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Lung Function, Arterial Blood Gases, and Carotid Intima–media Thickness as a Predictor of Cerebral Stroke

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Authors' contributions

This work was carried out in collaboration between all authors. Authors KWA, MME, MAH and HAY participated in design of the study, writing the protocol, and the first draft of the manuscript, management and analyses of the study, and management of the literature searches. Author SMA designed the patient and methods part, performed the statistical analysis, participated in writing the protocol, and the first draft of the manuscript and management of the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Elevated risk of cardiovascular disease mortality in patients with reduced lung function had been demonstrated in several studies. Fewer studies have investigated the relation between pulmonary function, arterial blood gases, and the risk of cerebral stroke.
Aim of the Work: The present work aimed to detect the link between lung function parameters (FEV_1, FVC, FEV_1/FVC%, PEF and MVV), arterial blood gases parameters (pH, PaO_2, $PaCO_2$,

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SPO_2%, and HCO_3) and carotid intima media thickness (cIMT) as risk factors in cerebral stroke and non stroke patients without chronic respiratory disease.

Patients and Methods: Our study was conducted on 50 cerebral stroke and 200 non stroke patients as a control group. Lung function was assessed by forced vital capacity (FVC) maneuver. Carotid ultrasonography to measure cIMT and arterial blood gases were done.

Results: The risk for cerebral stroke of our studied patients was higher among those with elevated cIMT than patients with normal cIMT. There were high statistical significant decrease in pH, forced expiratory volume in the first second/ forced vital capacity% (FEV_1/FVC%), and peak expiratory flow (PEF), and high statistical significant increase in $PaCO_2$, HCO_3, and cIMT in stroke patients compared to non stroke patients. Reduced FVC, FEV_1/FVC%, MVV, and PaO_2 were associated with elevated cIMT. Results of the stepwise multivariable regression model demonstrated that cIMT was directly proportional to age and FEV_1 and inversely proportional to FEV_1/FVC%, $PaO_{2,}$ FVC and maximum voluntary ventilation (MVV).

Conclusion: The risk for cerebral stroke was higher among patients with elevated cIMT. Reduced FVC, FEV_1/FVC%, MVV, and PaO_2 were associated with elevated cIMT. Stroke patients had reduced FEV1/FVC%), PEF, and pH than non stroke patients. These results suggest the requirement to perform pulmonary function and arterial blood gases in people without respiratory disease to screen those with impaired lung function for the presence of subclinical atherosclerosis to prevent the risk for cerebral stroke.

Keywords: Lung function; cerebral stroke; cIMT; arterial blood gases.

ABBREVIATIONS

cIMT : Carotid intima media thickness);
FVC : forced vital capacity;
FEV_1 : forced expiratory volume in the first second
MVV : maximum voluntary ventilation;
PEF : peak expiratory flow;
SPO_2 : O_2 saturation %.

1. INTRODUCTION

Elevated risk of cardiovascular disease mortality in patients with impaired lung function had been reported in several studies [1]. Other researchers have postulated that information on the link between pulmonary function and cerebral stroke mortality [2,3]. There was an inverse relation between FEV_1 and risk of first-time stroke in analyses adjusted only for age and sex. The risk rose steadily with decreasing FEV_1, especially in women, whereas in men there was a decrease in the risk among those with the lowest lung function [3]. Only a limited number of studies have reported the relationship between pulmonary function and stroke among non smokers [3-6]. Lower levels of FEV_1 were associated with a significant increase in the risk of stroke even after adjustment for age, smoking, social class, physical activity, alcohol intake, systolic blood pressure, antihypertensive treatment, diabetes, and preexisting ischemic heart disease [6]. Respiratory symptoms were related to ischemic stroke incidence as reported by Atherosclerosis Risk in Communities (ARIC) study, although whether asymptomatic patients with reduced pulmonary function are at increased risk for ischemic stroke remains unclear [7]. A Limited number of studies have analyzed the relation between pulmonary function and risk of fatal or non-fatal stroke. Impaired pulmonary function has been demonstrated to be a significant predictor of non-fatal ischemic heart disease, and of cardiovascular disease mortality [3]. Numerous studies have reported an association between reduced lung function and higher risk of coronary heart disease and cerebral stroke [8-10]. The relation between reduced lung function and risk of cerebral stroke is suggested by increased susceptibility to infections and elevated viscosity of blood. Another study demonstrated that reduced lung function was associated with white matter lesions and subclinical cerebral infarctions [11]. Chronic inflammation and/ or infection [12], impaired fibrinolytic activity [13], and oxidative stress [14] may be the suggested explanations for such associations. Söderholm et al, 2012 [15] hypothesized that reduced lung function could be associated with a higher incidence of subarachnoid hemorrhage, perhaps due to common pathogenic mechanisms in vessel wall degradation and destruction of lung parenchyma. Every 0.1 mm increase in carotid intima-media thickness (cIMT) increases the risk of myocardial infarction by 10% to 15% and of cerebral stroke by 13% to 18% [16]. So, cIMT is considered a sensitive marker for subclinical at her osclerosis

[16]. The purpose of this work is to detect the link between lung function parameters (FEV_1, FVC, FEV_1/FVC%, PEF and MVV), arterial blood gases parameters (pH, PaO_2, $PaCO_2$, SPO_2%, and HCO_3) and carotid intima media thickness (cIMT) as risk factors in cerebral stroke and non stroke patients without chronic respiratory disease.

2. PATIENTS AND METHODS

2.1 Study and Patients

Our case control study was carried out on 50 cerebral stroke patients and 200 non stroke patients as a control group. The control group was age and sex matched with the cases. The diagnosis of stroke was all made by referring neurologists from the admitting hospital proven by computed tomography (CT) and/or magnetic resonance imaging (MRI) of brain.

2.2 Inclusion Criteria

Our study included patients with confirmed cerebral stroke admitted to king Fahd hospital, Al-Madina Al-Munowara, KSA. Non stroke patients included diagnosis other than stroke. Both stroke and non stroke patients were without chronic respiratory disease.

2.3. Exclusion Criteria

Patients with a history of bronchial asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease, malignancy, and severe cerebrovascular disease were excluded from this study. Chronic lung diseases were not involved in this study because of the need to screen impaired lung function in participants without respiratory disease for the presence of subclinical atherosclerosis evidenced by elevated cIMT.

2.4 Study Design

All cerebral stroke and non stroke patients were assessed by careful history taking and clinical examination including age; sex; smoking habits; preexisting stroke, preexisting coronary heart disease, associated co morbidity (diabetes mellitus, hypertension and dyslipidemia). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters [17], and routine laboratory blood investigations were done. Pulmonary function testing by computerized spirometry with a Sensor medics Vmax 229 (Sensor medics, Yonda Linda,CA, USA) series flow-sensitive spirometer for all cases to measure FEV_1, FVC, FEV_1/FVC%, PEF, and MVV. Arterial blood gases were performed to measure pH, $PaO_{2,}$ $PaCO_{2,}$ O_2 Saturation, and HCO_3. Carotid ultrasonography was performed to measure carotid intima-media thickness (cIMT) using a high-resolution B-mode ultrasound system (ATL HDI 3500) with a 7.5 MHz linear transducer. The measurements were conducted on the far wall of the right and left common carotid arteries, 1.5 cm proximal to the bifurcation in the transverse plane and then longitudinally at a point free of plaques. The greater value of the right and left common cIMT were used for analysis [18]. The distance from the common carotid artery lumen–intima interface and the media–adventia interface measures 0.6–0.7 mm in healthy middle-age adults [19]. The pack-year smoking index was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.

Number of pack-years = (packs smoked per day) × (years as a smoker) [20]

2.5 Statistical Analysis

Analysis, using SPSS version 16 was performed with respect to the main study aim. The t test was used to show the significant difference between the continuous variable and Chi square test for the categorical variables. $P \leq 0.05$ was considered statistically significant. Odds ratio (OR) and confidence interval (CI) was used to test the risk of studied variable in association with cerebrovascular stroke. Multivariable linear regression was done to detect the association of carotid intima medial thickness as a dependent variable with the following independent variables: age, BMI and lung function parameters (pH, PaO_2, PCO_2, SPO_2, HCO_3, FVC, FEV_1, FEV_1/FVC%, PEFR, and MVV). Multivariable regression analysis was conducted to evaluate the independent association of cIMT and variables listed above. A P value of 0.05 was the significance criterion for covariates.

3. RESULTS

3.1 General Characteristics of Study Patients

This study was conducted on 50 stroke patients with a mean age of 50.4 ±8.37 years, and 200 non stroke patients with a mean age of 44.62 ± 9.78 years. 54% of stroke patients were males while 46 % were females with no statistical difference. The males constituted 55.5% among non stroke patients and females constituted 44.5%. The percentage of non smokers, mild , moderate and heavy smokers among patients with stroke were 24%, 16%, 38% and 22% respectively while among non stroke patients were 20.5%, 30%, 35% and 14.5% respectively with no statistical difference. There were high statistical significant decrease in pH, $EFV_1/FVC\%$, and PEF, and high statistical significant increase in $PaCO_2$, HCO_3, and cIMT in stroke patients compared to non stroke patients (Table 1).

Table 1. Characteristics of the studied cerebral stroke and non stroke patients

Variable	Stroke patients No=50	Non stroke patients No=200	P value
Age (years)	50.40 ± 8.37	44.62 ± 9.78	0.18
Sex			
Male	27 (54%)	111 (55.5%)	
Female	23 (46%)	89 (45.5%)	0.84
Smoking			
Non smoker	12(24%)	41(20.5%)	
Mild smoker	8(16%)	60(30%)	0.20
Moderate smoker	19(38%)	70(35%)	
Heavy smoker	11(22%)	29(14.5%)	
Body mass index (kg/m^2)	28.36 ± 3.78	26.64 ± 3.83	0.33
pH	7.37± 0.013	7.39 ± 0.02	0.00*
PaO_2 (mmHg)	85.10 ±.4.61	85.24±.4.77	0.99
$PaCO_2$ (mmHg)	47.48 ± 1.89	44.46 ± 2.84	0.00*
$SPO_{2\ \%}$	92.02 ± 2.25	94.80 ± 2.13	0.39
HCO_3 MIEq/L	27.70 ± 1.58	25.51 ± 2.19	0.00*
cIMT (mm)	1.96 ± 0.66	1.07 ± 0.41	0.00*
FVC (% of predicted)	88.48 ± 2.14	93.37 ± 2.07	0.45
FEV_1 (% of predicted)	90.48 ± 2.39	92.20 ± 1.91	0.59
FEV_1/FVC(% of predicted)	90.04 ± 2.38	94.61 ± 1.40	0.00*
PEF (% of predicted)	89.88 ± 1.66	92.06 ± 0.95	0.00*
MVV (% of predicted)	89.52 ± 2.21	90.60 ± 1.56	0.11

**significant difference; PaO2 (partial pressure of oxygen), PaCO2 (partial pressure of carbon dioxide), SPO2 % (arterial oxygen saturation %), HCO3 (bicarbonate), cIMT (carotid intima-media thickness), FVC (forced vital capacity), FEV1 (forced expiratory volume in the first second), FEV1/FVC% (forced expiratory volume in the first second/ forced vital capacity%), PEF (peak expiratory flow), MVV (maximum voluntary ventilation)*

Table 2. The association of cerebral stroke with the studied variables

Variables	Stroke patients No=50	Non stroke patients No=200	OR	95% CI
Sex				
Female	23	89	**1.00**	**Ref.**
Male	27	111	0.94	0.050-1.75
Smoking				
Nonsmoker	12	41	1.00	**Ref.**
Mild smoker	8	60	0.44	0.19-1.00
Moderate smoker	19	70	1.13	0.60-2.16
Heavy smoker	11	29	1.66	0.76-3.61
Carotid intima media thickness				
Normal	3	38	**1,00**	**Ref.**
Elevated	47	162	3.67	1.06-12.44*
Associated co morbidity				
No	24	122	**1.00**	**Ref.**
Diabetes mellitus	9	26	1.75	0.76-2.03
Hypertension	7	22	1.61	0.93-1.54
Dyslipaedemia	10	30	1.69	0.83-1.8

**Risk factor*

3.2 The Association of Cerebral Stroke with the Studied Variables

The risk for the cerebral stroke was higher among patients with elevated cIMT than those with normal cIMT among the studied variables (O.R. 3.67 with CI 1.06-12.44), while sex, smoking and associated co morbidity showed no significant risk for stroke (Table 2).

3.3 Age Adjusted Relations of Carotid Intima Media Thickness and Studied Covariates

The relations between cIMT (the only risk factor for stroke) as a dependent variable and the other variables as independent variables. The correlation was positive with age (Coefficient and standard error were 0.014 and 0.003) and FEV_1 (0.06 and 0.02) and was negative with PaO_2 (-0.022 and 0.006), FVC (-0.086 and 0.019), FEV_1/FVC% (-0.079 and 0.018), MVV (0.053) i.e. reduced FVC, FEV_1/FVC%, MVV, and $PaO_2$was associated with elevated cIMT (Table 3).

Table 3. Age adjusted relations of carotid intima media thickness and studied covariates

Variable	Coefficient (SE) * (No=250)	P
Constant	10.084 (8.347)	0.22
Age	0.014 (0.003)	0.00
Body mass index	0.013 (0.007)	0.06
pH	0.032 (1.100)	0.97
PaO_2	-0.022(0.006)	0.00
$PaCO_2$	0.012 (0.015)	0.41
SPO_2%	0.004 (0.013)	0.72
HCO_3	0.010 (0.019)	0.59
FVC	-0.086 (0.019)	0.00
FEV_1	0.061 (0.021)	0.00
FEV_1/FVC%	-0.079 (0.018)	0.00
PEF	0.050 (0.029)	0.08
MVV	-0.053 (0.019)	0.00

PaO2 (partial pressure of oxygen), $PaCO_2$ (partial pressure of carbon dioxide), SPO_2 % (arterial oxygen saturation %), HCO_3 (bicarbonate), FVC (forced vital capacity), FEV_1 (forced expiratory volume in the first second), FEV_1/FVC% (forced expiratory volume in the first second/ forced vital capacity%), PEF (peak expiratory flow), MVV (maximum voluntary ventilation)

3.4 Stepwise Multivariate Adjusted Relationships of Studied Co Varieties with Carotid Intima Media Thickness

All studied variables were entered in the stepwise multivariate regression analysis model. The criteria of regression model were FEV_1/FVC%, Age, PaO_2, FVC, $FEV_1$and MVV while the other variables (BMI, pH, $PaCO_2$, SPO_2, PEFR, and MVV) were excluded from the model. The model itself excludes these variables as it was insignificant. The cIMT was directly proportional to age and $FEV_{1,}$ and inversely proportional to FEV_1/FVC%, $PaO_{2,}$ FVC and MVV in models 4, 5 and 6 (Table 4).

4. DISCUSSION

Impaired pulmonary function has been demonstrated to be a significant predictor of non-fatal ischemic heart disease, and of cardiovascular disease mortality. Limited studies have analyzed the relation between pulmonary function and risk of fatal or non-fatal stroke [3]. Numerous studies have reported an association between reduced lung function and higher risk of coronary heart disease and cerebral stroke [8-10]. Our study revealed that the risk for cerebral stroke was higher among patients with elevated cIMT than those with normal cIMT (O.R 3.67 with CI 1.06-12.44). This is in accordance to Jain et al, 2012 [21] who reported a statistical significant increase in the intima-media thickness of CCA in patients with CT evidence of ischemic stroke. Chien et al, 2008 [22] reported similar findings in their study in Chinese adults and demonstrated a significant association between incidence of stroke and cIMT. Our study showed high statistical significant decrease in pH, FEV_1/FVC%, and PEF, and high statistical significant increase in $PaCO_2$, HCO_3, and cIMT in stroke patients compared to non stroke patients. Gulsvik et al, 2012 [23] found an association between baseline FEV1 (L) and fatal stroke was observed; HR=1.38 (95% CI 1.11 to 1.71) and HR=1.62 (95% CI 1.22 to 2.15) for men and women, respectively (adjusted for age and height). For male survivors with a valid FEV1 at follow-up (1988–1990) (n=953), baseline FEV1 (L) indicated a possible strong and independent association to the risk of fatal stroke after adjustments for individual changes in FEV1 (ml/year) (HR 1.95 (95% CI 0.98 to 3.86) [23]. Ezeugwu et al, 2013 [24] in their study found that the stroke survivor compared with the control group, had significant lower values for FEV_1 (1.99 ± 0.66 vs. 2.36 ± 0.45 L, p = 0.004), FVC (2.55 ± 0.70 vs. 2.90 ± 0.54 L, p = 0.014), PEF (3.88 ± 1.38 vs. 5.24 ± 1.30 L/ second (-1), p = 0.001). An inverse relation between pulmonary function expressed as (FVC, FEV_1/FVC%, and MVV) and cIMT has been shown in our study i.e. reduced FVC, FEV_1/FVC%; MVV was associated with elevated cIMT. This is in accordance to the results of Zhimin et al, 2013 [18] who showed reduced lung function, measured by FVC (% pred) and FEV1 (% predicted) was accompanied by raised cIMT in a middle-aged people without chronic lung diseases. karakas et al, 2013 [25] found that in patients with COPD, the mean CIMT values had a significant negative correlation with FEV1/FVC ratio and FEV1 measurement (both $P < 0.001$). Linear regression analysis revealed FEV1/FVC ratio and FEV1 measurement as an independent predictor of the mean CIMT values. Also, FEV_1 was inversely correlated with cIMT in smokers and community population as shown by Schroeder et al, 2005 [26]. Truelsen et al 2001 [3] demonstrated in adjusted analysis for age and sex an inverse relation between FEV_1 and risk of first-time stroke. The risk increased constantly with decreasing FEV_1, especially in females, whereas in males there was a reduction in the risk among those with the lowest pulmonary function. But no statistically significant differences between men and women. An inverse relation between arterial blood gases expressed as PaO_2 and cIMT has been shown in the present study i.e. lower $PaO_2$was associated with increased cIMT. But, no correlations between other parameters of arterial blood gases (PH, $PaCO_2$, O_2 Saturation, and Hco_3) and cIMT. Up to our knowledge, no available literatures concerning the changes in PaO_2 and its correlation with cIMT. Results of the stepwise multivariable regression model demonstrated that cIMT was directly proportional to age and $FEV_1$and inversely proportional to

Table 4. Stepwise multivariate adjusted relationships of studied co varieties with carotid intima media thickness

Model	Variable	Coefficient (SE)* (No=250)	Beta	P
1	Constant	13.687 (1.191)		.000
	FEV_1/FVC%	-0.133 (0.013)	-0.553	.000
2	Constant	10.558 (1.166)		.000
	FEV_1/FVC%	-0.110 (0.012)	-0.458	.000
	Age	0.022 (0.003)	0.362	.000
3	Constant	13.534 (1.414)		.000
	FEV_1/FVC%	-0.117 (0.012)	-0.486	.000
	Age	0.016 (0.003)	0.260	.000
	PaO_2	0.024 (0.007)	-0.194	.000
4	Constant	13.901 (1.398)		000
	FEV_1/FVC%	-0.084(0.016)	-0.348	000
	Age	0.016 (0.003)	0.270	000
	PaO_2	-0.022 (0.007)	-0.179	000
	FVC	-0.040 (0.014)	-0.192	000
5	Constant	10.684 (1.536)		000
	FEV_1/FVC%	-0.080 (0.016)	-0.334	000
	Age	0.014 (0.003)	0.238	000
	PaO_2	-0.023 (0.006)	-0.185	000
	FVC	-0.092 (0.018)	-0.443	000
	FEV_1	0.086 (0.020)	0.309	000
6	Constant	13.804 (2.084)		000
	FEV_1/FVC%	-0.073 (0.016)	-0.302	000
	Age	0.014 (0.003)	0.236	000
	PaO_2	-.024 (0.006)	-0.195	000
	FVC	-0.088 (0.018)	-0.427	000
	FEV_1	0.076 (0.020)	0.273	000
	MVV	-0.035 (0.016)	-0.104	000

* *Coefficients represent changes in carotid intima media thickness for an increase in the value of the predictor variables shown (1-SD) increase for the continuous predictor variables)*

PaO2 (partial pressure of oxygen), FVC (forced vital capacity), FEV1 (forced expiratory volume in the first second), FEV1/FVC% (forced expiratory volume in the first second/ forced vital capacity%, MVV (maximum voluntary ventilation)

FEV_1/FVC%, PaO_2, FVC and MVV in models 4, 5 and 6. A specific relation between pulmonary function and stroke has reported in limited researches. An inverse association has been reported in all the studies that have done [2,4,21,27,28,29] and the association was found independent of smoking and other potential risk factors for stroke in some studies [4,22,28]. The relationship was found non significant after adjustment for potential confounders in other researches [2,29 and 30].

5. LIMITATIONS

Firstly, the relative limited number of the studied patients Secondly, the non stroke patients who have lower respiratory function and PaO_2 need more time for the follow-up to detect those who developed cerebral stroke and confirm a specific relationship.

6. CONCLUSION

In conclusion the risk for cerebral stroke was higher among patients with elevated cIMT. Reduced FVC, FEV_1/FVC%, MVV, and PaO_2 were associated with elevated cIMT. Stroke patients had reduced FEV1/FVC%, PEF, and pH than non stroke patients. These results suggest the requirement to perform pulmonary function and arterial blood gases in people without respiratory disease to screen those with impaired lung function for the presence of subclinical atherosclerosis to prevent the risk for cerebral stroke.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this paper and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by Taibah University College of Medicine Research Ethics Committee (TUCM REC) organized and operated according to the Saudi national regulation of the national bioethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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