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Comparative effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on pulmonary function in hypertensive patients

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Abstract

Objectives: Hypertension is a very common cardiovascular disease. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) are widely used to treat hypertension. Many patients with hypertension are vulnerable to the antihypertensive adverse effects, which potentially reduces the adherence rate. Therefore, we conducted this study in order to evaluate the safety profile of both classes (ACEi and ARBs) on respiratory functions.

Methods: Two main groups of subjects were studied: first group is healthy control subjects and the second group is hypertensive patients, which was subdivided into subgroups in order to investigate the effect of all tested medications (captopril, enalapril, lisinopril, losartan, and valsartan). Respiratory efficiency was evaluated by measuring pulmonary function tests: FEV1, FVC, and FEV1%. Measurements were done using micromedical spirometer.

Results: We found that ARBs do not impair normal respiratory functions as measured by FEV1, FEV1%, and FVC in hypertensive patients. While ACEi treatments significantly reduced FEV1, FEV1%, and FVC compared to the other groups.

Conclusions: ARBs are not associated with any harmful effects on respiratory functions in hypertensive patients, unlike ACEi. As such, they could represent a first-choice treatment for hypertensive patients who are at high risk to the respiratory adverse effects.

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Introduction

Hypertension (HT) is a major cause of morbidity and mortality globally, albeit with reduced hospitalization rates over last years [1]. It has been shown that almost one billion persons are diagnosed with HT [2]. Many medications have been developed in order to control blood pressure, which proved their efficacy in a large percent of patients. However, most of these medications could cause unwanted adverse effects, resulting in a decreased tolerability. One of the most serious side effects that has been noticed with multiple classes of antihypertensive drugs is the restricted pulmonary function, which could substantially limit using these medications [3].

Blood pressure is controlled by various physiological processes mediated by endogenously produced chemicals. Angiotensin II (Ang II), an active endogenous compound, is one of these biochemical mediators. Ang II increases blood pressure via inducing muscle contraction surrounding our blood vessels. Small molecule inhibitors, such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs), have been synthesized to antagonize the vasoconstrictive effects of Ang II. ACEi act through blocking the conversion of inactive precursor angiotensin I (Ang I) to Ang II. ACE is a relatively nonspecific enzyme that modulates the metabolism of other substrates, other than angiotensin, such as bradykinin and tachykinins [4]. Therefore, these substrates are accumulated with ACEi, inducing dry cough and reducing respiratory functions of the lungs [5]. Captopril is the first member in ACEi group that was introduced to the markets. It is a very effective therapeutic agent for HT, heart failure, and myocardial infarction (MI). However, using captopril and other ACEi, such as enalapril and lisinopril, is associated with high incidence of undesired effects, which potentially reduces the tolerability to this class of drugs. As mentioned previously, side effects such as dry cough,

angioedema, and reduced respiratory functions are common with these medications [5].

ARBs exert their effect through blocking Ang II receptors type 1, thus preventing Ang II from binding to its receptors. This class has been developed to overcome side effects related to ACEi such as dry cough and/or angioedema since they do not interfere with Ang II production (no breakdown for kinins) [6]. It is likely that ARBs are protective against other adverse effects induced by ACEi, especially the respiratory ones [7]. ARBs, such as valsartan and Losartan, are used to treat hypertension, heart failure, and MI. Similar to ACEi, their pharmacological actions include vasodilatations and decreasing blood pressure and stress on the heart [8]. Losartan may be more beneficial for patients with diabetic nephropathy and those with high stroke risk. While, valsartan may be highly useful for individuals who have heart failure or previous heart attack [9]. As mentioned earlier, using these agents is not associated with serious side effects such as dry cough and angioedema, unlike ACEi. It remains unclear whether these agents (ARBs) could interfere with lung functions. Therefore, we conducted this study in order to evaluate the safety profile of both classes on the respiratory function.

Materials and methods

Lung function tests comprise a variety of evaluations that inspect the lungs effort. Spirometry is a simple test; this test detects the total of air the lungs can hold and force needed for emptying the air from the lungs. Spirometry evaluates the incorporated pulmonary, respiratory muscle and chest wall mechanical activity, through assessing the air exhaled total volume after a full lung, total lung capacity (TLC) to residual volume (RV) or maximal expiration, the forced vital capacity (FVC), and the first second forced expiratory volume forceful exhalation p (FEV1).

Patients

This is a comparative study conducted in Basra Teaching Hospital, Basra City, south of Iraq, for the period between January 2019 and November 2019. The total number of patients was 241. Study included two main groups of subjects of both sexes: The first group (Control) is 51 (12 females +39 males) apparently healthy volunteers at age range 46–68 years. Many criteria were determined such as, no smoking, free of respiratory diseases such as chronic obstructive pulmonary diseases (COPD) or restrictive pulmonary diseases or any other diseases that may affect pulmonary function tests. The second group is 190 (63 females +127 males) hypertensive patients, at age range 48–66 years who used an antihypertensive medication for more than one year. This group is further subdivided into five subgroups according to the type of antihypertensive drugs. The first subgroup consists of 61 hypertensive patients treated with lisinopril. The second subgroup consists of 55 hypertensive patients treated with captopril. The third subgroup consists of 55 hypertensive patients treated with enalapril. The fourth subgroup consists of 12 hypertensive patients treated with valsartan. Finally, the fifth subgroup consists of seven hypertensive patients treated with losartan. Scientific and ethical committees in the College of pharmacy, Basrah University, approved this study. The purpose of the study was explained to all participants and asked them to sign a written consent before enrollment.

Demographic details and required information such as health status, smoking, gender, duration of disease and drug taken were recorded for the patients by questionnaire. All participates in this study were apparently healthy without any anatomical or clinical disorders that may affect respiratory system function.

Exclusion criteria

- Subjects with history of bronchial asthma, chronic obstructive airway disease, tuberculosis, and known cardiac and respiratory diseases.
- Subjects with history of smoking, alcohol, severe chest trauma, obvious chest, and spinal deformity.
- Subjects who were chronically ill.
- Subjects on medications for long duration.
- Subjects with a history of any major surgery (cardiac, pulmonary, abdominal) related to study.
- Subjects undergoing any physical conditioning program.
- Subjects with a history of active sports training.
- Subjects with a history of hypertension, diabetes mellitus.
- Subjects suffering from arthritic disorders, skeletal deformities, or neuromuscular abnormalities.

Methods

Measurement of pulmonary function tests was done by using Micro Medical Spirometer (MIR Spirolab III Diagnostic Spirometer, Ltd., England). The measurement was performed by a single specialist physician to test patients in a sitting position. This test was done by applying the mouthpiece tightly with nose clip to prevent any leak. It is important to emphasize on that full inspiration is followed by a rapid and continuous exhalation until the procedure is stopped. In fact, spirometry depends on the cooperation of the patients, therefore, the test for each subject is repeated three times to record the best one. All measurements of pulmonary function tests and volumes were done before 12:00 pm. Parameters that were measured included FVC (forced vital capacity), FEV1(forced expiratory volume at the first second of expiration) and FEV% (Percentage of FEV1). Our procedures were done according to the American Thoracic Society guidelines

Statistical analysis

Statistical analysis was carried out using Statistical Package of the Social Sciences (SPSS) Statistical Software for Windows, Version 24.0 IBM (SPSS Inc., IL, USA). Data are represented as means value ± standard deviation (SD). Independent student-test and one way a nova was used to compare between the mean values of the two measurements. Results are considered significant at $p<0.05$.

Results

ACEi are very effective antihypertensive medications; however, they could cause serious side effects such as dry cough and reduced lung functions due to the accumulation of bradykinin [4]. On the other hand, ARBs are equally, if no more, effective antihypertensive compared to ACEi with a safer side effect profile [6]. Little scientific evidence exists that discusses the safety of ACEi and ARBs on lung functions in hypertensive patients. Therefore, we conducted this work to study the effects of ACEi and ARBs on respiratory functions. Demographics of patients enrolled in the study (age, sex, height, and weight) are summarized in Table 1. First, we measured blood pressure in the groups of treatments and did not find any remarkable differences among these groups (Supplementary Table 1). To assess pulmonary functions, we used spirometry and examined FEV, FVC, and FEV1% in both healthy individuals and hypertensive patients (Table 2). Then, we examined subgroups of treatments and found that lisinopril, captopril, and enalapril significantly reduce FEV1 (2.3 ± 0.6), (1.7 ± 0.6), and (1.8 ± 0.6), respectively, in comparison to the control group (3.4 ± 1.1). While we did not notice any significant changes in FEV1 values with losartan (3.2 ± 0.3) and valsartan (3.2 ± 0.3) compared to controls (Table 3 and Figure 1). In addition, we measured FVC in all groups of treatments. We found that ACEi in this study cause significant reduction in FVC values in comparison to controls (3.3 ± 1). FVC values of lisinopril, captopril, and enalapril were (2.8 ± 0.5), (2 ± 0.6), and (2.1 ± 0.8), respectively (Table 3 and Figure 2). On the contrary, ARBs did not cause any significant differences in FVC values from controls (Table 3 and Figure 2). The data of FVC of losartan and valsartan were (3.9 ± 0.3) and (3.9 ± 0.2), respectively (Table 3 and Figure 2). In addition to FEV1 and FVC, we examined FEV1% in the groups of treatments. We observed that ACEi and ARBs antihypertensive medications did not result in any remarkable changes in FEV1% from controls (87 ± 6) (Table 3 and Figure 3). FEV1% of lisinopril, captopril, enalapril, losartan, and valsartan were (82.8 ± 11.3), (78.4 ± 13.2), (83.6 ± 8.7), (83.1 ± 4.7), (82.2 ± 7.2), respectively (Table 3 and Figure 3). Taken together, these results suggest that ARBs do not exhibit harmful effects on normal respiratory functions in hypertensive patients, unlike ACEi, which profoundly impair the pulmonary functions. ARBs are much safer than ACEi regarding respiratory adverse effects and could represent a first-choice treatment for hypertensive patients who are more susceptible to these adverse effects.

Discussion

Hypertension is a major cause of morbidity and mortality around the world. Various antihypertensive medications have been developed to treat HT, but, unfortunately, many of these antihypertensives are associated with serious side effects such as worsening respiratory functions. ACEi, widely used antihypertensives, could induce such side effects since they are not specific drugs and increase bradykinin accumulation. On the contrary, ARBs are less likely associated with respiratory side effects since they are more specific antagonists than ACEi and do not enhance bradykinin accumulation. Therefore, we conducted this study to evaluate the safety of these classes on respiratory functions in hypertensive patients. We found that ACEi have a significant potential to decline normal physiological functions of the lungs, an effect never seen with ARBs. These findings represent a leading cause for the preference of using ARBs than ACEi in clinical practice especially in high risk patients (e.g. asthma, COPD patients, and patients with pneumonia).

Research indicates that there is a decrease in pulmonary function parameters in hypertensive patients, as

Table 1: Demographics of patients enrolled in study.

Groups	Number (♀+♂)	Weigh, kg (Mean ± SD)	Height, cm (Mean ± SD)	Age, years (Mean ± SD)
1-Healthy control group	51 (12♀+39♂)	79.6 ± 11.3	172.1 ± 10.4	51.8 ± 5.0
2-Hypertensive patients' group:	190 (63♀+127♂)	76.1 ± 7.7	170.2 ± 6.9	57.7 ± 5.6
Lisinopril	61 (20♀+41♂)	77.4 ± 6.5	171.7 ± 6.8	55.5 ± 5.1
Captopril	55 (13♀+42♂)	78.7 ± 2.9	170.1 ± 5.1	57.5 ± 5.5
Enalapril	55 (10♀+45♂)	75.1 ± 10.1	167.1 ± 9.1	57.4 ± 5.8
Valsartan	12 (3♀+9♂)	76.7 ± 7.6	169.9 ± 8.2	57.4 ± 6.7
Losartan	7 (7♂)	75.4 ± 16.9	170.2 ± 11.3	60.5 ± 5.1
p-Value		*0.05<	*0.05<	*0.05<

*p is considered statistically significant at level <0.05.

Table 2: Comparison of FEV1, FVC, and FEV1% between healthy controls and hypertensive patients' group.

	Healthy control group (n=51)	Hypertensive patients' group (n=190)	p-Value
FEV1	3.5 ± 1.2	2.5 ± 0.4**	0.0032
FVC	3.3 ± 1	2.9 ± 0.4**	0.0076
FEV1%	87 ± 6	81.749 ± 8.4*	0.012

*p is considered statistically significant at level<0.05. **p is considered statistically significant at level<0.01.

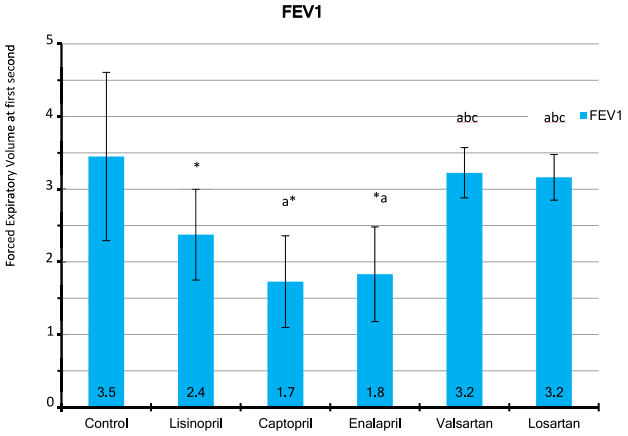

Figure 1: The effect of different treatments on FEV1. This figure shows that FEV1 is significantly reduced with lisinopril, captopril, and enalapril treatments in comparison with the control. While there is no noticeable difference with valsartan and losartan, suggesting no interference with lung function. FEV1, forced expiratory volume in 1 s *p significant (p<0.05) compared to control value, a significant (p<0.05) compared to lisinopril's value, b significant (p<0.05) compared to captopril's value, c significant (p<0.05) compared to enalapril's value.

evidenced by low FVC and FEV1 [10]. The pathophysiology is probably related to an interstitial edema of the lungs secondary to left ventricular failure, which is induced by a high sustained blood pressure and decreased elasticity of pulmonary parenchyma [1, 11]. In this work, we noted that pulmonary functions are dramatically declined in patients with hypertension in comparison to healthy controls (Table 2), which is in agreement with the above authors observations. Additionally, we did not see any effects for age on pulmonary functions of the tested groups. Ang II plays a vital role in vasomotor tone regulation and homeostasis of sodium and water. It has been described that promotion of renin and Ang II plasma concentrations is reported during acute severe attacks in asthmatic patients [12]. Ang II in subthreshold levels in mild to moderate asthmatic patients enhances bronchial sensitivity to methacholine, a bronchoconstrictive mediator. These effects are important underlying causes of reduced normal physiological functions of the respiratory system. Because ACEi block only one enzyme responsible for the production of Ang II [13], ARBs have the advantage of more complete inhibition of Ang II actions. Therefore, it is highly possible that the declined respiratory functions (FEV1 and FVC) that we observed in this study with ACEi (lisinopril, captopril, and enalapril; Table 3) are due to a partial reduction in Ang II levels. On the other hand, ARBs that were investigated in this study (losartan and valsartan; Table 3) have a superior safety profile regarding respiratory functions due to the complete blockage of Ang II effects [8].

Table 3: Comparison of FEV1, FVC and FEV1% among the healthy control group and subgroups of treatments: lisinopril, captopril, enalapril, losartan and valsartan.

Group	FEV1 (mean ± SD)	FVC (mean ± SD)	FEV1% (mean ± SD)
Healthy control	3.5 ± 1.2	3.3 ± 1	87 ± 6
Lisinopril	2.4 ± 0.6*	2.8 ± 0.5*	82.8 ± 11.3*
Captopril	1.7 ± 0.6*, a	2 ± 0.6*, a	78.4 ± 13.2*, a
Enalapril	1.8 ± 0.7*, a	2.1 ± 0.8*, a	83.6 ± 8.7*, b
Losartan	3.2 ± 0.3a, b, c	3.9 ± 0.3a, b, c	83.1 ± 4.7*
Valsartan	3.2 ± 0.3a, b, c	3.9 ± 0.2a, b, c	82.2 ± 7.2*
p-Values	<0.0001	<0.0001	0.001

*p significant (p<0.05) compared to control value. aSignificant (p<0.05) compared to lisinopril's value, bSignificant (p<0.05) compared to captopril's value, cSignificant (p<0.05) compared to enalapril's value.

ACEi could cause several adverse events in hypertensive patients. One of the most common side effects with these therapeutic agents is the persistent dry cough, which occurs in up to 20 percent of patients. This cough results from a type of respiratory activity called an "asthma equivalent", meaning that activity inside respiratory passages mimics the effects of asthma [3, 14]. Reports show that use of enalapril, captopril and lisinopril for HT or heart failure induces bronchospasm [15]. It is known that decrease FEV1 may reflect a drop in the lung's maximum inflation, weakness of respiratory muscle, and airways obstruction. Airway obstruction is a frequent cause of reduction in FEV1 [16]. Even though adverse reactions to ACEi are not common in people with asthma, they still have been noticed [17]. For these reasons, ACEi are not usually regarded as first-line antihypertensives in asthmatic patients; Nevertheless, they may still be prescribed as long as they are carefully monitored. Here, we found that ACEi induce significant reduction in pulmonary functions (FEV1 and FVC; Figures 1 and 2), but no change in these

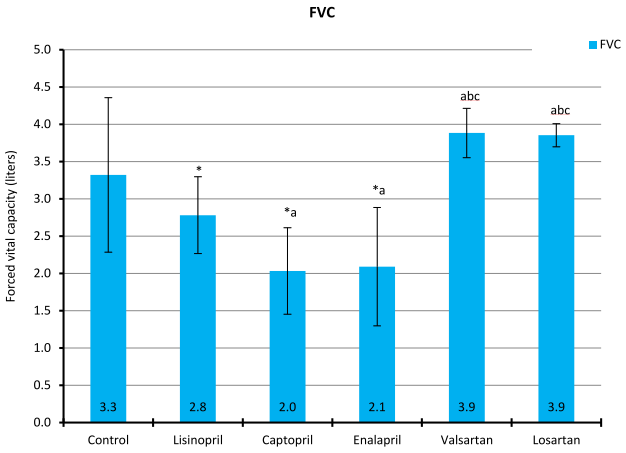

Figure 2: The effect of different treatments on FVC. This figure shows that there is a significant reduction in FVC with lisinopril, captopril, and enalapril treatments in comparison with the control. While valsartan and losartan treatment are not associated with any observable change in FVC, suggesting no interference with lung function. FVC, forced vital capacity. *p significant ($p<0.05$) compared to control value, a significant ($p<0.05$) compared to lisinopril's value, b significant ($p<0.05$) compared to captopril's value, c significant ($p<0.05$) compared to enalapril's value.

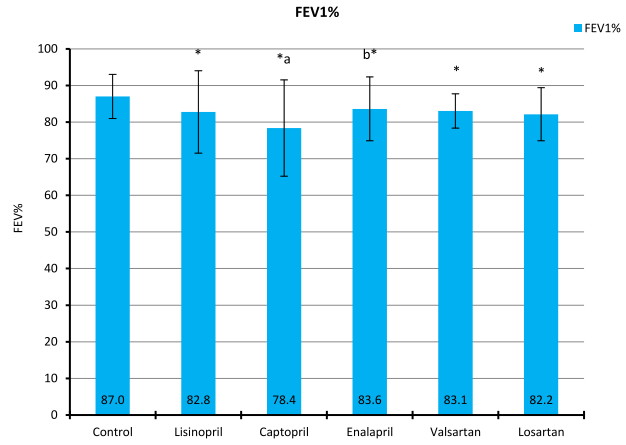

Figure 3: The effect of different treatments on FEV1%. This figure shows that FEV1% is not changed by a significant manner with any of the treatments that have been examined in this study. FEV1%, percentage of the forced vital capacity. *p significant ($p<0.05$) compared to control value, a significant ($p<0.05$) compared to lisinopril's value, b significant ($p<0.05$) compared to captopril's value, c significant ($p<0.05$) compared to enalapril's value.

parameters with ARBs (Figures 1 and 2). It is important to explore mechanistics of these findings, which needs further investigation.

In conclusion, ACEi and ARBs are cornerstones in the treatment of hypertension. However, safety profile of each class is crucial to consider during using these medications. Decline in normal respiratory functions could hugely influence on choosing one class over another. Here, we found that ACEi have a remarkable potential to worsening respiratory functions of the lungs, an effect never noticed with ARBs. Our finding is an early evidence demonstrates this decline in lung functions with ACEi and complete protection by ARBs, which is vital to take into consideration in clinical practice.

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Ethical approval: Scientific and ethical committees in the College of pharmacy, Basrah University approved this study.

References

1. Birhan MM, Abebe Y. Pulmonary function tests in hypertensive patients attending Zewditu Memorial Hospital, Addis Ababa, Ethiopia. Int J Hypertens 2018;2018:5492680.
2. Schnabel E, Karrasch S, Schulz H, Glaser S, Meisinger C, Heier M, et al. High blood pressure, antihypertensive medication and lung function in a general adult population. Respir Res 2011;12:50.
3. Schnabel E, Nowak D, Brasche S, Wichmann HE, Heinrich J. Association between lung function, hypertension and blood pressure medication. Respir Med 2011;105:727–33.
4. Tom B, Dendorfer A, de Vries R, Saxena PR, Jan Danser AH. Bradykinin potentiation by ACE inhibitors: a matter of metabolism. Br J Pharmacol 2002;137:276–84.
5. Packard KA, Wurdeman RL, Arouni AJ. ACE inhibitor-induced bronchial reactivity in patients with respiratory dysfunction. Ann Pharmacother 2002;36:1058–67.
6. Abdi R, Dong VM, Lee CJ, Ntoso KA. Angiotensin II receptor blocker-associated angioedema: on the heels of ACE inhibitor angioedema. Pharmacotherapy 2002;22:1173–5.
7. Ong HT, Ong LM, Ho JJ. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) in patients at high risk of cardiovascular events: a meta-analysis of 10 randomised placebo-controlled trials. ISRN Cardiol 2013;2013:478597.
8. Elliott WJ, Calhoun DA, DeLucca PT, Gazdick LP, Kerns DE, Zeldin RK. Losartan versus valsartan in the treatment of patients with mild to moderate essential hypertension: data from a multicenter, randomized, double-blind, 12-week trial. Clin Therapeut 2001;23:1166–79.
9. Hedner T, Oparil S, Rasmussen K, Rapelli A, Gatlin M, Kobi P, et al. A comparison of the angiotensin II antagonists valsartan and losartan in the treatment of essential hypertension. Am J Hypertens 1999;12:414–7.

10. Schnabel E, Karrasch S, Schulz H, Gläser S, Meisinger C, Heier M, et al. High blood pressure, antihypertensive medication and lung function in a general adult population. Respir Res 2011;12:50.
11. Kanazawa H, Hirata K, Yoshikawa J. Imbalance between vascular endothelial growth factor and endostatin in emphysema. Eur Respir J 2003;22:609–12.
12. Kanazawa H, Hirata K, Yoshikawa J. Effects of captopril administration on pulmonary haemodynamics and tissue oxygenation during exercise in ACE gene subtypes in patients with COPD: a preliminary study. Thorax 2003;58:629–31.
13. Williams B. Drug discovery in renin-angiotensin system intervention: past and future. Ther Adv Cardiovasc Dis 2016;10: 118–25.
14. Kanazawa H, Hirata K, Yoshikawa J. Influence of oxygen administration on pulmonary haemodynamics and tissue oxygenation during exercise in COPD patients with different ACE genotypes. Clin Physiol Funct Imag 2003;23:332–6.
15. Pinargote P, Guillen D, Guarderas JC. ACE inhibitors: upper respiratory symptoms. BMJ Case Rep 2014;2014.
16. Bhatt SP, Soler X, Wang X, Murray S, Anzueto AR, Beaty TH, et al. Association between functional small airway disease and FEV1 decline in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2016;194:178–84.
17. Bhatt SP, Terry NL, Nath H, Zach JA, Tschirren J, Bolding MS, et al. Association between expiratory central airway collapse and respiratory outcomes among smokers. J Am Med Assoc 2016;315: 498–505.

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