studied population. Both right and left diaphragmatic peripheral conduction (PMEPL and PMEPA) were positively correlated with different pulmonary function parameters ($p < 0.01$).

On the other hand, there was no statistically significant association between either CMEPs or PMEPs and COPD severity according to GOLD classification ($p > 0.05$). Similarly, there was no statistically significant correlation between diaphragmatic

187 CMEPs or PMEPs and age, smoking status, smoking index, BMI, serum albumin or
188 ABG parameters ($p > 0.05$).
189

190 ROC analysis

191 According to ROC analysis, DRMT ≤ 80% had diagnostic accuracy of 98.6% to
192 differentiate COPD from healthy control individuals with a sensitivity of 92% and
193 specificity of 94% "AUC= 0.986, CI95%= 0.936 - 0.998, p= 0.0001; figure 3A";
194 CMEPL > 12.9 ms had diagnostic accuracy of 83% and sensitivity of 77% and
195 specificity of 85% for differentiating COPD from healthy subjects "AUC= 0.828,
196 CI95%= 0.737 - 0.898, p= 0.0001; figure 3B"; CMCT > 6.7 ms had diagnostic
197 accuracy of 71.5% and sensitivity of 77% and specificity of 80% for differentiating
198 COPD from healthy subjects "AUC= 0.715, CI95%= 0.612 - 0.803, p= 0.0001; figure
199 3C"; CMEPA ≤ 160 µv had 92% diagnostic accuracy, 98% sensitivity and 73.5%
200 specificity for differentiating COPD from healthy subjects "AUC= 0.916, CI95%=
201 0.841 - 0.963, p= 0.0001; figure 3D".

202 Discussion

203 In the current study, COPD patients had significant delayed central and peripheral
204 diaphragmatic conduction latencies compared to the healthy control group, as well as
205 decreased amplitude that was correlated with several parameters of pulmonary
206 function testing. In addition, there was a statistically significant difference in COPD
207 patients between right and left central diaphragmatic conduction.

208 Previous studies and interpretation of the results

209 Hopkinson et al [18] found that diaphragmatic cortical motor thresholds were
210 significantly lower in COPD than healthy controls as well as significant longer mean

PMEPL. Similarly, Hamed et al [21] reported bilateral increase in CMEPL and CMCT in their studied COPD compared to healthy control group as well as decreased DRMT. Further, El-Tantawi et al [22] found peripheral phrenic nerve conduction abnormalities in 42.5% of their studied COPD patients that did not correlate with disease severity. These results are in accordance of the current results and could be explained by increased excitation of motor cortex and corticospinal pathways to the respiratory muscles in the COPD patient [23] and less excitability of intracortical facilitatory circuits at long interstimulus intervals using paired stimulation denoting ceiling effect of motor control output to the respiratory muscles of case of COPD. [18]

Interestingly, we found significant increase in CMEPL and CMCT of left versus right diaphragm in COPD group which correlated inversely with FEV_1% and FVC% but not ABG parameters. This denotes that there is heterogeneity in affection of respiratory muscles which is in accordance with disease heterogeneity on one hand. [24] On the other hand, increased inspiratory load of respiratory muscles has been associated with significant activation of several motor cortical areas as demonstrated by increased regional cerebral blood flow using positron emission tomography [25] which could be affected asymmetrically. More recently, Dodd et al [26] demonstrated by magnetic resonance imaging techniques that generalized functional activation of resting-state networks in COPD patients compared with controls.

Further, we proposed cutoff point for CMEPs that had good diagnostic accuracy and sensitivity for predicting corticospinal pathway affection in case of COPD. Lissens [8] demonstrated values for diaphragmatic CMEPs in 10 healthy man only. However, to our knowledge, there are no specific values proposed to date that could be reference for CMEPs responses in COPD. We suppose that the presented values could

be considered as reference, however, further studies with larger population should be considered to confirm the current values.

Clinical implementation

Diaphragmatic dysfunction is strongly correlated with FEV_1 in COPD [27] and correlated with the perception of dyspnea among this group of patients. [28] Coticospinal pathway affection could be another factor for development of diaphragmatic dysfunction in COPD patients accordingly its evaluation could help in personalization of COPD management especially pulmonary rehabilitation programs. Chun et al found significant improvement of diaphragmatic motility after pulmonary rehabilitation using sonography. [29]

Further, assessment of diaphragmatic corticospinal pathway could be of value in evaluation noninvasive ventilation use in stable severe/ very severe COPD. [30] This has been demonstrated by Hopkinson et al, [23] who found that the excitability of the corticospinal pathway to the diaphragm reduced in 6 COPD patients after acute noninvasive ventilation use. This could be explained by the fact that noninvasive ventilation reduced inspiratory muscles loads [30] through reduces the cortical motor areas excitability supplying the respiratory muscles especially the diaphragm. [31] Accordingly, TMS could be a good applicable tool for evaluation of central and peripheral diaphragmatic neural pathway which may affect the management of COPD patients.

Limitations

The current study has some limitations. Firstly, we studied only the diaphragm as the main respiratory muscle and we did not study the intercostals or abdominal muscles. Further, the cortical area for the diaphragm has been previously validated in healthy man [9, 12] rather than other respiratory muscles. Secondly, we used surface

electrodes for diaphragm CMEPs recording and we did not use diaphragm needle electromyography. However, intercostal surface electrodes have been validated previously [19] and needle electromyography is more invasive and could be associated with complications as pneumothorax. Lastly, we did not study the diaphragmatic CMEPs response at different intervals of time of at maximal inspiratory efforts in COPD patients. However, Sharshar et al [32] studied before the response to cortical stimulations at different points of time or inspiratory efforts in healthy men and they concluded that cortical motor control of diaphragm is identical during different inspiratory tasks.

Conclusions

Central cortico-diaphragmatic motor system is affected in COPD patients with heterogeneity of both sides that is correlated with airway obstruction as being detected with spirometry but not with COPD severity or ABG changes. The cutoff values for CMEPs in COPD patients in the current study had good diagnostic value in predicting diaphragmatic corticospinal affection. The current data could be a step for future studies for evaluating the diaphragm using noninvasive tool - the TMS - after therapeutic interventions for COPD.

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Conflict of interest:

None of the authors have potential conflicts of interest to be disclosed

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407 Table (1): Demographic and baseline clinical characteristics of study population

Character	**COPD (n=30)**	**Control (n=17)**	***p* value**
Age (years)	59 (55- 63)	55 (50 - 59.5)	0.055
Gender Male / Female	30 (100) / 0 (0)	17 (100) / 0 (0)	1.0
BMI (Kg/mm^2)	24.3 ± 4.7	22.8 ± 3.6	0.338
Smoking history smoker / ex-smoker smoking index (PYI)	14 (46.7) / 16 (53.3) 60 (45 - 80)	11 (64.7) / 6 (35.3) 20 (10-30)	0.375 <0.0001*
Comorbidities Hypertension IHD Obesity and OSA	10 (33.3) 6 (20) 1 (3) 3 (10)	0 (0)	0.029*
Spirometry FVC% predicted	56 (50.3 - 66.3)	109 (98 - 123)	< 0.0001*
FEV_1% predicted	42.9 (29 - 54)	123 (112 - 136.5)	< 0.0001*
FEV_1/FVC	57.6 ± 8.7	86.6 ± 8.5	< 0.0001*
ABG pH PaO_2 (mmHg) $PaCO_2$ (mmHg) HCO_3 (mmol/L) SaO_2	 7.43 ± 0.048 78.43 ± 20.8 40.5 ± 8.9 25 (22 - 30) 96 (94.8 - 97.0)	NA	NA

Laboratory tests FBS (mg/dl) Hb (g/dl) BUN (mg/dl) Cr (mg/dl) Na (mmol/L) K (mmol/L) AST (U/L) ALT (U/L) Albumin (g/dl)	 101.5 (72 - 111) 13.9 ± 1.3 15 (12 - 20) 0.81 ± 0.24 140 (137 - 144) 4.1 ± 0.35 29.5 (22 - 41) 27.5 (20- 41) 3.0 (2.9 - 3.4)	NA	NA

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409 *: Statistically significant at $p \leq 0.05$, BMI: body mass index, OSA: obstructive sleep

410 apnea, IHD: ischemic heart disease, PYI: pack/year index, PaO_2 : arterial partial

411 pressure of oxygen, $PaCO_2$: arterial partial pressure of carbon dioxide, HCO_3:

412 bicarbonate, SaO_2: oxygen saturation, FBS: fasting blood sugar, Hb: hemoglobin,

413 BUN: blood urea nitrogen, Cr: creatinine, Na: sodium, K: potassium, AST: aspartate

414 transferase, ALT: alanine transferase.

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417 Table (2): Comparison between the two studied groups regarding diaphragmatic

418 CMEP and PMEP parameters

Parameter	COPD (n=30)	Control (n=17)	*p* value
Right diaphragm conduction			
DRMT (%)	66.9 ± 8.2	89.5 ± 5.2	< 0.0001
CMEPL (ms)	14.4 (11.9 - 16.5)	11.2 (10.5 - 12.4)	0.006
CMEPA (µv)	120 (110-140)	177 (158.3 - 180.0)	< 0.0001
PMEPL (ms)	6.99 ± 1.05	5.4 ± 0.6	< 0.0001
PMEPA (µv)	135.0 (117.0 - 160.0)	190 (179.5 - 196.3)	< 0.0001
CMCT (ms)	7.7 (4.9 - 9.2)	5.9 (5.6 - 6.6)	0.376
Left diaphragm conduction			
DRMT (%)	68.6 ± 7.6	89 ± 4.4	< 0.0001
CMEPL (ms)	16.8 (14.5 - 18.0)	10.9 (10.6 - 12.8)	< 0.0001
CMEPA (µv)	127.1 ± 23.8	173.9 ± 34.2	< 0.0001
PMEPL (ms)	7.4 (6.0 - 8.4)	5.1 (4.7 - 5.75)	< 0.0001
PMEPA (µv)	147.3 ± 21.7	183.0 ± 35.9	0.001
CMCT (ms)	9.3 (8.1 - 10.1)	6.2 (5.5 - 6.95)	< 0.0001

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420 *: Statistically significant at $p \leq 0.05$, DRMT: diaphragmatic resting motor threshold,

421 CMEPL: cortical motor evoked potential latency in milliseconds (ms), CMEPA:

422 cortical motor evoked potential amplitude in microvoltage (µv), PMEPL:

423 peripheral motor evoked potential latency, PMEPA: peripheral motor evoked

424 potential amplitude, CMCT: central motor conduction time.

426 Table 3: Comparison between right and left diaphragmatic CMEP and PMEP in both
427 groups

Parameter	COPD group (n=30)			Control group (n=17)		
	Right	Left	*p* value	Right	Left	*p* value
DRMT (%)	66.9 ± 8.2	68.6 ± 7.6	0.417	89.5 ± 5.2	89 ± 4.4	0.778
CMEPL (ms)	14.4 (11.9 - 16.5)	16.8 (14.5 - 18.0)	0.003*	11.2 (10.5 - 12.4)	10.9 (10.6 - 12.8)	0.783
CMEPA (µv)	122.8 ± 22.3	127.1 ± 23.8	0.472	177 (158.3 - 180.0)	173.9 ± 34.2	0.959
PMEPL (ms)	6.99 ± 1.05	7.4 (6.0 - 8.4)	0.427	5.2 (4.9 - 5.8)	5.1 (4.7 - 5.8)	0.593
PMEPA (µv)	138.3 ± 25.7	147.3 ± 21.7	0.147	190 (179.5 - 196.3)	190 (147.5 - 196.5)	0.986
CMCT (ms)	7.7 (4.9 - 9.2)	9.3 (8.1 - 10.1)	0.001*	5.9 (5.6 - 6.6)	6.2 (5.5 - 6.95)	0.629

428

429 *: Statistically significant at $p \leq 0.05$, DRMT: diaphragmatic resting motor threshold,
430 CMEPL: cortical motor evoked potential latency in milliseconds (ms), CMEPA:
431 cortical motor evoked potential amplitude in microvoltage (µv), PMEPL:
432 peripheral motor evoked potential latency, PMEPA: peripheral motor evoked
433 potential amplitude, CMCT: central motor conduction time.

434

435 **Figures**

436 Figure 1. A: CMEP of diaphragm in COPD patient noticing that there is delayed
437 latency and low amplitude of the response versus figure 1-B which represents
438 healthy subject; C: PMEP of diaphragm in COPD patient with low amplitude of
439 the response versus figure 1-D which represents healthy subject.

440

441 Figure 2. Correlations between spirometric parameters (FEV% predicted and FVC%
442 predicted) and left CMEPs (A-F).

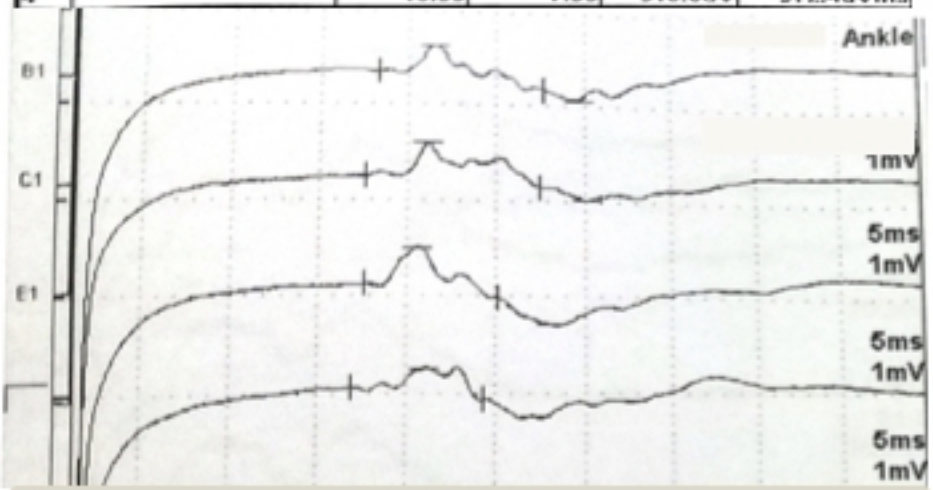
443

444 Figure 3. ROC analysis in COPD patients for predicting cutoff for CMEPs; A: for
445 DMRT% (AUC= 0.986, CI95%= 0.936 - 0.998, *p*= 0.0001); B: for CMEPL
446 (AUC= 0.828, CI95%= 0.737 - 0.898, *p*= 0.0001); C: CMEPA (AUC= 0.715,
447 CI95%= 0.612 - 0.803, *p*= 0.0001); D: CMCT (AUC= 0.916, CI95%= 0.841 -
448 0.963, *p*= 0.0001).

449

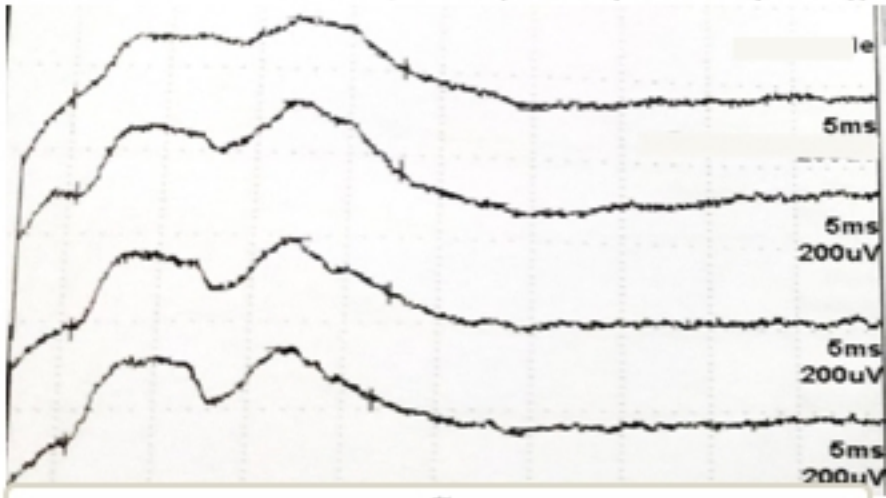
450

No.	Site	Lat.(ms)	Dur.(ms)	Amp.	Area
1		18.30	9.40	560.0uV	1.025mVms
2		17.60	9.85	570.0uV	1.558mVms
3		17.60	7.50	790.0uV	1.186mVms
4		16.95	7.35	510.0uV	972.4uVms



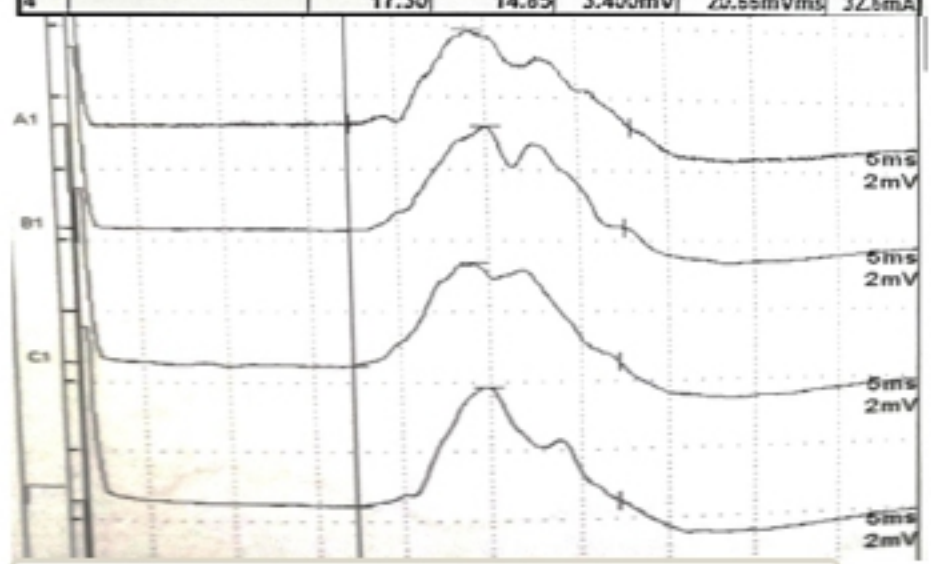
A

No.	Site	Lat.(ms)	Dur.(ms)	Amp.	Area	Stim.
1		4.95	18.00	207.0uV	1.797mVms	0mA
2		5.40	17.40	233.0uV	1.873mVms	0mA
3		5.55	16.80	188.0uV	1.592mVms	0mA
4		5.55	16.05	183.0uV	1.608mVms	0mA



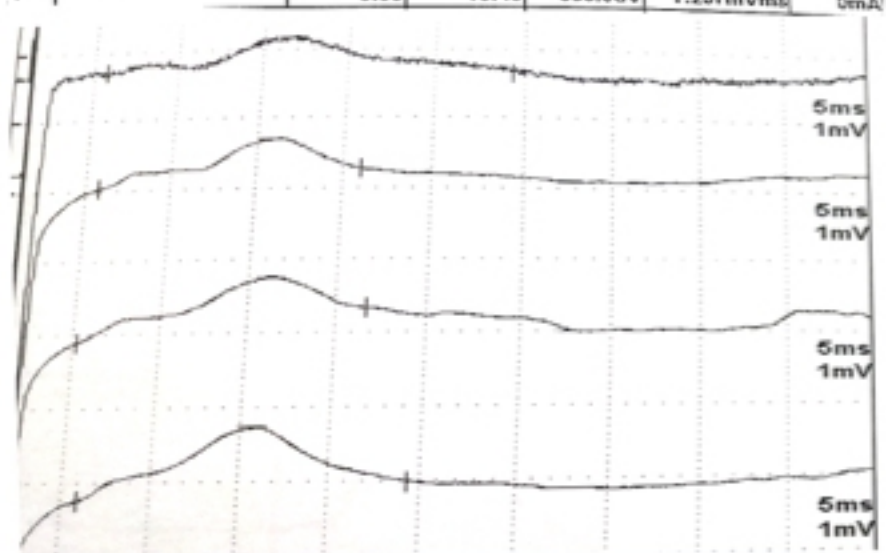
C

No.	Site	Lat.(ms)	Dur.(ms)	Amp.	Area	Stim.
1		17.45	15.50	2.620mV	19.40mVms	32.6mA
2		17.30	15.20	2.910mV	20.33mVms	32.6mA
3		17.25	14.90	2.900mV	22.15mVms	32.6mA
4		17.30	14.85	3.400mV	20.65mVms	32.6mA



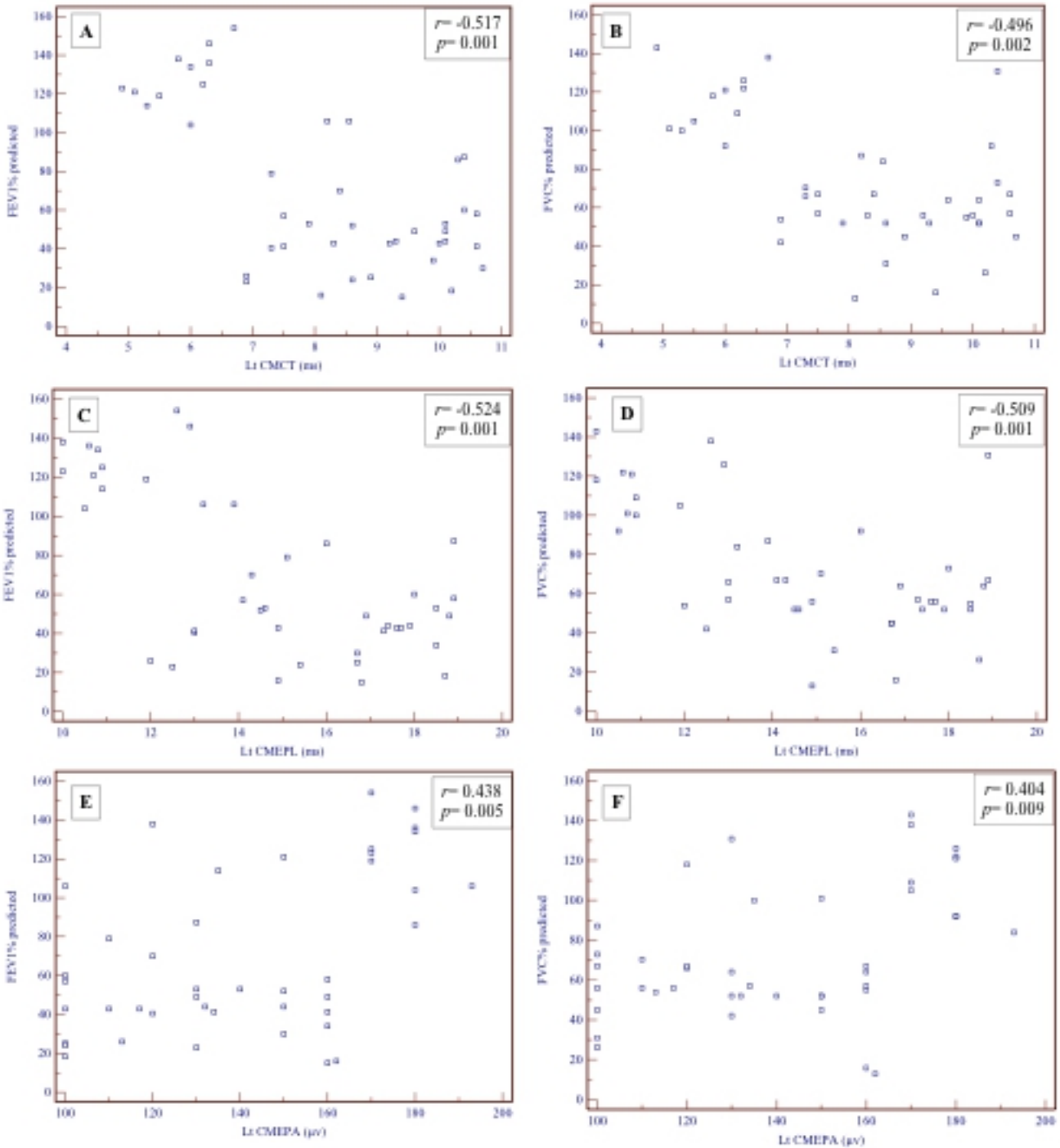
B

No.	Site	Lat.(ms)	Dur.(ms)	Amp.	Area	Stim.
1		5.80	23.55	630.0uV	4.778mVms	0mA
2		5.75	15.25	590.0uV	3.603mVms	0mA
3		5.20	16.50	760.0uV	4.756mVms	0mA
4		5.85	18.45	850.0uV	7.207mVms	0mA

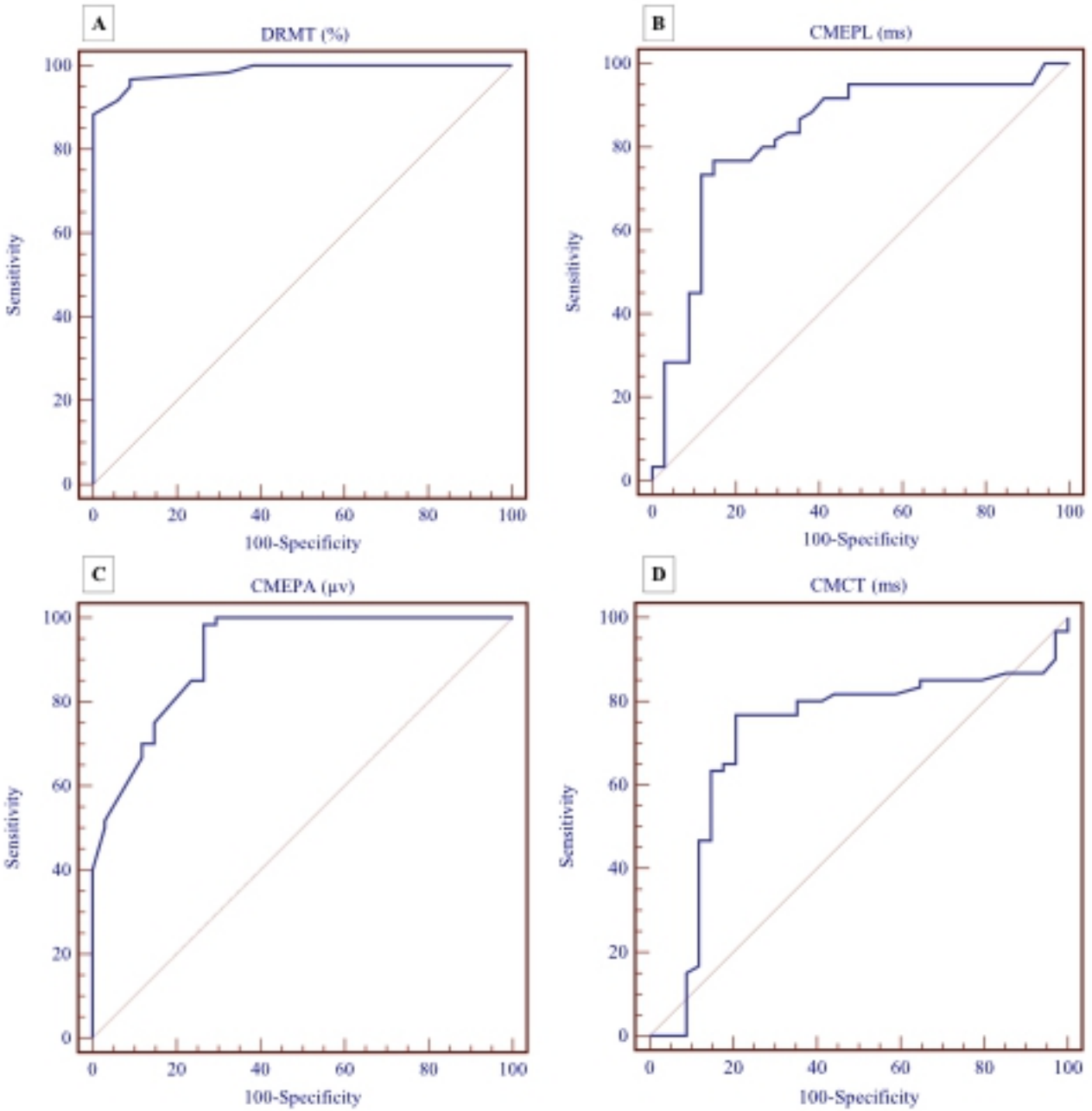


D

Figure


A
r= -0.517
p= 0.001
FEV1% predicted
Lt CMCT (ms)
B
r= -0.496
p= 0.002
FVC% predicted
Lt CMCT (ms)
C
r= -0.524
p= 0.001
FEV1% predicted
Lt CMEPL (ms)
D
r= -0.509
p= 0.001
FVC% predicted
Lt CMEPL (ms)
E
r= 0.438
p= 0.005
FEV1% predicted
Lt CMEPA (μv)
F
r= 0.404
p= 0.009
FVC% predicted
Lt CMEPA (μv)

Figure


A
DRMT (%)
Sensitivity
100-Specificity
B
CMEPL (ms)
Sensitivity
100-Specificity
C
CMEPA (μv)
Sensitivity
100-Specificity
D
CMCT (ms)
Sensitivity
100-Specificity

Figure