Selective echocardiographic analysis of epicardial and endocardial left ventricular rotational mechanics in an animal model of pericardial adhesions

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Aims Diagnosis of pericardial adhesions is challenging. Twisting of the left ventricle (LV) is essential for normal LV functioning. We experimentally characterized the impact of pericardial adhesions on epicardial and endocardial LV rotational mechanics with velocity vector imaging (VVI).

Methods and results In nine open-chest pigs, the heart was exposed while preserving the pericardium. Early-stage pericardial adhesions were simulated by instilling tissue glue to pericardial space. Using VVI, LV rotational mechanics was quantitatively assessed endocardially and epicardially along with hemodynamic data at baseline and following the experimental intervention. End-diastolic volume, ejection fraction, stroke volume, late diastolic filling velocity, and LV endocardial torsion decreased significantly. LV epicardial torsion showed only a trend towards decrease ($P=0.141$). Endocardial twist and torsion decreased significantly ($P=0.007$) from $8.6\pm2.2$ degree and $1.497\pm0.397$ degree/cm to $5.3\pm1.8$ degree and $0.97\pm0.38$ degree/cm, respectively; epicardial twist showed a trend towards a decrease in its magnitude. Gradients of endocardial/epicardial twist and torsion did not significantly change.

Conclusion The model suggests that early-stage pericardial adhesions reduce both epicardial and endocardial LV twist and torsion without a significant alteration in their transmural gradient. Selective endocardial/epicardial analysis of LV twisting mechanics may have a diagnostic role in detection of early formation of pericardial adhesions.

KEYWORDS
Left ventricular twist; Pericardial adhesion; Velocity vector imaging

Introduction

Development of pericardial adhesions and thickened, less pliable pericardium is a pathophysiological marker of constrictive pericarditis (CP). Early recognition of CP would contribute to reduction in related morbidity and mortality.1 However, diagnosis of CP represents a challenge because it is an uncommon disease and its signs and symptoms are non-specific and often mimic clinical presentations of other cardiac disease processes.2

Left ventricular (LV) twist is defined as the net rotation between the apical counterclockwise and basal clockwise rotations, which occur due to the helical arrangement of cardiac fibres.3,4 LV torsion is defined for the purpose of this study as LV twist magnitude normalized to LV length.5,7 Twist and torsion have been shown to play an important role in LV systolic and diastolic function.6,9 Reduced magnitudes in LV twisting and apical rotation have been demonstrated in CP, as opposed to restrictive cardiomyopathy, in which both apical rotation and LV twist remained without significant changes compared with control subjects.6 In the present study, LV twist and torsion are analysed endocardially and epicardially. Such selective analysis links rotational motion evaluation10–12 with the arrangement of cardiac fibres to right-handed (subendocardial) and left-handed (subepicardial) helices.13

We hypothesized that (i) the magnitude of LV twist and torsion can be measured selectively within the endocardial and epicardial myocardial layers by echocardiographic velocity vector imaging (VVI) and (ii) the presence of developing pericardial–epicardial adhesions will measurably disrupt the rotational, twisting, and torsional gradient across the myocardial wall thickness. To test our hypothesis, we introduce an animal model of patchy pericardial adhesions intended to simulate early stages of CP.

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Methods

The study was approved by the Institutional Animal Care and Use Committee.

Animal preparation

Eleven adolescent swine weighing 40–45 kg were studied under general anaesthesia induced with an intramuscular injection of Telazol (5 mg/kg), Xylazine (2 mg/kg), and Glycopyrrolate (0.006 mg/kg) and maintained by inhalation of 1.5% isoflurane. Each animal was intubated, mechanically ventilated (Ohmeda 7800 Ventilator, Datex-Ohmeda Inc., Madison, WI, USA), and blood gases were periodically checked. Cut downs of the jugular vein and carotid artery were secured with 8F sheaths (Cordis Corp., Miami Lakes, FL, USA), which served for administration of fluids and medications, and insertion of catheters (Millar Instruments Inc., Houston, TX, USA) in the LV and ascending aorta was used for pressure monitoring. After medial sternotomy, the heart was exposed while sparing the pericardium.

Experimental pericardial adhesions

We simulated pericardial–epicardial adhesions by using an instant ethyl-cyanoacrylate glue (Super Glue™, Pacer Technology, LLC, Rancho Cucamonga, CA, USA) instilled by a thin plastic tube (‘butterfly’ catheter; ~2 mm in diameter), which was advanced in various directions through a small pericardial incision located at the mid-level of the anterior wall. This created patchy adhesions with a thickened, constructive shell that encompassed ~70% of the LV epicardial surface and could be visually checked as pale areas underneath the pericardium (Figure 1). Just prior to glue instillation, we carefully placed 8–12 Proline stitches that sutured the pericardium to the epicardium along the apical LV circumference. These pericardial stitches not only contributed as additional ‘adhesions’, but their main purpose was to prevent the glue from spreading to the very tip of the apical pericardial space where it would form a bulk, dissimilar to pericardial adhesions, and severely attenuate apical ultrasound projections, based on preliminary pilot tests.

Haemodynamic analysis

Measurements included heart rate (HR), aortic systolic blood pressure (SBP), and diastolic blood pressure (DBP), as well as LV end-diastolic pressure (LVEDP). The latter was determined by the peak of the R-wave on the synchronous electrocardiographic tracing. Besides peak positive and peak negative dP/dt (i.e. +dP/dt and −dP/dt), respectively, the time constant of LV pressure decay during the isovolumic relaxation period (i.e. tau) was ascertained by using a zero-asymptote model.

Echocardiography

An ACUSON Sequoia C512 ultrasound system (Siemens Medical Solutions, Inc., Mountain View, CA, USA) equipped with a 8V3C transducer set to 3.5 MHz was used to acquire echocardiographic scans. The transducer was placed on the pericardium and acoustically coupled by a small amount of gel. Scans included: (i) apical 2- and 4-chamber views for measurements of LV end-diastolic (EDV), end-systolic (ESV), and stroke (SV) volumes, ejection fraction (EF), and cardiac output (CO); (ii) short-axis apical and basal views for analysis of rotation by VVI and calculation of torsion magnitude; (iii) flow Doppler spectra with early (E-wave) and atrial (A-wave) component of LV filling; and (iv) tissue Doppler E’ and A’ velocities measured in the basal medial septum. For each scan, 2–3 cardiac cycles were acquired at a frame rate of 60–70 Hz.

Syngo VVI technology software (Siemens Medical Solutions, Inc.) was used offline to track myocardial motion and, specifically, to determine the rotation of endocardial and epicardial myocardial layers in apical and basal short-axis projections. Tracking was initiated by manually tracing the endocardial border placing (7–8 points). On the basis of this initial tracing, the system applies a sequence of processing steps to follow the motion of endocardial layer through time,14 which we refer to as endocardial layer (Figure 2). The VVI system also approximates the motion of the epicardium and, in addition, alerts the user if tracking cannot be generated reliably so that interaction can be made.

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Haemodynamic, 2D, and Doppler echocardiographic measurements were obtained at baseline and following the intervention (i.e. after inducing pericardial–epicardial adhesions) and were compared by a two-tailed paired t-test. A P-value of <0.05 was considered statistically significant.

Interclass correlation coefficient (ICC) was calculated with a 95% confidence interval (CI) and the following grading scale was used for evaluation of reproducibility: ICC > 0.75 was considered as very good, 0.4–0.75 as good, and <0.04 as poor.15

Results

From a total of 11 pigs, two were excluded after application of tissue glue, one due to sustained ventricular arrhythmias and the other due to severe hypotension and a haemodynamic collapse. Complete data were obtained from nine animals.

Haemodynamic data

Heart rate, DBP, and LVEDP did not significantly change (Table 1). SBP only showed a trend towards a decrease after intervention. However, magnitudes of +dP/dt, −dP/dt, and tau decreased suggesting an inhibiting effect of the experimental pericardial adhesions on the rate of LV contraction and relaxation.

Figure 1 The heart after sternotomy with pericardium and its diaphragmatic attachment preserved. Pericardial stitches (block arrows) are placed around the apical circumference of the left ventricle. Tissue glue has been instilled in a pericardial space, predominantly around the mid and basal regions, and two patches are approximated by dashed delineations. LV, left ventricle; RV, right ventricle.
While ESV did not significantly change, EDV decreased, resulting in a post-intervention drop in SV, EF, and CO (Table 2). Together with a borderline decrease in A-wave (but not in E-wave) velocity, these results suggest LV preload impairment. E’ and A’ tissue velocities did not change significantly.

**Table 1** Haemodynamic findings

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Intervention</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>78.4 ± 7.9</td>
<td>91.1 ± 26.1</td>
<td>0.116</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>112.7 ± 10.4</td>
<td>98.6 ± 22.5</td>
<td>0.06</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.1 ± 7.8</td>
<td>69 ± 21.8</td>
<td>0.14</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>17.8 ± 5.6</td>
<td>20.3 ± 6.5</td>
<td>0.43</td>
</tr>
<tr>
<td>+dp/dt</td>
<td>1096.5 ± 236.4</td>
<td>795.5 ± 155.0</td>
<td>0.00052</td>
</tr>
<tr>
<td>−dp/dt</td>
<td>−1490.6 ± 198.6</td>
<td>−1044.7 ± 219.3</td>
<td>0.00015</td>
</tr>
<tr>
<td>Tau (ms)</td>
<td>42.5 ± 9.1</td>
<td>70.7 ± 34.8</td>
<td>0.047</td>
</tr>
</tbody>
</table>

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEDP, left ventricular end-diastolic blood pressure.

**Velocity vector imaging analysis data**

Apical rotation represented 87.5% and 84% of the LV twist in the endocardial and epicardial myocardial layers, respectively, and decreased in both layers significantly. On the other hand, the apical endocardial (RotEndo-Api) and epicardial (RotEpi-Api) rotations were significantly reduced with the adhesions (P < 0.0002 and < 0.008, respectively, Table 2). However, their gradient, i.e. RotEndo-Api/RotEpi-Api, did not significantly change (P = 0.9960), which suggests a proportional reduction in rotation with a preserved transmural gradient. Selectively measured basal rotation magnitudes (RotEndo-Bas and RotEpi-Bas) and their gradients (RotEndo-Bas and RotEpi-Bas) have not statistically changed from baseline to the intervention.

The LV twist magnitude in the endocardial layer (TwEndo) decreased, whereas a decrease in the epicardial twist magnitude (TwEpi) was not significant, although the proportional decreases (intervention/baseline) of TwEndo and TwEpi were nearly identical (5.3/8.6 = 0.62 and 2.4/3.7 = 0.65, respectively). The gradient of endocardial to epicardial twist (TwEndo/TwEpi) has not significantly changed from baseline to the intervention. Endocardial LV torsion (TorEndo) decreased, epicardial LV torsion (TorEpi) showed
Table 2 Functional findings

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Intervention</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESV (mL)</td>
<td>26.5 ± 7.8</td>
<td>24.8 ± 6.5</td>
<td>0.1514</td>
</tr>
<tr>
<td>EDV (mL)</td>
<td>62.9 ± 18.2</td>
<td>42.9 ± 10.6</td>
<td>0.0204</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>35.1 ± 10</td>
<td>17.3 ± 4.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF (%)</td>
<td>56.6 ± 2.6</td>
<td>40 ± 6.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>2.8 ± 0.9</td>
<td>1.6 ± 0.6</td>
<td>0.0002</td>
</tr>
<tr>
<td>E-wave (cm/s)</td>
<td>0.5 ± 0.16</td>
<td>0.4 ± 0.04</td>
<td>0.18</td>
</tr>
<tr>
<td>A-wave (cm/s)</td>
<td>0.52 ± 0.10</td>
<td>0.4 ± 0.15</td>
<td>0.04</td>
</tr>
<tr>
<td>E' (cm/s)</td>
<td>0.185 ± 0.26</td>
<td>0.116 ± 0.05</td>
<td>0.450</td>
</tr>
<tr>
<td>A' (cm/s)</td>
<td>0.193 ± 0.22</td>
<td>0.259 ± 0.26</td>
<td>0.728</td>
</tr>
<tr>
<td>RotEndo-Bas</td>
<td>7.53 ± 1.91</td>
<td>3.41 ± 1.25</td>
<td>0.0002</td>
</tr>
<tr>
<td>RotEpi-Bas</td>
<td>3.11 ± 1.91</td>
<td>1.21 ± 0.62</td>
<td>0.008</td>
</tr>
<tr>
<td>RotEndo-Api</td>
<td>3.09 ± 1.52</td>
<td>3.10 ± 1.00</td>
<td>0.9960</td>
</tr>
<tr>
<td>RotEpi-Api</td>
<td>-1.03 ± 0.74</td>
<td>-1.84 ± 0.88</td>
<td>0.123</td>
</tr>
<tr>
<td>RotEndo-Bas (degree)</td>
<td>-0.58 ± 0.56</td>
<td>-1.22 ± 0.98</td>
<td>0.21</td>
</tr>
<tr>
<td>RotEpi-Bas</td>
<td>1.55 ± 0.59</td>
<td>3.29 ± 4.38</td>
<td>0.2536</td>
</tr>
<tr>
<td>T wEndo (degree)</td>
<td>8.6 ± 2.2*</td>
<td>5.3 ± 1.8*</td>
<td>0.007</td>
</tr>
<tr>
<td>T wEpi (degree)</td>
<td>3.7 ± 2.1</td>
<td>2.4 ± 1.3</td>
<td>0.14</td>
</tr>
<tr>
<td>T wEndo/T wEpi</td>
<td>3.06 ± 1.67</td>
<td>2.53 ± 0.91</td>
<td>0.49</td>
</tr>
<tr>
<td>TorEndo (degree/cm)</td>
<td>1.497 ± 0.397</td>
<td>0.971 ± 0.376</td>
<td>0.007</td>
</tr>
<tr>
<td>TorEpi (degree/cm)</td>
<td>0.617 ± 0.33</td>
<td>0.443 ± 0.23</td>
<td>0.141</td>
</tr>
<tr>
<td>TorEndo/TorEpi</td>
<td>3.08 ± 1.72</td>
<td>2.473 ± 0.919</td>
<td>0.426</td>
</tr>
</tbody>
</table>

E' and A', early and atrial, respectively, components of diastolic filling velocities by TDI from septal mitral annulus; E' and A-wave, early and atrial, respectively, components of diastolic filling velocities; CO, cardiac output; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; RotEndo-Api and RotEndo-Bas, rotation magnitude of endocardial layer at apical and basal levels, respectively; RotEpi-Api and RotEpi-Bas, rotation magnitude of epicardial layer at apical and basal levels, respectively; T wEndo and T wEpi, twist of the endocardial and epicardial layers, respectively; TorEndo and TorEpi, left ventricular torsion magnitude, endocardial and epicardial layers, respectively.

*aP < 0.0001 vs. T wEpi.

Our study also documents the ability of echocardiographic VVI to measure the LV torsion and twist selectively in the endocardial and epicardial layers of the myocardium and suggests that assessing apical rotation, as well as LV twist and torsion magnitudes layer-selectively could have a role in detecting and evaluating the functional impact of early stages of formation of pericardial adhesions.

Myocardial layer-selective assessment of left ventricular twist and torsion

The finding that endocardial twist and torsion magnitudes are higher than those in the epicardial layer is consistent with observations by Akagawa et al. As in our work, these investigators explored LV twist and torsion selectively in the endocardial and epicardial layers and found a similar gradient in the transmural twist magnitudes. In our study, the intent was to simulate early stages of pericardial constriction by only patchy distribution of adhesions. Consequently, some conventional echocardiographic findings of pericardial constriction, such as high E/A ratio and significant transmitral or tricuspid E-wave respiratory variation, were absent. On the other hand, isovolumic contraction and relaxation rates of pressure increase and decrease, respectively, were reduced and so was myocardial torsion and twisting, as is expectable in constriction. However, it was the endocardial (but not epicardial) torsion and twisting that reduced significantly, suggesting that analyses of LV torsion and twist, selectively in the endocardial and epicardial layers of the myocardium, could have a role in early diagnosis of pericardial adhesions.

Using inotropic stimulation, Akagawa et al. showed that a corresponding increase in LV twist and torsion was more pronounced in the endocardial layer than in the epicardial layer of the myocardium. Rademakers et al. confirmed by tagged magnetic resonance imaging of endocardial and epicardial torsion the accentuation of LV torsion and, in addition, demonstrated dissociation between LV untwisting and filling in response to catecholamines. Our layer-selective analysis documented a statistically significant inhibitory effect of the experimentally induced pericardial adhesions on LV twist and torsion magnitudes in the endocardial layer but not in the epicardial layer of the myocardium. We cannot exclude the possibility, however, that epicardial rotation was not captured in its exact magnitude because tracking of epicardium was, based on our experience, rather challenging. Also, the relatively large SDs in the T wEpi values during both baseline and intervention could prevent reaching the statistical significance.

Table 3 Intraobserver and interobserver variability

<table>
<thead>
<tr>
<th>Intraobserver</th>
<th>95% CI for ICC</th>
<th>Interobserver</th>
<th>95% CI for ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Endo</td>
<td>0.99</td>
<td>Baseline Endo</td>
<td>0.78</td>
</tr>
<tr>
<td>Baseline Epi</td>
<td>0.99</td>
<td>Baseline Epi</td>
<td>0.88</td>
</tr>
<tr>
<td>Post Int. Endo</td>
<td>1.00</td>
<td>Post Int. Endo</td>
<td>0.92</td>
</tr>
<tr>
<td>Post Int. Epi</td>
<td>0.99</td>
<td>Post Int. Epi</td>
<td>0.76</td>
</tr>
</tbody>
</table>

CI, confidence interval; Endo, endocardial (rotation); Epi, epicardial (rotation); ICC, interclass correlation coefficient; Post Int., post intervention; Var., variability.
Our results of TwEndo and TwEpi (Table 2) closely match the endocardial and epicardial twist magnitudes obtained by echocardiography in patients and by magnetic resonance tagging in open-chest dogs.

Apical rotation appears to be the determining factor of LV twisting. In our study, apical rotation represented >84% of the overall twist magnitude in both the endocardial and the epicardial layers. When only apical rotation (rather than LV twist) was considered, the decrease from baseline to intervention was significant in both layers (Table 2). Basal rotation magnitude, on the other hand, showed a trend towards an increase in its mean value during intervention, and we speculate that this observation may reflect a functional compensatory effect in rotational mechanics of the LV base. However, considering that Lorenz et al. found clinically by tagged magnetic resonance imaging that during systole the apical segments rotated consistently in counterclockwise direction, whereas the basal segments changed angular directions, the basal rotation mechanics needs to be further investigated.

The TwEndo/TwEpi and TorEndo/TorEpi ratios, which we refer to as the transmural twisting and torsion gradients, respectively, remained without a statistically significant change between baseline and pericardial adhesion states (Table 2). Also, the gradient of the rotational magnitude during the intervention to that at baseline remained similar in both the endocardial and the epicardial layers. These results suggest that while the experimentally induced pericardial constriction limited the rotation, twist, and torsion mechanics of the LV, the transmural interplay of the myocardial fibres remained largely preserved.

Besides the transmural gradient in the LV twist and torsion magnitudes, several investigators demonstrated an analogous gradient in radial LV deformation: radial strains in the endocardial layer of the myocardium are greater when compared with those in the epicardial layer. The present study extends the previous reports by showing that the transmural gradient in LV twist and torsion can continue also during early stages of pericardial constriction. The gradient in twist and torsion between the endocardial and the epicardial layers originates from the helical structure of the myocardium and is consistent with greater fractional thickening in the endocardial layer of the myocardium due to cross-fibre shortening and circumferential-radial shear.

Utility of velocity vector imaging analysis

Velocity vector imaging is an angle-independent measurement technique, which has been applied to studies on LV twist and torsion in health and disease and validated against sonomicrometry. In this context, the diagnostic utility of VVI echocardiography could be extended by quantitative analyses of LV rotation, twist, and torsion magnitudes selectively in the endocardial and epicardial layers of the LV wall.

Experimental model

Pericardial adhesions can be induced by instilling talc into the pericardial space. However, such an experimental model requires several weeks for the adhesions to develop and the resulting thickened pericardium would likely cause artefacts and attenuation in echocardiographic images.

To our knowledge, our experimental study is the first that attempts to experimentally replicate the early (acute and subacute) formation of pericardial adhesions. In particular, the animal model was designed to induce pericardial adhesions rapidly and control their distribution. This created areas of stiffened (constrictive to LV expansion) pericardium with patchy pericardial–epicardial adhesions, which we considered experimentally desirable to simulate the early stages of CP.

Clinical perspectives

Pericardial adhesions after cardiac operation are a widely known phenomenon. They may severely complicate reoperation by making surgical re-entry risky, increase bleeding, and prolong the operation time. Pericardial adhesions are also important clinical precursors of subacute and chronic CP.

There are limited data regarding the effects of pericardial adhesions on LV twist and torsion in a clinical setting. We have recently described the pattern of LV rotational mechanics in patients with restrictive cardiomyopathy in comparison with CP: myocardial muscle disease predominantly affected longitudinal LV mechanics, while relatively sparing LV twisting, whereas CP primarily affected LV circumferential and rotational mechanics while relatively preserving longitudinal function.

Our current work is consistent with the previous finding, but explores the concept of rotational mechanics in pericardial adhesions further by studying subendocardial and subepicardial rotation, twist, and torsion selectively and shows that although the transmural twist gradient has not statistically significantly changed, it was predominantly the endocardial twisting that was reduced (Table 2). Our data thus provide preliminary insights to mechanical consequences of developing pericardial adhesions that may occur, for example, in an immediate post-operative period.

Limitations

We employed an open-chest model, which allowed the experimental intervention, i.e. the induction of pericardial adhesions. Despite keeping pericardium, opening the chest impacts cardiovascular haemodynamics and mechanics. However, we compared the baseline and intervention measurements at otherwise the same experimental conditions.

Epidermal scans provided excellent image quality but such transducer placement could theoretically limit LV rotation. However, we were scanning through a bulk of transmission gel that acted as an interposed soft layer and minimized the compressive effect of the transducer on the LV.

Spreading the tissue glue within the pericardial space was a manual process, which could introduce variations in the impact of adhesion on LV function. However, despite the subjectivity of this process, we observed a consistent and statistically significant decrease in LV rotational mechanics from baseline to the intervention. Two animals had to be excluded due to unmanageable ventricular arrhythmias and severe cardiovascular shock that occurred at the time of glue application. Although electromechanical irritation cannot be excluded, these events could have been a coincidence as well. Ethyl-cyanoacrylate tissue glue has not been shown to cause foreign body, inflammatory, necrotic, or...
other histopathologic reactions when used for bonding of cardiovascular tissues.\textsuperscript{28}

The rapid development of the adhesions was both the purpose and advantage of the model, but the acuteness of adhesion formation could also have limited the full development of all haemodynamic and functional characteristics of CP.

**Conclusions**

Our animal model of early stages of pericardial constriction, represented by patchy pericardial stiffening and pericardial–epicardial adhesions, suggests that LV torsion and twist magnitudes in the endocardial and pericardial layers decrease by a similar proportion, as documented by preserved transmural gradients of twist and torsion. Impairments in endocardial twist, torsion, and apical rotational magnitudes in both the endocardium and the epicardial layers of the myocardium may have diagnostic roles in detection of early stages of CP. Selective analyses of rotation and twist in the epicardial and endocardial layers of the myocardium are experimentally feasible by the novel echocardiographic VVI method.

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