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Pulmonary function correlates with arterial stiffness in asthmatic patients

Zeev Weiler [a,*], Yuri zeldin [b], Eli Magen [c], Doron Zamir [c], Mona I. Kidon [d,]**

[a] *Pulmonary Unit, Barzilai Medical Center, Ashkelon 78306, Israel Affiliated to the faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheba*
[b] *Allergy and Immunology Unit, Barzilai Medical Center, Ashkelon, Israel*
[c] *Internal Medicine Ward B, Barzilai Medical Center, Ashkelon, Israel*
[d] *Allergy and Immunology Unit, Chaim-Sheba Medical Center, Tel-Hashomer, Israel*

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Summary
Background: At the population level, asthma has been associated with chronic systemic inflammation as well as adverse cardiovascular outcomes.
Objectives: The aim of this study was to investigate peripheral vascular hemodynamic variables of arterial stiffness (AS) and their relationship to pulmonary function tests in asthmatic patients.
Methods: Young asthmatic patients from the tertiary center for pulmonary diseases at the Barzilai Medical Center underwent pulmonary function evaluation and non-invasive radial artery hemodynamic profiling, pre- and post-exercise. Results were compared to age matched, non-asthmatic controls.
Results: 23 young asthmatics and 41 controls, completed all evaluation points. Pulmonary flow parameters were significantly reduced in the asthma group at all points. There were no differences between groups in BMI, blood pressure, pulse rate or measurements of AS at baseline or after bronchodilation. The % predicted forced expiratory volume in the first second at baseline (FEV1%) in asthmatics was positively correlated with the small arteries elasticity index (SAEI) and negatively correlated with the systemic vascular resistance (SVR) in these patients. These correlations were not observed in non-asthmatic controls. In multifactorial regression FEV1 remained the major factor associated with measurements of AS in asthmatic patients, while gender was the only significant factor in non-asthmatic controls.

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; CET, estimated cardiac ejection time; ECI, estimated cardiac index; ECO, estimated cardiac output; ECT, exercise challenge tests; ESV, estimated stroke volume; ESVI, estimated stroke volume index; FEV1, forced expiratory volume in the first second; FEV1%, % predicted forced expiratory volume in the first second; LAEI, large artery elasticity index; MAP, mean arterial BP; Mch, methacholine; MCTs, methacholine challenge tests; PFTs, pulmonary function tests; PP, pulse pressure; PR, pulse rate; SAEI, small artery elasticity index; SBP, systolic blood pressure; SVR, systemic vascular resistance; TVI, total vascular impedance.

* Corresponding author. Tel./fax: +972 86745473.
** Corresponding author. Tel./fax: +972 39412038.
E-mail addresses: weil@barzi.health.gov.il (Z. Weiler), drkidon@yahoo.com (M.I. Kidon).

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Conclusions: Significant correlations between measurements of AS and FEV1 in young asthmatics, suggest the presence of a common systemic, most likely inflammatory pathway involving both the cardiovascular and respiratory systems.

Background

Bronchial asthma is a chronic inflammatory disease characterized by airway inflammation and bronchial hyper responsiveness together with recurrent bouts of cough, wheezing, shortness of breath, chest tightness and reversible airways obstruction.[1] The systemic nature of the chronic inflammation in asthma was emphasized recently by studies, showing an increased risk of asthma associated with the higher percentiles of C-reactive protein (CRP) in serum,[2–5] correlation between severe asthma and highly sensitive CRP,[6] high serum levels of tumor necrosis factor-alpha and interleukin-8 in severe asthma,[7] multiple markers of chronic systemic inflammation associated with asthma and the risk of atherogenesis[8] and positive epidemiological associations of asthma with the risk for myocardial infarction and stroke in some populations.[9–11]

Chronic inflammation has also been increasingly associated with atherosclerosis[12] endothelial dysfunction[13] and arterial stiffness (AS)[14] and these in turn with adverse cardiovascular events[15] and common inflammatory pathways.[16,17]

Measurements of peripheral arterial stiffness (AS) correlate well with atherosclerotic cardiovascular disease (ASCVD) and adverse cardiovascular outcomes.[18–22] Non-invasive techniques measuring arterial stiffness and vascular resistance of large and small vessels are increasingly used as surrogate markers for early atherosclerosis and the risk of cardiovascular events.[19,23,24]

Previous studies[25,26] have shown that mean aortic pulse wave velocity as well as inflammatory markers and augmentation index, were significantly greater in COPD patients compared to healthy control subjects. The authors concluded that the increased arterial stiffness is related to the severity of the airflow obstruction in COPD. Similar data however have not been published in asthmatic patients.

Pulmonary function tests obtained by spirometry are the golden standard for the diagnosis and evaluation of asthma and loss of pulmonary function constitutes a major hallmark of the progression of asthma in adults.[1]

In view of the above we aimed to investigate the correlations of peripheral vascular hemodynamic variables (arterial stiffness) and pulmonary function tests in asthmatic patients.

Material and methods

Study subjects

Otherwise healthy, young stable asthmatic patients, less than 40 years of age, from the tertiary center for pulmonary diseases at the Barzilai medical center were offered the extensive evaluation as part of a routine follow-up. Patients were excluded if they had sustained an acute asthma exacerbation requiring oral steroids and/or unscheduled emergency room visit and/or hospitalization during the 3 months preceding their visit. Additional exclusion criteria included smoking of more than 1 pack a day. The study was approved by the hospital's internal review board and all patients signed a written informed consent. None of our patients had any history of cardiovascular or other significant chronic disease other than bronchial asthma. Patients underwent pulmonary function evaluation and non-invasive radial hemodynamic profiling, pre- and post-exercise testing and 15 min after an inhaled bronchodilator. In our case control study design, each individual patient in the study group was age and sex matched to 2 non-asthmatic controls. Allergic testing was not performed as part of the routine evaluation of the study or control groups.

Pulmonary function tests (PFT)

Pulmonary function tests were performed using a JAEGER MasterLab Spirometer by an experienced technician and according to the published ATS criteria[27] and in comparison to Knudson's predicted values.[28] After having undergone an initial pre- and post-bronchodilator pulmonary function tests (PFTs), all study as well as control group patients underwent arterial compliance measurements at baseline, after a standardized exercise test and again 15 min after an inhaled bronchodilator.

Exercise challenge test

Exercise challenge tests (ECTs), were performed on a treadmill to 85% of predicted maximum heart rate for 6—8 min and PFTs performed before and after exercise at 5 min intervals for 15 min according to ATS published guidelines.[29] A decrease of 12 percent in FEV1 in comparison to baseline FEV1 was considered a positive test.

Methacholine test

The methacholine (Mch) bronchoprovocation challenge test was performed using a series of Mch chloride solutions ranging from the most dilute concentration of 0.06 mg/ml of Mch, to a concentration of 16 mg/ml at two-fold incremental concentration intervals.[29]

The diluted doses were administered by nebulizer and after each concentration inhalation of the aerosol, the FEV1 was measured at 1, 3, 5 and 10 min. The inhalation of increasing Mch concentrations continued until a 20 percent drop in FEV1 was observed or until the maximal concentration was inhaled (16 mg/ml). The dose which provoked a 20 percent drop in FEV1 was referred to as the PC20. The

Mch provocation test was considered positive, if the PC20 was achieved with a concentration of 8 mg/ml Mch or less or if PC20 was reached at a maximal dose of 16 mg/ml where the physical findings or clinical story were significant.

Asthma diagnosis

A diagnosis of asthma was made according to GINA asthma diagnosis guidelines (Global Initiative for Asthma, Global Strategy for Asthma Diagnosis and Prevention, Global Initiative for Asthma, 2004). All study group patients had established stable asthma according to clinical criteria and proven reversibility of FEV1 on PFTs and/or positive exercise challenge test, and/or a positive methacholine challenge test while in the control group, exclusion of asthma diagnosis was based on negativity of the same pulmonary functions and challenge tests.

Arterial stiffness measurement

Arterial stiffness/compliance measurements were performed in a quiet, temperature controlled laboratory. The patients had been fasting for at least 3 h and none had consumed caffeine containing beverages or alcohol.

Radial artery waveforms were recorded for 30 s for each subject in the supine position just before, immediately after exercise testing as well as 15 min after 2 puffs of an inhaled beta-agonist bronchodilator. The pressure transducer amplifier system was connected to a specially designed device (Model CR-2000, Hypertension diagnostics, Inc, Eagen, MN). The passive transient response of the arterial vasculature to the initial loading conditions was determined by analyzing the diastolic portion of the pressure pulse waveform. This technique which has been used and described extensively,[21] was used with the simple non-invasive radial pulse wave recording and a computer analysis of the diastolic decay. This provided separate assessment of the large artery (capacitive or conduit) compliance (C1) and small artery (reflective or oscillatory) compliance (C2). Both artery types were measured because studies have demonstrated an age-dependent decline in both C1 and C2 parameters, reflecting structural or functional changes in the large conduit arteries, as well as in the smaller reflective sites.

Systemic vascular resistance (SVR) was calculated as the mean arterial pressure (MAP) divided by cardiac output. The MAP was derived from waveform analysis, integrating the area under the curve and calculating the mean area of recording during 30 s.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD) and were analyzed by the ANOVA test or paired *t* test. Spearman non-parametric correlation analysis was chosen to estimate correlations between FEV1% and measures of arterial stiffness/compliance, because of the relatively small number of measurements. A *p*-value <0.05 was considered statistically significant. Multivariate regression analysis with the forward conditional model was used to elicit factors of significance for the various measurements of arterial stiffness. All statistical tests were performed using the SPSS 15.0 software for Windows, SPSS Inc., Chicago, USA.

Results

64 patients from the outpatient pulmonary clinic of the Barzilai Medical Center in Ashkelon, were included in the study. 23 (15 males and 8 females) with established stable asthma, served as the study group while 41 patients (22 males and 19 females) in whom asthma diagnosis was excluded by both pulmonary function and provocation tests, some served as a control group (Table 1) The mean age range of the study group was 23 years with a mean body mass index (BMI) of 22 while the control's group mean age and BMI were 24 and 23 respectively. There were no statistically significant differences in the reported smoking history, however the non-asthmatic smokers reported mildly heavier use.

All study group patients had established stable asthma according to clinical criteria and proven reversibility of FEV1 on PFTs and/or positive exercise challenge test, and/or a positive methacholine challenge test while in the control group, exclusion of asthma diagnosis was based on negativity of the same pulmonary functions or challenge tests. At the time of initial study evaluation 14 (61%) of asthmatics were using short acting beta-agonists (SABA) compared to 10 (24%) among controls, however none had used their SABA medications at least 6 h before tests were administered. 9 asthma patients (39%) were using inhaled corticosteroids at a dose of less than 400 mcg of Budesonide (or equivalent) per day compared to 3 (7%) among controls, and 2 (9%), were on a leukotriene receptor antagonists (Montelukast) compared to none among the control group.

At all measured points, pulmonary function tests as reflected by the mean % predicted FEV1 (FEV1%) were significantly reduced when compared to age matched non-asthmatic controls $-$ 77.9% vs 99.7%, $p < 0.001$ at baseline, 67% vs 98.6%, $p < 0.001$ after the exercise test and 83.2% vs 99.9%, $p < 0.001$, after bronchodilators (Table 1).

There were no differences in blood pressure, pulse rate or measurements of small or large vessel elasticity/stiffness between asthmatics and non-asthmatic controls at baseline (Table 1).

A good correlation was observed between the FEV1% in asthmatic patients at rest (baseline) and the estimated cardiac output (ECO) at rest (Spearman correlation coefficient rho $= 0.678$, $p < 0.001$), as well as the small arteries elasticity index (SAEI) at rest (rho $= 0.418$, $p < 0.05$), Fig. 1. Conversely a negative correlation was observed between baseline FEV1% and the systemic vascular resistance (SVR) as well as the total vascular impedance (TVI) at rest, (Spearman correlation coefficients rho $= -0.429$, $p < 0.05$ and rho $= -0.489$, $p < 0.05$ respectively), Fig. 2.

Baseline % predicted FEV1 (FEV1%) in our asthmatic patients correlated well with systolic blood pressure (spearman correlation coefficients rho $= 0.560$, $p < 0.005$), mean arterial blood pressure (spearman correlation coefficients rho $= 0.419$, $p < 0.05$), pulse pressure (spearman correlation coefficients rho $= 0.549$, $p < 0.01$), and pulse rate (spearman correlation coefficients rho $= 0.484$,

Table 1 Clinical characteristics of asthmatic patients and non-asthmatic controls.

	Asthma ($n = 23$)	Controls ($n = 41$)	p
Age mean (range)	23 (18–37)	24 (19–39)	NS
BMI mean (range)	22 (17–28)	23 (18–30)	NS
Smokers (%)	38%	38%	NS
Use of anti-inflammatory meds[a]	35%	0%	<0.001
FEV1% baseline	77.9% (52.3–106)	99.7% (79.3–115.7)	<0.001
FEV1% post ECT	67% (42.9–94.1)	98.6% (77.6–123.2)	<0.001
FEV1% postBD	83.2% (63.6–106.6)	99.9% (82.5–130.7)	<0.001
sBP at baseline mmHg mean (95% CI)	114.6 (110.9–118.2)	114.9 (111.6–118.2)	NS
dBP at baseline mmHg mean (95% CI)	61.7 (58.5–64.8)	64.7 (61.5–67.8)	NS
PP at baseline mmHg mean (95% CI)	52.9 (50.5–55.4)	53.4 (50.0–56.8)	NS
PR at baseline beats/min mean (95% CI)	68.4 (64.6–72.1)	68.3 (65.4–71.3)	NS
LAEI mean (95% CI)	14.4 (12.8–16.0)	15.3 (14.0–16.5)	NS
SAEI mean (95% CI)	7.4 (6.6–8.2)	7.0 (6.3–7.6)	NS

NS – not significant, FEV1% – percent of predicted forced expiratory volume in the 1st second, ECT – exercise challenge test, BD – bronchodilator, sBP – systolic blood pressure, dBP – diastolic blood pressure, PP – pulse pressure, PR – pulse rate, LAEI – large arteries elasticity index, SAEI – small arteries elasticity index.

[a] At a dose of less than 400 mcg budesonide (or equivalent) or less than 250 mcg fluticasone or equivalent or Montelukast at a dose of 10 mg per day.

$p < 0.05$), measured after exercise (as detailed in text) and again after rescue bronchodilation (similar correlation coefficients and significance values).

FEV1% after bronchodilator (postBD) rescue also correlated positively with postBD SAEI in asthmatic patients, (spearman correlation coefficients rho = 0.434, $p < 0.05$), Fig. 3.

In the control group, no correlation was seen between measurements of pulmonary function and arterial stiffness/compliance at any time point.

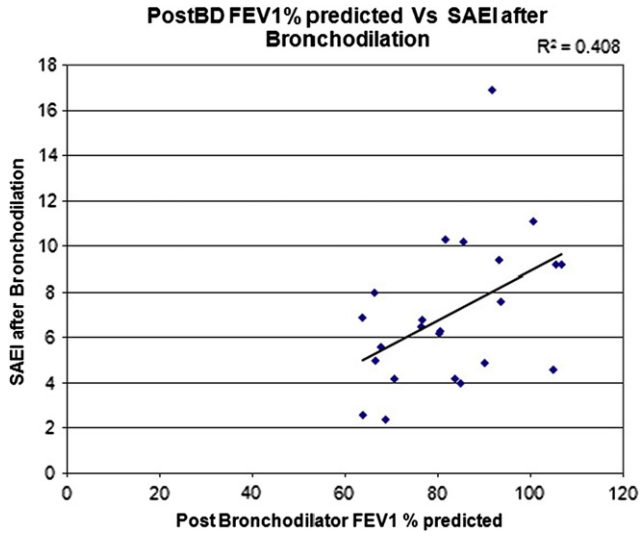

Figure 1 FEV1% at baseline correlates positively with small arteries elasticity index in asthmatic patients. SAEI – small arteries elasticity index, FEV1% – forced expiratory volume in the first second. Expressed as a percentage of the predicted FEV1 for gender, height and age, R – spearman coefficient (rho), p – level of significance.

In multivariate linear regression analysis, evaluating the impact of gender, BMI. Smoking status and baseline FEV1% are elements of large and small vessel elasticity, only gender, but not smoking status or FEV1% was a significant factor in the measurements of small arteries elasticity index (SAEI) at rest in non-asthmatic controls.

In asthmatic patients on the other hand, the same multivariate analysis showed that only FEV1% remained positively correlated with the small arteries elasticity index at rest (rho = 0.401, $p < 0.05$) and after rescue bronchodilation (rho = 0.455, $p < 0.05$).

Discussion

Since our goal was to reveal a possible correlation between asthma as a chronic inflammatory airway disease and early-on vascular changes, we based the study on a young population of otherwise healthy patients, less than 40 years of age, in whom the risk of significant atherosclerotic cardiovascular disease was very low.

All patients included in the study, subjects as well as controls were referred to the pulmonary unit because of clinical chest complaints, for whom also received bronchodilator and anti-inflammatory medication such as inhaled corticosteroids or leukotriene antagonists. Following an extensive evaluation including, pulmonary functions, exercise and pharmacological challenge testing, subject patients had a confirmed diagnosis of asthma according to accepted ATS criteria, while control patients tested negative to all the above mentioned tests. Nevertheless some of the control patients at recruitment were taking anti-asthmatic medication as detailed in the Results section.

Our study shows a positive correlation between peripheral arterial stiffness measurements and the degree of airway limitation in young asthmatic patients. This is

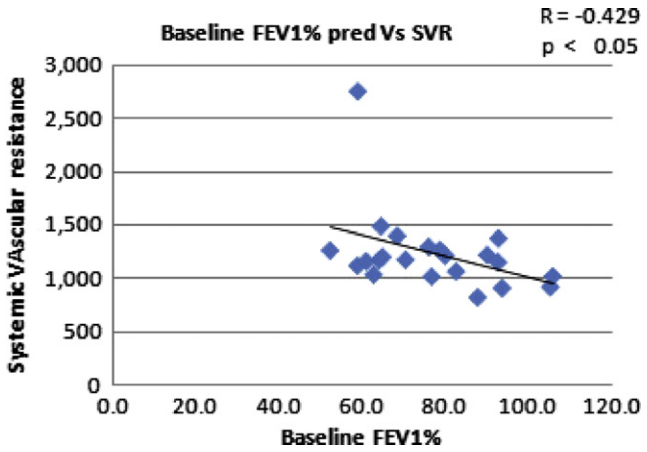

Figure 2 FEV1% at baseline correlates negatively with systemic vascular resistance in asthmatic patients. SVR — systemic vascular resistance, FEV1% — forced expiratory volume in the first second. Expressed as a percentage of the predicted FEV1 for gender, height and age, *R* — spearman coefficient (rho), *p* — level of significance.

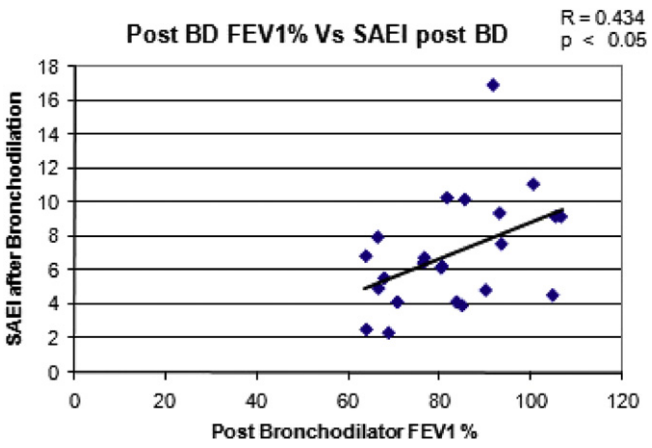

Figure 3 FEV1% after bronchodilator (postBD) rescue correlates positively with postBD SAEI in asthmatic patients. SAEI — small arteries elasticity index (measured after rescue bronchodilation), FEV1% — forced expiratory volume in the first second. Expressed as a percentage of the predicted FEV1 for gender, height and age (measured after rescue bronchodilation), *R* — spearman coefficient (rho), *p* — level of significance.

strongly suggested by a significant correlation between baseline FEV1% values and ECO, SVR and TVI in asthmatics but not in controls, and significant correlations between % predicted FEV1 and mostly small arteries stiffness at baseline and postBD again in asthmatics but not in controls.

FEV1% at rest and after response to bronchodilation are a generally accepted surrogate marker of asthma severity. In prospective studies in young children, FEV1 at rest and post-bronchodilator FEV1 were reduced in children with severe atopic asthma and correlated well with asthma severity, and airway inflammation.[30] The correlation of baseline FEV1% with indexes of arterial stiffness/compliance observed in our study in patients with asthma but not in non-asthmatic controls suggests that a common inflammatory pathway at work in the asthmatic airways of individual patients, is associated with chronic changes in the systemic cardiovascular system. This finding may be part of the underlying mechanism linking longstanding asthma and asthma severity with increased risk of CVS adverse outcomes, myocardial infarction and/or strokes.[9,10,31,32]

Another readily available explanation may be that common mechanisms in the pathway of endothelial changes/arterial stiffness development and asthma development may be at work in asthmatic individuals. This was demonstrated in our study by the positive correlation between baseline (resting) as well as post exercise FEV1 and SAEI as well as LAEI. Such pathways may involve smooth muscle reactivity[33] and proliferation[34] or alternatively genetic changes in leukotriene production pathways and function. Yet another possibility is that the use of certain drugs such as beta-agonists may be the link between asthma and adverse CVS outcomes.[35,36] However, most of our patients (61%) received short acting bronchodilators (SABAs) as did 24% of controls, and all patients as well as controls had not used this medication at least 6 h before testing, therefore our data does not support beta-agonists as an immediate explanation for the differences observed between groups.

Whatever the molecular basis of this correlation, it confirms at the individual level the population derived data of increased risk of atherosclerotic cardiovascular disease in patients with asthma and proposes that these risks may be commensurate with the degree of airflow limitation as measured by FEV1% in pulmonary function testing. The systemic inflammation theory is strengthened by research showing a decreased risk of ASCVD and death in asthmatic patients taking anti-inflammatory medications.[37–39] Although the correlation found between FEV1 and measures of peripheral arterial stiffness in asthmatics is striking, the absolute hemodynamic measurements in this young healthy population were not significantly different from non-asthmatic controls. This finding is diametrically opposed to the findings of Sabit and Boussuges in COPD patients,[25,26] most likely secondary to our choosing of young, otherwise healthy patients, lacking significant cardiovascular disease for this study.

In the past few years increasing awareness of the limitation of preventative therapy has changed our therapeutic approach in mild and moderate asthmatics towards symptoms oriented therapy, whereby control of untoward symptoms is the primary outcome. This change has been advocated mainly because of the lack of data supporting any long-term effects of anti-inflammatory medication on the outcome of airway disease. However, our study implies that long term cardiovascular changes may also be part of the associated morbidity in asthmatics and additional data published and cited above would seem to suggest that these may indeed respond to long-term anti-inflammatory medication. If supported by larger and long-term prospective data, using peripheral arterial stiffness as an outcome of asthma follow-up and treatment, this data may change the recommended policy to one of continuous anti-inflammatory treatment similar to what is now advocated for other ASCVD risk factors such as hypertension and hypercholesterolemia.

The limitations of this study are clear. Only a relatively small number of individuals participated. We have also not shown a clear correlation with individual markers of

systemic inflammation. Previous studies looking at markers of inflammation in asthmatic patients, have used a large cross sectional population design to show increased risk of asthma in patients on the higher CRP quartiles Since the documented absolute changes were small and they represent only surrogate markers of inflammation we decided not to include these measurements in our study.

However as all cross sectional studies may be, ours is indeed able to generate a working hypothesis — and that is the systemic inflammation associated with bronchial asthma has measurable cardiovascular outcomes that ultimately may increase an individual's risk of myocardial infarction and/or stroke. A larger prospective, long-term study is needed to validate the results and answer the question of which anti-inflammatory treatment may best influence the vascular systemic changes associated with asthma.

Conclusion

The correlation between measurements of arterial compliance and pulmonary function tests in otherwise healthy young asthmatics suggests that the chronic airway inflammation characteristic of asthma may have severe additional effects in the systemic vasculature, and these may require prospective monitoring and treatment.

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