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Characteristics of Pulmonary Artery Pressure Waveform for Differential Diagnosis of Chronic Pulmonary Thromboembolism and Primary Pulmonary Hypertension

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Objectives. **The accurate diagnosis of chronic pulmonary thromboembolism (CPTE) is a prerequisite for life-saving surgical interventions. To help in the differential diagnosis of CPTE and primary pulmonary hypertension (PPH), we characterized the configuration of the pulmonary artery pressure waveform.**

Background. **Because CPTE predominantly involves the proximal arteries, whereas PPH involves the peripheral arteries, we hypothesized that patients with CPTE would have stiff or high resistance proximal arteries, whereas those affected by PPH would have high resistance peripheral arteries. These differences in the primary lesions would make arterial pulsatility relative to mean pressure larger in CPTE than in PPH.**

Methods. **In 34 patients with either CPTE (n = 22) or PPH (n = 12) whose pulmonary systolic pressure was ≥50 mm Hg, we measured pulmonary artery pressure using a fluid-filled system that included a balloon-tipped flow-directed catheter.**

Results. **To quantify the magnitude of pulsatility relative to mean pressure, we normalized pulse pressure by mean pressure, hereinafter referred to as *fractional pulse pressure* (PP_f). PP_f was markedly higher in CPTE than in PPH (mean [± SD] 1.41 ± 0.20 and 0.80 ± 0.18, respectively, $p < 0.001$) and was diagnostic in separating the two groups without overlap. Similarly, the coefficient of variation of pulmonary artery pressure also separated the two groups without overlap (0.45 ± 0.06 and 0.25 ± 0.06, respectively, $p < 0.001$). Fractional time to half the area under the pressure curve separated the two groups reasonably well (0.35 ± 0.02 and 0.43 ± 0.03, respectively, $p < 0.001$).**

Conclusions. **The analysis of pulsatility of pulmonary artery pressure is useful in the differential diagnosis of CPTE and PPH.**

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Differential diagnosis between chronic pulmonary thromboembolism (CPTE) and primary pulmonary hypertension (PPH) remains a clinical challenge. In particular, the correct diagnosis of CPTE is a prerequisite for life-saving surgical procedures (1). Although various diagnostic measures differentiate the two diseases (2–5), a differential diagnosis based on pulmonary artery pressure waveform configuration has not been established. Because pulmonary artery pressure is relatively easy to measure, a differential diagnosis using arterial pressure waveform configuration is extremely useful in clinical settings. Thus, the purpose of this investigation was to characterize the configuration of the pulmonary artery pressure waveform for differentiating CPTE from PPH.

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In CPTE, thrombi obstruct the proximal arteries preferentially (i.e., from the main pulmonary artery to the pulmonary segmental arteries) (6). Hence, it is conceivable that thrombi attached to the proximal arteries mechanically stiffen the arterial wall and increase proximal resistance without comparably increasing peripheral arterial resistance. In contrast, PPH primarily involves peripheral arteries with a diameter <1,000 μm. Major histologic findings include intimal thickening and fibrosis of the pulmonary arterioles, increased thickness of the media of the muscular pulmonary arteries and muscularization of the arterioles (7,8). These vascular changes, in turn, would increase arterial peripheral resistance without inducing comparable changes in stiffness or resistance of the proximal arteries. Because the increases in stiffness and resistance in the proximal arteries would increase pulse pressure (9–12), whereas those in peripheral resistance increase mean arterial pressure (9,13), we hypothesized that the pulsatility of pulmonary artery pressure relative to mean arterial pressure would be higher in CPTE than in PPH. The results of our study indicated that pulsatility was indeed significantly higher in CPTE than in PPH, indicating that pulmonary artery pressure configuration is useful in differentiating between CPTE and PPH.

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Abbreviations and Acronyms

CPTE = chronic pulmonary thromboembolism
CV = coefficient of variation
PP_f = fractional pulse pressure
PPH = primary pulmonary hypertension
$TA_{1/2}$ = fractional time to half the area under the pulmonary artery pressure curve

Methods

Study subjects. We conducted a retrospective, unblinded study of 34 patients who were admitted to the National Cardiovascular Center, Osaka, Japan because of symptomatic pulmonary hypertension (New York Heart Association functional classes II to IV) and who were subsequently diagnosed as having CPTE or PPH. The entrance criteria to the study included a pulmonary systolic pressure ≥50 mm Hg. CPTE was diagnosed when thromboembolism was positively diagnosed by means of both pulmonary angiography and radioisotope ventilation–perfusion imaging in patients with a clinical history compatible with CPTE. PPH was a diagnosis of exclusion, made when other possible etiologies of pulmonary hypertension (i.e., secondary causes), such as mitral valve diseases, congenital heart disease, left ventricular failure and CPTE, were excluded. We excluded from the PPH group patients with signs of collagen vascular disease, positive antinuclear antibodies, history of drug abuse, use of diet pills or history of liver disease. There were 22 patients with CPTE (10 men, 12 women; mean [± SD] age 52 ± 11 years, range 26 to 67) and 12 with PPH (3 men, 9 women; mean age 39 ± 13 years, range 19 to 63). The duration of the disease was not significantly different between patients with CPTE (37 ± 17 months) and those with PPH (26 ± 23 months, p = NS). Medical therapy for pulmonary hypertension included loop diuretic drugs (n = 16), digoxin (n = 14), warfarin (n = 17), calcium channel antagonists (n = 4) and beraprost sodium (oral prostaglandin I_2 derivative) (n = 12). Three of 22 patients with CPTE and 1 of 12 with PPH were taking calcium channel antagonists (p = NS). Eight of those with CPTE and 4 with PPH were taking beraprost sodium (p = NS). The protocol was in accordance with our Institutional Guidelines for Human Research, and each patient provided a written statement of informed consent for diagnostic procedures required for examination by cardiac catheterization, which stated that the results of the examination could be used for the retrospective study.

Measurement of hemodynamic variables. We measured hemodynamic variables in the supine position. Pulmonary artery pressure was measured at end-expiration during a short episode of breath-holding using a fluid-filled system that included a balloon-tipped flow-directed catheter (7F Swan-Ganz catheter) in the main pulmonary artery. A hard copy was made of the pressure tracing using a chart recorder (Nihon Koden, Surgical Monitoring System, Tokyo) at a paper speed of 100 mm/s. The waveform of instantaneous pulmonary artery pressure was subsequently digitized from the recorder tracing using an optical scanner (Epson, model 8000, Tokyo) at an effective sampling rate of 200 Hz at 12-bit resolution. We measured cardiac output taking advantage of the oxymetric principle of Fick. Because the clinical diagnosis was not performed in blinded manner by the person who analyzed the pressure tracings, there might have been some bias in the results. However, the marked differences in the pressure waveform between CPTE and PPH minimized the possibility that bias would have significance.

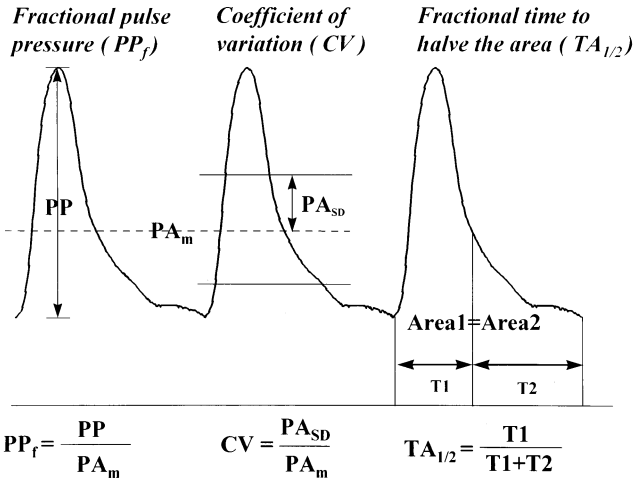

Figure 1. Schematic representation of three different indexes of pulsatility relative to mean pressure. **Left,** Fractional pulse pressure (PP_f) is the ratio of pulse pressure (PP) to mean pressure (PA_m). **Middle,** Coefficient of variation (CV) is the ratio of the standard deviation of pulmonary artery pressure (PA_{SD}) to mean pressure. **Right,** T_1 is defined as the time at which the area under the pressure curve over the T_1 period (Area1) equals the rest of the area (Area2). Fractional time to half the pressure area ($TA_{1/2}$) is the ratio of T_1 to $T_1 + T_2$.

Because CPTE predominantly involves the proximal arteries, whereas PPH involves the peripheral arteries, we hypothesized that patients with CPTE would have stiff or high resistance proximal arteries, whereas those with PPH would have high resistance peripheral arteries. These differences in the primary lesions would make arterial pulsatility relative to mean pressure larger in the case of CPTE than in PPH. To quantify this accentuated pulsatility in CPTE, we developed three indexes.

Fractional pulse pressure of pulmonary artery. As shown in Figure 1 (left), we characterized the pulsatility as the ratio of pulse pressure to mean pressure (i.e., fractional pulse pressure of the pulmonary artery [PP_f]). The larger the PP_f, the larger the pulsatility relative to mean pressure.

Coefficient of variation. As shown in Figure 1 (center), we derived the coefficient of variation (CV) of pulmonary artery pressure over a cardiac cycle. The CV represents the ratio of the variation around the mean to the mean value of pulmonary artery pressure waveform. In other words, CV is the square root of the ratio of pulsatile power to static power of pulmonary artery pressure. We calculated CV by taking the ratio of

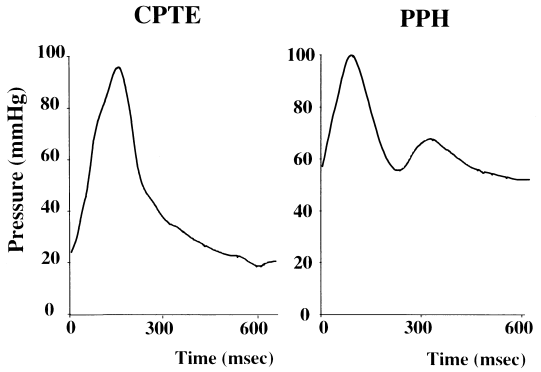

Figure 2. Representative pulmonary artery pressure tracings from a patient with CPTE (**left**) and one with PPH (**right**). Although systolic pressures are comparable between CPTE and PPH, pulse pressure is much higher in CPTE than in PPH.

the standard deviation of pulmonary artery pressure over one cardiac cycle to the mean pulmonary artery pressure. The larger the CV, the larger the pulsatility for a given mean pressure.

Fractional time to half the area under the pulmonary artery pressure curve. As shown in Figure 1 (right), we defined the fractional time ($TA_{1/2}$) to half the area under the pulmonary artery pressure curve over one cardiac cycle. The larger the area under the pulmonary pressure curve in systole (i.e., larger pulsatility [as expected of CPTE]), the shorter $TA_{1/2}$ should become. We compared the performance of these three indexes in the differential diagnosis of CPTE and PPH.

Statistical analysis. Results are expressed as mean value ± SD. Differences in the mean values between the two groups were compared by an unpaired *t* test. A p value <0.05 was considered significant.

Results

Illustrated in Figure 2 are the waveforms of pulmonary artery pressure for CPTE (left) and PPH (right). Although peak pressures are similar in the two cases, diastolic and mean pressures are lower for CPTE than in PPH. As a result, pulse pressure was higher by far in CPTE than in PPH.

Illustrated in Figure 3 are the pooled data representing pulmonary hemodynamic variables. Systolic pulmonary artery pressure was statistically significant, being only slightly lower in CPTE than in PPH (84 ± 17 and 97 ± 17 mm Hg, respectively, $p < 0.05$) (Fig. 3A). Diastolic pulmonary artery pressure was lower in CPTE than PPH (23 ± 7 and 48 ± 12 mm Hg, respectively, $p < 0.01$) (Fig. 3B). Mean pulmonary artery pressure was also significantly lower in CPTE than in PPH (43 ± 10 and 64 ± 14 mm Hg, respectively, $p < 0.01$) (Fig. 3C). Pulse pressure was significantly higher in CPTE than in PPH (61 ± 12 and 50 ± 10 mm Hg, respectively, $p < 0.05$) (Fig. 3D). Although cardiac index was not different between the two groups (2.2 ± 0.6 and 2.0 ± 0.6 liters/min per m^2, respectively, p = NS), total pulmonary resistance was significantly lower in CPTE than in PPH (11 ± 5 and 20 ± 6 U, respectively, $p < 0.01$). Despite these significant differences in pulmonary hemodynamic variables, no variable was capable of separating these two groups without significant overlap.

Illustrated in Figure 4 are comparisons of the three proposed indexes for differentiating CPTE from PPH. As shown in Figure 4 (left), PP_f was significantly higher in CPTE than in PPH (1.41 ± 0.20 and 0.80 ± 0.18, respectively, $p < 0.001$) and separated the two groups without overlap. The cutoff value to separate the two groups was 1.1. Figure 4 (center) illustrates the CV of pulmonary artery pressure. The CV was significantly higher in CPTE than in PPH (0.45 ± 0.06 and 0.25 ± 0.06, respectively, $p < 0.001$) and was also capable of separating the

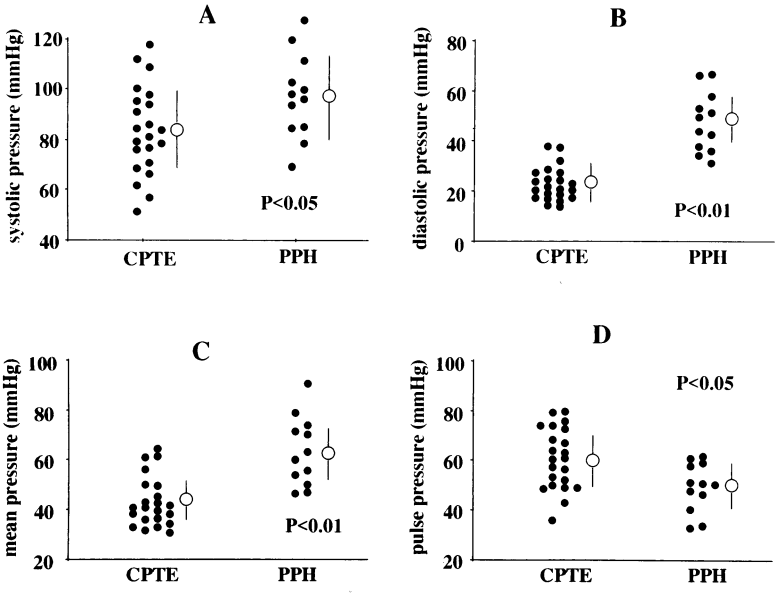

Figure 3. Pulmonary hemodynamic variables in CPTE and PPH. Systolic pulmonary artery pressure was slightly lower in CPTE than in PPH (**A**). Diastolic pulmonary artery pressure was much lower in CPTE than in PPH (**B**). Mean pulmonary artery pressure was also significantly lower in CPTE than in PPH (**C**). Pulse pressure was significantly higher in CPTE than in PPH (**D**). **Solid circles** = individual data; **open circles** = mean values; **bars** = ± SD.

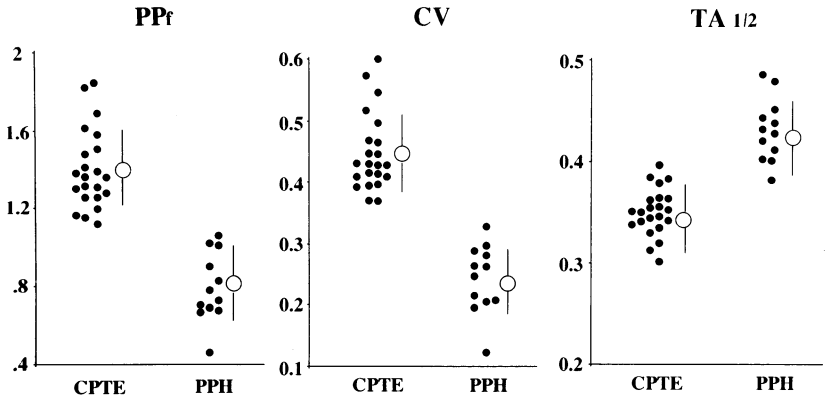

Figure 4. Comparison of pulsatility between CPTE and PPH. Fractional pulse pressure (PP_f) was significantly higher in CPTE than in PPH ($p < 0.001$) and separated the two groups without overlap (**left**). The average coefficient of variation (CV) was significantly higher in CPTE than in PPH ($p < 0.001$) (**center**) and was capable of separating the two groups without overlap. The average fractional time to half the pressure area ($TA_{1/2}$) was significantly lower in CPTE than in PPH ($p < 0.001$) (**right**). Symbols as in Figure 3.

two groups without overlap. The cutoff value to separate the two groups was 0.35. Figure 4 (right) depicts $TA_{1/2}$, which was significantly lower in CPTE than in PPH (0.35 ± 0.02 and 0.43 ± 0.03, respectively, $p < 0.001$), and separated the two groups reasonably well. Receiver operating characteristic curve analysis indicated that sensitivity of $TA_{1/2}$ to differentiate CPTE from the combined group of CPTE and PPH was 0.96, when the cutoff value was chosen as 0.385 (14). The specificity for excluding CPTE from the combined group of CPTE and PPH was 0.92. Thus, accentuated pulsatility relative to mean pressure would be useful in differentiating between CPTE and PPH. None of the three indexes (i.e., PP_f, CV and $TA_{1/2}$) significantly correlated with age in the CPTE or PPH groups.

Discussion

We have showed that although conventional variables of pulmonary artery pressure failed to differentiate between CPTE and PPH, waveform analysis focusing on pulsatility made this differentiation possible.

Clinical implications in differentially diagnosing CPTE and PPH on the basis of configuration of pulmonary artery pressure waveform. In clinical settings, the etiologic diagnosis of pulmonary hypertension remains a challenge. Noninvasive techniques, such as radioisotopic ventilation and perfusion scanning and computed tomography, have been extremely useful in the differential diagnosis of pulmonary hypertension. However, these techniques can sometimes fail to make the diagnosis, necessitating angiographic studies (15). Although pulmonary angiography is a well established technique for evaluating pulmonary artery disease, it can occasionally lead to sudden cardiovascular collapse and even death (16). Thus, there is an obvious need to develop tools to help in the etiologic diagnosis of severe pulmonary hypertension. We demonstrated in the present study that analysis of the pulmonary artery pressure waveform configuration provides useful information in differentiating between CPTE and PPH. Because measurement of pulmonary artery pressure by a balloon-tipped flow-directed catheter is relatively safe compared with pulmonary angiography, the finding that analysis of the pulmonary artery pressure waveform configuration helped to differentiate CPTE from PPH makes it an extremely attractive clinical tool.

Why do CPTE and PPH have different waveforms? In CPTE, thrombi attached to the proximal arteries narrow their lumen size and possibly stiffen the arterial wall. Narrowing the arteries would result in increased resistance of the proximal arteries. Stiffening the proximal arteries would also increase characteristic impedance of the pulmonary artery. Although characteristic impedance reflects the dynamic mechanical properties of the proximal arteries, the impedance behaves as if it were viscous resistance (17). Namely, thrombi in the proximal arteries would effectively increase proximal artery resistance through various mechanisms. Pulmonary peripheral resistance would not markedly increase because the peripheral arteries are not the site of primary lesions of CPTE. Thus, the ratio of proximal resistance to peripheral resistance would increase markedly in CPTE. This makes systolic pressure, that is, in-phase with arterial flow, high relative to mean pressure. In contrast, diastolic pressure relative to mean pressure would be low because the stiffened arteries shorten the time constant of diastolic pressure decay. Thus, large pulse pressure relative to mean pressure would be the characteristic waveform of CPTE. Various investigators (10–12,18) have attributed the widened pulse pressure to decreased arterial compliance and increased characteristic impedance in systemic arteries.

In contrast, in PPH, the peripheral arteries were narrowed. Thus, it is likely that peripheral arterial resistance would preferentially increase without comparable changes in characteristic impedance. These changes in mechanical properties would increase mean arterial pressure without comparable increases in pulse pressure. Thus, differences between the waveforms of pulmonary artery pressure in CPTE and PPH would be most manifest through a comparison of their pulsatilities.

Indexes to quantify pulmonary artery pulsatility relative to mean pressure. In this investigation, we used three indexes to quantify pulsatility. PP_f is the ratio of pulse pressure to mean pressure. Suga (19) demonstrated that a pure increase in characteristic impedance resulted in the prolongation of ejection time. This means that in CPTE, both prolongation of the ejection time and widening of the pulse pressure would take

place. Because PP_f does not take into account the prolongation of ejection time, we derived the other two indexes.

The CV of pulmonary artery pressure is defined as the ratio of the square root of pulsatile power to the static power of pulmonary artery pressure. Because prolongation of ejection time will increase the dynamic power of pulmonary artery pressure, this index is capable of quantifying both the prolongation of ejection time and the widening of pulse pressure. As we anticipated, it also separated the two groups well.

In this investigation, we used a fluid-filled pressure recording system. We anticipated that the recorded pressure would erroneously oscillate in some patients. Because both PP_f and CV would be sensitive to the oscillation, we derived $TA_{1/2}$ as an index relatively insensitive to the oscillation. It also separated the two groups reasonably well.

Although all three indexes indeed differentiated CPTE from PPH, we conjecture that under poor recording conditions they might behave differently. The performance of these indexes under such conditions remains to be investigated.

Effects of vasodilators. In this investigation, so as to avoid possible clinical deterioration, we did not discontinue vasodilators. The number of patients who received beraprost sodium and those who received calcium channel antagonists was not different between the CPTE and PPH groups. Thus, it is unlikely that the vasodilators systematically biased the results of this study.

Moreover, we separately analyzed the diagnostic significance of pulmonary artery pulsatility in the subgroups with no vasodilator therapy (CPTE: $n = 14$; PPH: $n = 8$). The results indicated that PP_f was markedly higher in CPTE than in PPH (1.42 ± 0.21 and 0.78 ± 0.17, respectively, $p < 0.001$). The CV also separated the two groups (0.47 ± 0.07 and 0.24 ± 0.05, respectively, $p < 0.001$), as did $TA_{1/2}$ (0.35 ± 0.03 and 0.44 ± 0.03, respectively, $p < 0.001$). These results were in line with those obtained from the total group. Thus, vasodilator therapy did not appear to significantly modulate the basic characteristics of the pulmonary artery pressure waveform of CPTE or PPH.

Study limitations. There are several limitations of the present study. We retrospectively analyzed a limited number of patients only. Obviously, the performance of the proposed indexes, such as sensitivity and specificity in differentiating between CPTE and PPH, depends on the patient cohort investigated. To generalize the results of this study, prospective studies involving many patients are essential. Nevertheless, accentuated pulsatility relative to mean pressure in CPTE would be expected to remain a useful, valid observation because it is based on the fundamental mechanical characteristics of CPTE and PPH.

Many investigators have suggested (20,21) that the pathophysiology of CPTE and PPH may overlap to a certain extent. We made the diagnosis of CPTE only when we could document thrombi in the proximal arteries. Thus, it is possible that CPTE that did not have angiographically detectable thrombi was diagnosed as PPH. Conversely, PPH that happened to have detectable thrombi would have been diagnosed as CPTE. Although there exists this degree of uncertainty in diagnosis, the proposed analysis of the pulmonary artery waveform provided useful information consistent with angiographic findings and revealed the mechanical properties of the pulmonary arteries. These features of the proposed analysis are particularly important because the correct diagnosis of CPTE is vital for life-saving surgical procedures such as thromboendarterectomy (1). Thus, we believe that the waveform analysis is useful as a clinical tool.

We used a fluid-filled system to record pulmonary artery pressure. If we could have used a high fidelity pressure transducer, the recorded pressure waveform would have been more accurate. However, this does not mean that the waveform analysis using the fluid-filled recording system is invalid. The fact that we could differentiate CPTE from PPH using the fluid-filled system should be interpreted not as a weakness but as a strength of the study.

In this investigation, we hypothesized that characteristic impedance would be higher in CPTE than in PPH. One can directly measure characteristic impedance when high fidelity instantaneous pulmonary flow and pressure are available (22–24). Further, more elaborate studies are essential to deepen our understanding of the mechanism that differentially modulates the pulmonary artery waveform in CPTE and PPH.

Conclusions. Pulmonary artery pressure waveform analysis can offer an additional, new approach in the differential diagnosis of CPTE and PPH.

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