Dilated Left Atrium and Pulmonary Veins in Patients with Calcified Coronary Artery: A Potential Contributor to the Genesis of Atrial Fibrillation

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Ischemic Remodeling of Left Atrium and Pulmonary Vein. ***Introduction:*** **Coronary artery disease (CAD) is an important etiology of atrial fibrillation (AF). Coronary artery calcification is a marker of coronary atherosclerosis and coronary events. The purpose of this study was to investigate whether larger left atrium (LA) and pulmonary veins (PVs) were seen by multidetector computed tomography (MDCT) scans in those patients with higher coronary calcium scores.**

Methods and Results: **A total of 166 patients undergoing MDCT for general check-up (n = 128, 77%) or suspected CAD (n = 38, 23%) were enrolled and divided into a control (calcium score = 0, n = 60), medium calcium score (calcium score = 100∼400, n = 47), and high calcium score (calcium score >400, n = 59) groups. Diameters and areas of the LA, left atrial appendage (LAA), and PVs were measured by MDCT. The high calcium score group had significantly larger PVs diameters, LAA orifice area (1.9 ± 1.4 cm^2, 0.9 ± 0.5 cm^2, 0.8 ± 0.4 cm^2, P < 0.005), LA anterior-posterior distance (32.2 ± 6.8 mm, 30.4 ± 6.5 mm, 27.3 ± 6.0 mm, P < 0.05), and transverse distance (52.6 ± 7.3 mm, 50.2 ± 9 mm, 49.5 ± 4.6 mm, P < 0.05) than the medium calcium score and control groups. Six (3.6%) patients with paroxysmal AF had higher calcium scores and larger diameters of LA, LAA, and PVs than those (96.4%) without paroxysmal AF. Two patients in the high calcium score group had calcified PVs localized to the right upper and left upper PVs. The incidence of calcified PVs was 1.2% for the total patients and 3.3% for the high calcium score patients.**

Conclusion: **In the presence of high calcium scores in this patient population, the LA, LAA, and PVs were enlarged.** *(J Cardiovasc Electrophysiol, Vol. 20, pp. 153-158, February 2009)*

coronary artery calcification, atrial fibrillation, pulmonary vein

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia observed in clinical practice and induces cardiac dysfunction and strokes.[1,2] Myocardial ischemia is an important risk factor of AF.[3,4] Coronary artery disease (CAD) can induce myocardial dysfunction with an increase of ventricular filling pressure, which is closely reflected by enlarged left atrium (LA).[5,6] Atrial myocardial perfusion abnormalities may have a role in AF.[7] Moreover, the elevated ventricular filling pressure may increase atrial remodeling and stretch, which may further produce electrical changes with the enhancement of the inhomogeneity of the atrial conduction and refractoriness.[8,9] Those findings suggest that myocardial ischemia can induce electrical and structural remodeling of AF substrate, which can facilitate AF maintenance. Pulmonary veins (PVs) are the main sources of ectopic beats with the initiation of paroxysmal AF or foci of ectopic atrial tachycardia and focal AF.[10] However, limited information has been available on the effects of myocardial ischemia on the structural changes in the PVs. Since stretched PV may enhance the arrhythmogenesis and induce more AF,[11,12] it should be very important to study the relationship between CAD and PV structures. In addition, it is not clear whether the PVs could also become calcified as is found in coronary arteries.

Calcified coronary arteries are a marker of coronary atherosclerosis and are associated with a higher incidence of coronary events.[13,14] A previous study has shown that high coronary calcium score patients have an increased left ventricular (LV) wall thickness and LV diastolic dysfunction in African-Americans.[15] Because myocardial dysfunction can alter the atrial structure, a highly calcified coronary artery may produce an abnormal atrial and PV structure that could facilitate AF genesis. Multidetector computed tomography (MDCT) provides better and reliable imaging of smaller cardiac structures such as vascular structures and

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coronary calcification.[16-19] A previous study has also shown that MDCT provided accurate and detailed imaging of the LA and PVs.[20] Therefore, the purpose of this study was to investigate whether larger left atrium (AF substrate) and PVs (AF initiators) were seen by MDCT scans in those patients with higher coronary calcium scores.

Methods

Patient Selection

This study received IRB approval and enrolled 166 consecutive individuals (110 men and 56 women with a mean age of 58 ± 17 years) for 64-row scan MDCT. The patients were evaluated because of suspected CAD in 38 (23%) patients and for general checkup in 128 (77%) patients.[21,22] Six patients (3.6%) had a history of paroxysmal AF (5 patients for general checkup and 1 patient for suspected CAD), while 160 patients (96.4%) did not have paroxysmal AF. The AF was documented by 12-lead ECG or ambulatory ECG. For the reliability and accuracy of the results of the MDCT, we did not include the patients with persistent or permanent AF. All patients had sinus rhythm during the MDCT examinations. Each participant underwent a medical history, weight, height, blood pressure, and laboratory assessment. The significant coronary artery stenosis was defined as over 50% luminal obstruction by MDCT calculation.[23] We grouped the patients according to the calcium score data.[22] There were 40 patients with a zero calcium score (control group), 37 patients with a 100∼400 calcium score (medium calcium score group), and 49 patients with a >400 calcium score (high calcium score group). The patients with renal function impairment (Cr >2.0 mg/dL) were excluded.

Computed Tomography

The patients underwent a 64-row scan (LightSpeed VCT, GE Healthcare, USA) using an EKG synchronized tube modulation. The patients with a heart rate >70 bpm were given a single oral dose of propranolol (10∼40 mg) at least 40 minutes before the examination. Images were reconstructed retrospectively in the diastolic phase (at 60% of the start of the RR interval). Nonionic contrast medium was given in a test dose of 250 mL. The total calcium score was calculated as the sum of the individual lesion scores in all coronary arteries as the following formula: slice thickness × Σ (area cofactor). To avoid any interobserver variability, all CT scans were scored by an experienced radiologist that measured the calcium score.

Measurement of the Left Atrium and PV

The left inferior, left superior, right inferior, right superior PV (LI, LS, RI, RSPV) diameters were measured by the maximal transverse diameter of the four PV trunk orifices by a virtual endoscopic view. The left atrium (LA) diameters were measured by the maximal anterior-posterior distance (LA1) and maximal transverse distance (LA2). The LA1 was measured in the oblique sagittal view and LA2 was measured in the oblique coronal view from the LSPV to the RSPV. The orifice of the LA appendage (LAA) was defined as the deflection between the LAA and LA free wall. The largest diameter and area were measured in the oblique sagittal view where the LAA area was traced. The LV wall thickness was measured at septum and lateral free wall at the level of the papillary muscle in the end-diastolic phase in the four-chamber axial view.

Statistical Analysis

Continuous variables are expressed as the mean ±SD. The comparisons between the control, medium, and high calcium score groups were analyzed by a one-way ANOVA with a post hoc Tukey test. Nominal variables were compared by a Chi-square analysis with a Yates correction or Fisher's exact test. A P value less than 0.05 was considered to be statistically significant.

Results

Patient Characteristics

The age, gender distribution, incidence of hypertension, diabetes, dyslipidemia, smoking and CAD family history were similar among the three groups (Table 1). Otherwise, the CAD vessel numbers found by results of MDCT were significantly different among the three groups (Table 1).

Structural Differences among Different Calcium Score Patients

The LAA orifice was oval shaped in all subjects according to the MDCT oblique sagittal section and endoscopic view. The largest area of the LAA orifice was significantly larger in the high calcium score group than in the other two groups (Table 1 and Fig. 1). Moreover, the high calcium score group had a larger LA1 and LA2 than the zero calcium score group (Table 1 and Fig. 2). The LV anterior and posterior walls were also significantly thicker in the high calcium score group than the other two groups (Table 1 and Fig. 2).

The high calcium score group had larger LSPV, RSPV, LIPV, and RIPV diameters than the other two groups (Table 1 and Fig. 1). Compared with the zero calcium score group, the high calcium score group had an increased PV diameter by 12% for LSPV, by 19% for RSPV, by 16% for LIPV, and by 17% for RIPV. In addition, two patients were found to have calcified PVs (Fig. 3). The incidence of calcified PVs was 1.2% for the total patients and 3.3% for the high calcium score patients. The two patients with calcified PVs were older (age, 76 and 73 years) and had very high calcium scores (2,684 and 2,420) with significant three-vessel CAD. Both the two patients had diabetes, history of smoking, hypertension, dyslipidemia, and family history of CAD. In contrast, none of the patients in the control group or medium calcium score group had calcified PVs. The two patients with calcified PVs had significantly enlarged LAA (orifice area, 3.8 cm^2 and 4.6 cm^2), LA (anterior-posterior distance, 39.4 mm and 38.7 mm; transverse distance, 58.3 mm and 61.5 mm), LSPV (12.6 mm and 12.4 mm), RSPV (11.2 mm and 12.4 mm), LIPV (11.7 mm and 12.7 mm), and RIPV (12.6 mm and 12.6 mm). The LAA orifice, LA diameter, and four PV diameters were beyond the average data from the high calcium score patients. The calcified PVs were located at the right upper PV (11 mm from the orifice) and left upper PV orifices, respectively.

Moreover, as the results shown in Table 2, the patients with paroxysmal AF have higher calcium scores (3,064, 2,684,

TABLE 1
Baseline Characteristics

Calcium Score	0 (n = 60)	100∼400 (n = 47)	>400 (n = 59)	P Value
Calcium score average	0	261 ± 84*	1254 ± 599*,†	<0.001
Age	57 ± 8	59 ± 14	60 ± 13	NS
Male	38 (63.3%)	30 (63.8%)	42 (71.2%)	NS
Hypertension	38 (63.3%)	36 (76.6%)	38 (64.4%)	NS
Diabetes	8 (13.3%)	11 (23.4%)	14 (23.7%)	NS
Dyslipidemia	6 (10%)	11 (23.4%)	10 (16.9%)	NS
CAD family history	16 (26.7%)	20 (42.6%)	22 (37.3%)	NS
Smoking	35 (58.3%)	36 (76.6%)	41 (69.5%)	NS
CAD vessel number by MDCT results				
One-vessel disease	13 (21.7%)	17 (36.2%)	7 (11.9%)†	<0.05
Two-vessel disease	1 (1.7%)	7 (14.9%)*	16 (27.1%)*	<0.001
Three-vessel disease	0	7 (14.9%)*	24 (40.7%)*,†	<0.001
LA1 (mm)	27.3 ± 6	30.4 ± 6.5*	32.2 ± 6.8*	<0.001
LA2 (mm)	49.5 ± 4.6	50.2 ± 9	52.6 ± 7.3*	<0.05
LAA orifice				
Diameter (mm)	13.6 ± 0.4	13.8 ± 0.8	14 ± 1.2*	<0.05
Area (cm^2)	0.8 ± 0.4	0.9 ± 0.5	1.9 ± 1.4*,†	<0.001
LSPV (mm)	8.9 ± 1.1	9.2 ± 1.3	10 ± 1.8*,†	<0.001
RSPV (mm)	9.0 ± 1.4	9.9 ± 1.5*	10.7 ± 2.1*,†	<0.001
LIPV (mm)	9.0 ± 1.3	10 ± 1.6*	10.4 ± 2.1*,†	<0.001
RIPV (mm)	9.6 ± 1.0	10.2 ± 2.2	11.2 ± 2.6*,†	<0.001
LV wall thickness (mm)	8.3 ± 1.4	9 ± 1.5	13.8 ± 2.0*,†	<0.001

CAD = coronary artery disease; LAA = left atrial appendage; LV = left ventricle; LA1 = anterior-posterior distance; LA2 = transverse distance; LI/LS/RI/RSPV = left inferior/left superior/right inferior/right superior pulmonary vein; NS = not significant. P value = comparisons among the three groups. *P < 0.05 versus calcium score 0, †P < 0.05 versus calcium score 100∼400.

1,176, 1,104, 1,021, and 680) and larger diameters of LA, LAA, and PVs than those without paroxysmal AF.

Discussion

The genesis of AF arises from the changes in the AF substrate (atrium) and initiators (PVs). This study found that highly calcified coronary arteries were seen on MDCT scans with larger PVs and larger LA. This finding suggests a relationship of CAD with dilated LA and PVs. The increase of atrium and PV size would facilitate the genesis of atrial reentrant circuits.[24] Moreover, as compared with those without paroxysmal AF, our paroxysmal AF patients had significantly higher calcium scores with larger LA, LAA, and four PVs. However, the majority of patients who had high calcium scores did not have paroxysmal AF. Because the patients with paroxysmal AF had significantly enlarged PVs, LA, and LAA, it is possible that the PVs and LA were not dilated enough to induce AF in the high calcium score patients without paroxysmal AF. These findings also suggest a potential relationship of AF and high calcium scores. Similarly, Schwartzman *et al*. also used MDCT to find that AF patients have a larger LA and PVs than non-AF patients.[20] Since dilated LA and PVs may facilitate the occurrence of AF, the patients with high calcium scores should cautiously prevent progressively structural changes of atrium and PVs.

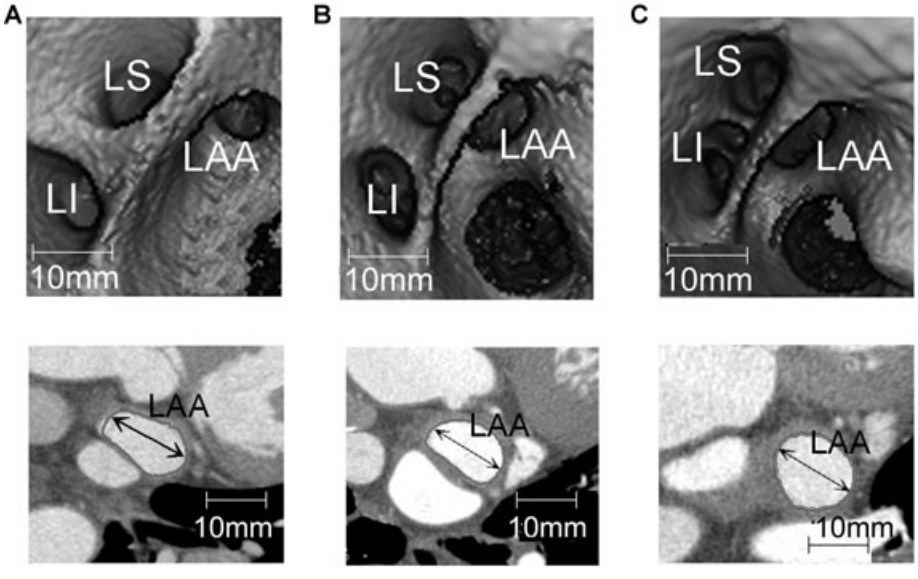

Figure 1. *Intraatrial oblique sagittal views during the multidetector computed tomography in the patients in the control (panel A), medium calcium score (panel B), and high calcium score (panel C) groups. The largest diameter (LS) of the left superior pulmonary vein and the largest diameter (LI) of left inferior pulmonary vein (LI) were measured using the virtual intraatrial view. The left atrial appendage (LAA) orifice area and diameter were measured using the oblique sagittal view. Panel A: LS = 8 mm, LI = 7.5 mm, LAA orifice diameter = 12.4 mm, and LAA orifice area = 0.83 cm^2. Panel B: LS = 9.5 mm, LI = 9.3 mm, LAA = 13.6 mm, and LAA area = 0.98 cm^2. Panel C: LS = 11 mm, LI = 11.6 mm, LAA = 15.5 mm, and LAA area = 1.9 cm^2.*

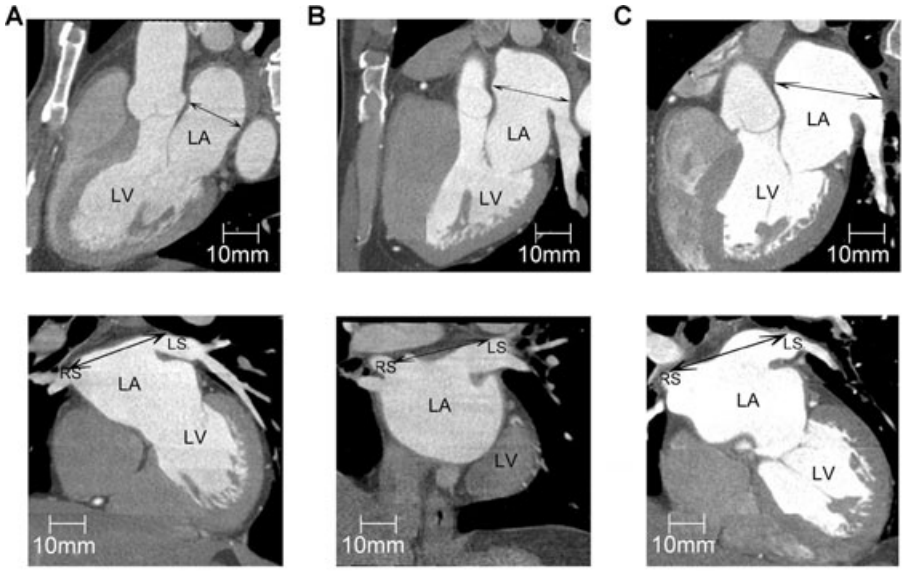

Figure 2. *Oblique sagittal view (upper panels) and oblique coronal (lower panels) view during the multidetector computed tomography in the patients in the control (panel A), medium calcium score (panel B), and high calcium score (panel C) groups. The LA1 was measured in the oblique sagittal view using the anterior-posterior largest distance; the LA2 was measured in the oblique coronal view from the left superior to right superior distance. Panel A: LA1 = 30 mm, LA2 = 47 mm. Panel B: LA1 = 33 mm, LA2 = 50 mm. Panel C: LA1 = 36 mm, LA2 = 59 mm.*

In addition to the treatment of underlying CAD and control of multiple atherosclerosis risk factors, the patients with high calcium scores may consider angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for hypertension control. Besides, these patients should receive statins for treating hypercholesteremia.[25]

Mechanoelectrical feedback has been found to play an important role in the pathophysiology of AF.[11,12] Previous studies have shown that enlarged PVs are associated with an enhanced PV arrhythmogenic activity. Through in vitro experiments, stretch was also found to increase the PV electrical activity and to induce AF.[11,12] The mechanisms may be caused by an increasing PV firing and generation of triggered activity or reentrant circuits. In this study, we have found that high calcium scores were associated with dilated PVs. Similarly, Herweg *et al*. found that hypertension and hypertensive heart disease are associated with PV dilation, which supports the role of stretch in the PV arrhythmogenesis.[26] The PV dilation could increase the PV arrhythmogenesis and provoke AF. Therefore, the association of high calcium score and

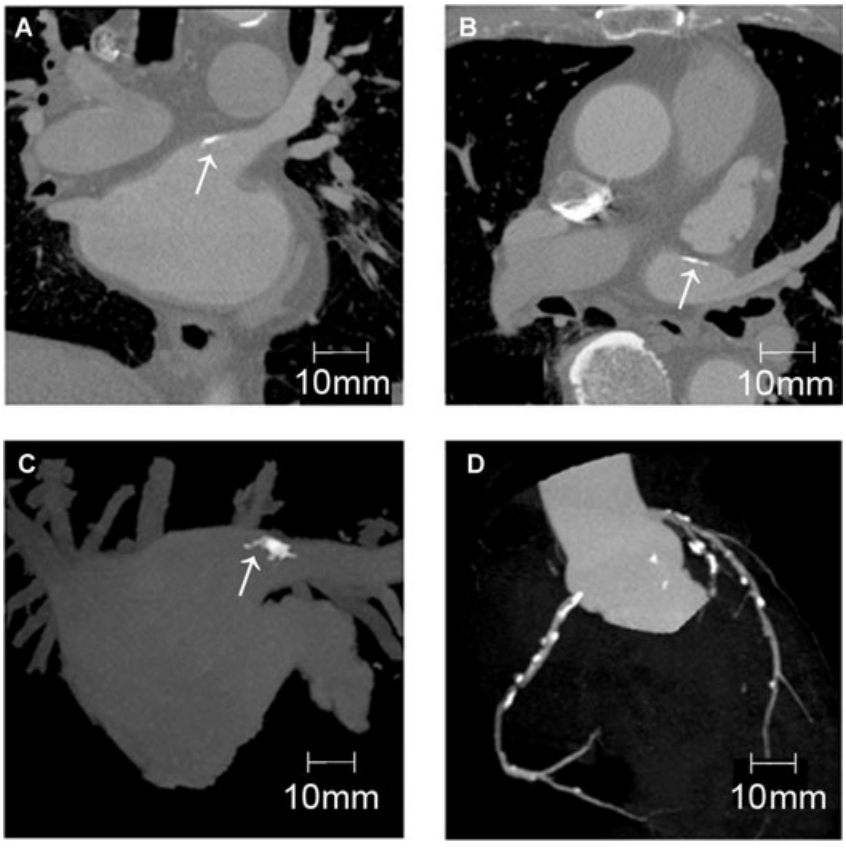

Figure 3. *Multidetector computed tomography of a calcified left superior pulmonary vein (LSPV) in a patient with a high calcium score (2684). Panel A shows that calcified lesions (↑) were found in the coronal view. Panel B shows calcified lesions in the axial view. Panel C shows calcified lesion in the angiographic view of left atrium. Panel D shows the calcified coronary artery lesions in angiographic view.*

TABLE 2

Patients and Structural Characteristics between PAF and Non-PAF Groups

	Non-PAF (n = 160)	PAF (n = 6)	P Value
Calcium score	478 ± 614	1621 ± 992	<0.001
Age	59 ± 12	68 ± 4	NS
Male	105 (66%)	5 (83%)	NS
Hypertension	106	6	NS
Diabetes	28	3	NS
Dyslipidemia	23	4	<0.005
CAD family history	54	4	NS
Smoking	107	5	NS
LA1 (mm)	30.7 ± 6.3	39.4 ± 4.4	<0.001
LA2 (mm)	50.8 ± 7.2	61.2 ± 3.7	<0.001
LAA orifice			
Diameter (mm)	13.7 ± 1.0	15.6 ± 1.3	<0.001
Area (cm^2)	1.2 ± 0.8	3.2 ± 1.0	<0.001
LSPV (mm)	9.4 ± 1.2	13.1 ± 2.6	<0.05
RSPV (mm)	9.3 ± 1.3	12.9 ± 2.7	<0.05
LIPV (mm)	9.6 ± 1.5	13.7 ± 2.6	<0.005
RIPV (mm)	9.7 ± 1.5	13.2 ± 2.9	<0.001
LV wall thickness (mm)	11.9 ± 1.5	14.2 ± 1.6	<0.05

CAD = coronary artery disease; LAA = left atrial appendage; LV = left ventricle; LA1 = anterior-posterior distance; LA2 = transverse distance; LI/LS/RI/RSPV = left inferior/left superior/right inferior/right superior pulmonary vein; NS = not significant; PAF = paroxysmal atrial fibrillation.

dilated PVs may account for the high incidence of AF in the CAD patients in part.

In this study, for the first time, we demonstrated the presence of calcified PVs in the patients with high calcium scores. Arterial calcification is a common picture in atherosclerosis found in patients with hypertension, aging, metabolic diseases, and chronic renal failure.[27,28] However, studies on venous calcification are limited. Only chronic renal failure patients have been reported in the literature to have calcified PVs, and the mechanism is not clear.[29] In our study, we found that 3.3% of the high calcium score patients had calcified upper PVs with a normal renal function. The patients with calcified PVs were older and had very high calcium scores, dyslipidemia, diabetes, hypertension, and family history of CAD. Therefore, multiple atherosclerosis risk factors seem to contribute to the occurrence of PV calcifications. Vascular calcification could impair the endothelial function with an increased susceptibility to stretch and mechanoelectrical feedback. Nevertheless, only two patients were found to have calcified PVs; thus, it is difficult to make any conclusions about why and where the calcified lesions were found by the current study. Moreover, it is not clear whether PV calcifications may have a role in the increased prevalence of AF in chronic renal failure patients.[30,31]

The data in this study should be interpreted with caution due to the limitations of this study. First, this study did not include persistent/permanent AF patients. We did not know whether chronic AF patients had higher calcium scores. However, our study has found that paroxysmal AF patients were associated with high calcium scores. Second, we did not know how many patients would develop AF and the electrophysiological correlations were not available. Thus, at best we can suggest that the presence of CAD and atherosclerosis, exemplified by higher calcium scores, relates indirectly to the structural findings previously associated with the development of AF.

Conclusion

In the presence of high calcium scores in this patient population, the LA, LAA, and PVs were significantly enlarged.

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