Evidence of Structural Remodeling in the Dyssynchronous Failing Heart

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Abstract

Ventricular remodeling of both geometry and fiber structure is a prominent feature of several cardiac pathologies. Advances in magnetic resonance imaging and analytical methods now make it possible to measure changes of cardiac geometry, fiber and sheet orientation at high spatial resolution. In this report, we use diffusion tensor imaging to measure the geometry, fiber and sheet architecture of eight normal and five dyssynchronous failing canine hearts, which were explanted and fixed in an unloaded state. We apply novel computational methods to identify statistically significant changes of cardiac anatomic structure in the failing and control heart populations. The results demonstrate significant regional differences in geometric remodeling in the dyssynchronous failing heart versus control. Ventricular chamber dilatation and reduction in wall thickness in septal and some posterior and anterior regions are observed. Primary fiber orientation showed no significant change. However, this result coupled with the local wall thinning in the septum implies an altered transmural fiber gradient. Further, we observe that orientation of laminar sheets become more vertical in the early-activated septum, with no significant change of sheet orientation in the late-activated lateral wall. Measured changes in both fiber gradient and sheet structure will affect both the heterogeneity of passive myocardial properties as well as electrical activation of the ventricles.

Keywords: Cardiac Remodeling, Computational Anatomy, Fiber Architecture, Dyssynchrony
Introduction

Dilated cardiomyopathy (DCM) is one of the most common forms of heart muscle disease. In this disease, chronic hemodynamic overload leads to increased wall stress. Subsequent adaptive responses of the heart include both ventricular chamber dilation and myocyte hypertrophy to equalize wall stress\textsuperscript{1-3}. While such adaptations help to maintain pump function over the short term, chronically, inadequate compensation leads to heart failure. Patients with DCM may also exhibit intraventricular conduction delays, particularly of the left bundle branch (LBB) type\textsuperscript{4-6}. The resulting asynchronous electrical activation produces dyssynchronous mechanical contraction and regional heterogeneity in wall stress\textsuperscript{7-9}. In particular, strain magnitude shows a marked phase delay between early septal and late lateral shortening, with early systolic stretch of the lateral wall occurring during septal shortening\textsuperscript{10}. In patients with congenital heart block and chronic RV pacing, dyssynchronous contraction has been shown to result in significant structural remodeling of left ventricular (LV) morphology as the early activated septum thins and the later-activated lateral wall hypertrophies\textsuperscript{11}. Understanding LV remodeling in the dyssynchronous failing heart, including alteration of ventricular geometry as well as fiber architecture, is therefore of critical importance to understanding DCM and such an understanding may lead to improved pacing therapies that will reverse remodeling\textsuperscript{12-14}.

Ventricular myocardium has a complex structural organization. Fiber orientation was first studied by means of fiber dissections\textsuperscript{15-17} and histologic measurements in transmural plugs of ventricular tissue\textsuperscript{18-20}. The principle conclusions of this work were that cardiac fibers are arranged as counter-wound helices encircling the ventricles and that fiber orientation is a function of transmural location, with fiber direction being oriented
predominantly in the base-apex direction on the epicardial and endocardial surfaces and rotating to a circumferential direction in the midwall. Subsequently, LeGrice et al. showed that collagen binds adjacent myocytes together, forming layers known as lamina or sheets\textsuperscript{21}. Reorientation of sheets are responsible for substantial wall thickening during contraction\textsuperscript{22}. Nielsen et al. developed histological methods for the systematic reconstruction of cardiac ventricular geometry and primary fiber organization and efficient computational methods for representing these anatomical data through the use of finite-element (FE) models\textsuperscript{23}. Development of these approaches has contributed significantly to our understanding of ventricular anatomy and its influence on both electrical and mechanical properties. However, histological reconstruction has limitations; taking weeks to months to reconstruct a single heart and yielding a low spatial resolution.

Diffusion tensor imaging\textsuperscript{24} (DTI) has emerged as a means to overcome both these limitations by allowing non-invasive characterization of cardiac tissue structure\textsuperscript{25,26}. In this technique, a tensor that represents the 3D diffusion of water in each image voxel is estimated. The primary eigenvector of this tensor points in the direction in which the rate of diffusion is largest. Comparing DTI with histological measurements, it has been shown that the primary eigenvector of the diffusion tensor is aligned with the cardiac fiber long axis\textsuperscript{25,26}. In addition, in myocardial regions where diffusion is anisotropic, we have recently shown that the tertiary eigenvector of the diffusion tensor is aligned with the surface normal to the cardiac sheets\textsuperscript{27}. Finally, we have demonstrated that DTI may be used to reconstruct the fiber and sheet architecture of the heart at a spatial resolution of 350x350x800\textmu m, yielding fiber structure estimates at two orders of magnitude more
points in a fraction of the time (~40 hours versus weeks to months per heart) than can be achieved histologically\textsuperscript{28}. We have used these methods to image and reconstruct the geometry and fiber structure of populations of normal and failing canine hearts.

Using these imaging data, we have recently developed computational methods to quantify variation of anatomic structure both within and between populations of DTI reconstructed hearts\textsuperscript{28,29}. The method is adapted from the field of computational anatomy\textsuperscript{30,31}, whereby different anatomies are registered to an anatomical template using the large deformation diffeomorphic metric mapping (LDDMM) method\textsuperscript{32}. Prior, computational methods have used low-dimensional transformations requiring landmarks\textsuperscript{33} or high-dimensional transformations but suffer from small deformation assumptions\textsuperscript{34,35}. LDDMM uses high-dimensional transformation working under the assumption of large deformations thereby enabling registration of cardiac pathology which may have large geometric variation. Similar methods have been used previously to analyze brain structures and their variation in disease, in particular, to identify deformations in the shape of the hippocampus that discriminate patients with schizophrenia from matched controls and to define hippocampal shape and volume abnormalities in patients with mild symptoms of Alzheimer's disease\textsuperscript{36}. Here, we combine, for the first time, high resolution DTMRI with rigorous computational methods to quantify differences in the anatomic structure of a population of normal and dyssynchronous failing canine hearts.

**Materials and Methods**

*Model of Dyssynchronous Heart Failure*
The experimental model of cardiac dyssynchrony and heart failure was generated in canines via radio-frequency ablation of the LBB followed by three weeks of tachypacing (210min\(^{-1}\))\(^{37,38}\). This model has been well described in the literature as one which reproduces many of the molecular, cellular, and structural features of human dilated cardiomyopathy\(^{39-41}\). Once ventricular dyssynchrony and heart failure were established, animals were euthanized and hearts explanted. Hearts were retrogradely perfused with a formalin solution and fixed in an unloaded state before imaging with DTMRI\(^{42}\). All studies were conducted in accordance with the guidelines of the Animal Care and Use Committee of the National Heart, Lung, and Blood Institute.

**Diffusion Tensor Magnetic Resonance Imaging**

Details of the imaging sequence have been reported previously\(^{27,43}\). Hearts were placed in an acrylic container filled with Fomblin (Ausimon, Thorofare, NJ) and a 3D Fast Spin-Echo (3D-FSE) sequence was used to acquire diffusion images. MR parameters varied slightly depending on heart size. The field of view ranged from 8-10cm yielding image in-plane resolutions of 312.2x312.5 - 390x390\(\mu\)m. The volume was imaged with 110-120 slices at 800-1000\(\mu\)m thickness. Diffusion gradients were applied in a minimum of sixteen non-collinear directions with a maximum diffusion weighting of 1500s/mm\(^2\).

**DTI Processing and Ventricular Fiber / Sheet Analysis**

The three principal components were computed from the diffusion tensors at each image voxel\(^{24,26}\). Voxels in the 3D DTMRI images representing compact myocardium were identified using a semi-automated contouring method\(^{43}\). LV geometry was modeled
using 3D finite elements (FE), as described by Nielsen et al.\textsuperscript{23}. In the contouring process endocardial trabeculation was removed from the images, allowing a smoother description of the geometry and consequently smaller endocardial fitting errors than those reported by Nielsen et al.\textsuperscript{23}. Diffusion eigenvectors originating from voxels within the FE boundaries were used to study the fiber structure of the ventricles. These eigenvectors were transformed into the local geometric coordinates of the model as described by LeGrice et al.\textsuperscript{44}. Fiber angle, $\theta$, was defined as the angle formed by the local circumferential tangent vector and the projection of the primary eigenvector, $1'$, onto the epicardial tangent plane, as shown in Fig 2. Using methods developed previously for the analysis of DTI\textsuperscript{27}, regions of each heart exhibiting anisotropic diffusion were identified. The sheet angle, $\phi$, (see Fig. 2) was computed in these regions, where $\pi/2 + \phi$ was defined as the angle formed by the radial vector and the projection of the tertiary eigenvector $3'$ into the plane defined by radial and circumferential vectors.

\textit{Anatomical Registration (Large Deformation Diffeomorphic Metric Mapping)}

Anatomical variability is studied by placement of imaged anatomic structures into standard coordinates using the LDDMM algorithm\textsuperscript{29,45}. A flow chart and accompanying illustrations shown in Fig. 1 summarize the method. MR images of each heart were contoured and re-sampled to a common uniform (900 $\mu$m) lattice. A normal canine heart from the set of imaged hearts was chosen as an initial template anatomy (#1 in Fig. 1B). Using the LDDMM algorithm, high order transformations were computed to register (green arrows) the template anatomy to the remaining hearts (target anatomies) such that every voxel in the template heart maps to a voxel in each target heart. The quality of
registration is measured by the ratio of overlapping image-intensity volumes subsequent to transformation to that prior to transformation. The mean trajectory (red arrow) computed from each mapping (green arrows) is used to deform the template, defining yet another new template anatomy. The process is iterated until the mean trajectory length is zero. The resulting template anatomy is called the Procrustes mean and resides within the center of possible geometric shapes (Fig. 1C).

Geometric variation about this Procrustes mean is studied using Principle Component Analysis (PCA) of the final mapping trajectories (green arrows, Fig 1C). In PCA, a set of orthogonal basis vectors oriented along the directions of maximal variance of the data are computed\(^45\).

Under high-order transformations, such as those computed using LDDMM, the principle eigenvectors, which define fiber architecture, are not all preserved\(^{46,47}\). As a result reorientation of the eigenvector must be performed if they are transformed in the mapping. Alternatively, the eigenvectors may be referenced within a geometric coordinate system, which deforms with the anatomy, thereby eliminating the need to reorient the eigenvectors. In this report, instead of performing structure analysis on the eigenvectors in the space of the template, we use the mapping method to identify corresponding regions within each un-deformed heart and study fiber /sheet angles (derived from eigenvectors and referenced in local geometric coordinates) within these regions. For example, within the template anatomy, an ROI is defined and using the target specific mappings a corresponding ROI is defined on each target. Structural differences within a population are observed by comparing fiber angles, within each
corresponding target ROI. Mean values of this pooled information from target ROIs are naturally visualized within the template ROI.

Geometric Analysis

Referencing geometric images of each target heart into the common coordinate system of the template, as described above, enables quantitative comparison of geometric features within corresponding regions of different imaged hearts. Evaluation of relative wall thickness (RWT) was performed by comparing corresponding regions in each target heart. The Laplace relation defines wall stress as being inversely proportional to RWT, defined as the ratio between wall thickness and chamber radius. RWT provides an indication of myocyte hypertrophy relative to ventricular dilation and is well preserved in normal hearts, independent of body weight and ventricular volume. Epicardial points in the template were identified and corresponding points in each target were computed using the LDDMM method. The wall thickness at these points was defined as the length of the transmural segment between each epicardial point and the nearest endocardial point. The radius of the ventricle was determined from a best fitting circle that encompassed all endocardial points on corresponding slices in each target.

Statistical Analysis

Using the LDDMM method, RWT, fiber and sheet angles within corresponding regions of each target heart were determined. Statistical significance (p) for geometry was determined using a non-paired Student's t-test. Circular statistics were used to compute the circular mean and circular variance of fiber and sheet angles. Statistical significance for angles was determined using Watson-Williams F-test. P-values <0.01 were considered statistically significant.
Results

**LDDMM Matching**

Eight normal and five failing explanted canine hearts were imaged using 3D-FSE-DTMRI. The average registration error for matching the template heart to the normal targets was 5.80±1.47% and for matching the template heart to the failing hearts 4.42±0.47%. These values are not statistically different from each other and are comparable to those reported in the literature for matching of brain imagery\(^{51, 52}\) and demonstrates that the LDDMM method successfully overlays cardiac target geometries with high accuracy to a common coordinate system\(^{29}\).

**Geometric Variability**

The mean geometry for the normal population was computed using a Procrustes alignment (Fig. 1) and used as the normal template. Regions in the anterior, lateral, posterior, and septum of this template were selected and corresponding regions in each target anatomy were identified. RWT within corresponding regions at the base and apex are shown in Table 1. The normal population showed an average RWT of 0.52±0.04 with no statistical difference over the entire ventricle except for the apical septum. Within the apical septum, the RWT was larger at 0.61±0.04. This difference may be attributed to the errors associated with identifying the RV endocardial surface given the extent of trabeculation within the RV apex. The failing population showed a significant reduction of this ratio, indicating a greater ventricular dilation relative to myocyte hypertrophy. There was also significant regional disparity of this ratio. RWT within the
lateral region was significantly different (p<0.01) than that found in the septal wall, (0.42±0.07 and 0.29±0.06, respectively). Regional disparity was not as evident in the apical regions. Differences in RWT between the normal and failing populations are depicted in Fig. 3. The top row (Fig. 3A) shows the template heart (in anterior/posterior view and two cut-away perspectives) colored according to mean RWT for the normal population. The middle row (Fig. 3B) shows the template heart colored according to mean RWT for the failing population. Regional disparity is clearly evident. The statistical differences between normal and failing populations are shown graphically in the bottom row (Fig. 3C). The template heart is colored such that regional differences that are statistically significant (p<0.01) are blue and regional differences that are not significant are cyan.

We next examined geometric variability of the normal population about the normal template using PCA applied to the mapping trajectories defined from the template anatomy. Analyses were limited to assessment of the principal eigenvector $\alpha_n$, (i.e. direction of highest geometric variability). Figure 4 shows different time steps in the evolution of the normal template (middle top image) in the direction of $\alpha_n$ (top right) and $-\alpha_n$ (top left). The insertion of the RV shows the greatest variability in the normal population. There is some septal wall deviation, which may be due in part to variability in the RV insertion. Figure 4 also shows evolution of the normal template (middle bottom image) in the principal direction of highest variation for the failing population, $\alpha_f$. As expected, the most notable variation was dilation of the left ventricular chamber and reduction of wall thickness. Movies showing the deformation of the template heart in
the direction of highest geometric variance for both normal and failing populations are available in the online supplement.

**Fiber structure variability**

Before studying diffusion eigenvectors, a ventricular coordinate system from which fiber and sheet angles are referenced was defined. On average, each MR study resulted in 50,000 epicardial and 27,000 LV endocardial data points to which the radial component of a 24-element prolate spheroidal FE mesh was fit. The average root mean squared (RMS) errors of the FE fit on epicardial and left ventricular endocardial surface were 0.81±1.08 mm and 0.68±0.83 mm, respectively. Fiber and sheet angles were determined from the primary and tertiary eigenvectors using the ventricular coordinate system as shown in Fig 2. On average, each study resulted in 550,000 measurements of fiber and sheet angle within the myocardium.

Plots of mean fiber angle in the normal and failing hearts are shown in Fig. 5. The top row (Fig. 5A) shows the template heart colored according to mean fiber angle for the normal population while the middle row (Fig. 5B) shows the template heart colored according to average fiber angle for the failing population. The bottom row (Fig. 5C) displays the statistical significance of regional differences in fiber orientation between the normal and failing hearts. Despite large regional differences in wall thickness in the septal and lateral walls, the majority of the LV showed no significant change in fiber structure. Some regions on the epicardial and endocardial surfaces showed an increase in fiber angle for the failing population as noted in yellowish color but these differences
were not significant at p<0.01. These data therefore demonstrate that fiber orientation assessed at corresponding points in failing and control hearts are largely similar.

*Laminar structure variability*

Variability of laminar structure was also studied. The top row (Fig. 6A) shows the template heart colored according to dominant sheet angles for the normal population. Two dominant populations of sheet angles were identified: one at approximately -45° and the other at +45°. The majority of the lateral wall (both apex and base) showed a single dominant angle at approximately -45°, while the majority of the septum showed a dominant angle of +45° at the base and -45° at the apex. Transmural variation in the dominant angles is also seen in some LV regions as the angles toggled from -45 to +45 and sometimes back (lateral wall). A statistical assessment of differences in laminar structure between normal and failing hearts is shown in the bottom (Fig. 6C) set of images. The majority of the LV showed no significant difference between the laminar structure in the normal and failing populations; however in the septal region of the failing heart both population of sheet angles (±45) became steeper (less radial) by about 15°. These differences were statistically significant (p<0.01).

**Discussion**

To our knowledge this is the first report which combines high resolution diffusion tensor imaging techniques with methods of computational anatomy to demonstrate
quantitatively, global and local remodeling in a population of normal and failing hearts with a LBBB. There are several important findings.

First, our results show regional differences in anatomical remodeling in the dyssynchronous failing heart. Significant ventricular chamber dilatation and reduction of RWT in septal, posterior and anterior regions was observed, while the lateral wall showed little change in RWT. It has been shown previously that the tachycardia-induced heart failure model leads to greater ventricular dilation relative to ventricular mass; hence, RWT should reduce as compared with normal hearts. We observed a similar global reduction in RWT as a result of tachycardia pacing. However, our model additionally includes a LBBB block. Such dyssynchronous electrical activation results in early and late mechanical activated regions of myocardium and hence subjects these regions to different loading conditions. In early systole, the late-activated lateral wall dilates (stretches) due to contraction of the early-activated septum. A reversal of this effect occurs during late systole/early diastole when the lateral wall contracts against a relaxing septum. These regional differences in wall stress ultimately lead to different patterns of hypertrophy/remodeling as we observed. Prinzen et al. showed similar differences in hypertrophy response in early-activated versus late-activated myocardium using ventricular pacing studies.

Second, despite regional differences in gross remodeling, fiber orientation at corresponding points remains similar in control versus failing hearts. These results are consistent with other canine models of failure induced with arteriovenous fistule. Such studies indicate global dilation with little change in fiber orientation. These results, coupled with gross remodeling of wall thickness (particularly in the septum) imply a
statistically significant change in transmural fiber gradient. Given that the gradient of fiber orientation is a major determinant of electrical propagation, this has important implications for electrical activation of the ventricle.

Finally, we demonstrate significant (p<0.01) regional difference in sheet structure remodeling which may explain regional difference in wall thickness. Specifically, we find an increase of sheet angle in the early-activated septum but no change in that of the late-activated lateral wall. These data imply a possible slowing of transmural electrical conduction, since conductivity is smaller in the cross-sheet direction. A possible mechanism of remodeling occurring in the septum is shown graphically for a small transmural tissue slab in Fig. 7. The normal sheet structure is shown in panel A. As sheet angle $\phi$ increases, the laminar sheets assume a more vertical orientation, thus reducing overall wall thickness (panel B). This mechanism has been proposed and substantiated by others. Such reorientation also implies an elongation of the septal wall, which is observable in figure 4. Unlike the lateral wall, the septal wall showed large variation in its apex to base arc-length. We observed no significant changes in the laminar architecture of the lateral wall.

These data have important clinical implications. Mechanical dyssynchrony is common in patients with dilated cardiomyopathy, ventricular pacemakers and/or post-myocardial infarction. Our data shows regional differences in remodeling in the dyssynchronous failing heart particularly within the laminar sheet structure. Sheet structure influences the apparent passive properties of myocardium; thus regional differences in sheet structure may impart heterogeneity of myocardial function within the ventricle. Although it is yet unclear whether these structural changes coupled with
altered electrical conduction due to increased fiber gradient are beneficial or detrimental to function, a better appreciation of the remodeling process is important in the understanding of, improvement in and development of therapeutics.

In conclusion, unlike previous studies of myofiber architecture, we have employed a high resolution, 3D imaging modality coupled with rigorous mathematical assessment of variability to demonstrate significant regional changes in ventricular structure in the dyssynchronous, failing heart, thereby enabling quantitative understanding of the nature of ventricular remodeling and heart failure progression.

Acknowledgements

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List of Tables:

Table 1: Tabulated are RWT (x 100) measurements for various regions within the LV of normal and failing canine hearts. † denotes statistical significance (p<0.01) relative to basal lateral wall of normal population. Within the failing population * denotes statistical significance (p<0.01) relative to basal lateral wall.

List of Figures:

Figure 1: A simplified flow chart (A) and accompanying illustrations (B,C) summarizes the computational anatomy methods. A normal heart was chosen as an initial template anatomy from a set of imaged heart structures. Using the LDDMM, different high order transformations were computed to map (green arrows) the template anatomy to the remaining hearts (target anatomies) (B). The mean trajectory (red arrow) computed from each mapping (green arrows) was used to deform the template, defining yet another new template anatomy. The process was iterated until the mean trajectory from the template anatomy to each target heart was zero. At this stage the template anatomy resided within the center of possible geometric shapes (C).

Figure 2: The coordinate system used to define the fiber angle $\theta$ and the sheet angle $\phi$. The fiber angle, $\theta$, is the angle formed by the circumferential tangent vector and the projection of the primary eigenvector, $l'$, into the epicardial tangent plane. The sheet angle, $\phi$, is defined relative to the tertiary eigenvector of diffusion where $\pi/2 + \phi$ is the angle formed by the radial vector and the projection of the tertiary eigenvector, $3'$, into the plane defined by radial and circumferential vectors.

Figure 3: The top row (A) shows the template heart (three different views) colored according to the mean RWT for the normal population. The middle row (B) shows the
template heart color according to the mean RWT for the failing population. Note the reduced thickness in the septal wall. The RV (gray) was not analyzed but included in the figure for a reference. The bottom row (C) shows the statistical difference (p) as determined by the Student's t-test between the normal and failing population. The color cyan represents no difference and the color blue represents a statistical difference at (p<0.01).

**Figure 4:** With $\alpha_n$ defined as a vector pointing in the direction of highest geometric variance of a population on normals (see methods), we illustrate the evolution of normal template (middle top image) in the direction of $\alpha_n$ (top right) and -$\alpha_n$ (top left). The insertion of RV (gray arrows) shows highest variability in the normal population. There is some septal wall deviation (gray arrows) mostly due to the variability in RV insertion. In the bottom row, we illustrate the evolution of the normal template in the principal direction of highest geometric variance, $\alpha_f$ for the failing population. Changes occurred in the LV diameter (gray arrows), wall thickness and expanse of the septal wall.

**Figure 5:** The top row (A) shows the template heart (three different views) colored according to average fiber angle [degrees] for the normal population. The middle row (B) shows the template heart color according to average fiber angle for the failing population. There is a very slight increase in fiber angles on the epicardial and endocardial surface for the failing heart as noted by the more yellow/red color on these surfaces. The bottom row (C) shows the statistical difference between the normal and failing population. The color cyan represents no difference and the color blue represents a statistical difference at (p<0.01).
**Figure 6:** The top row (A) shows the template heart (three different views) colored according to sheet angle [degrees] for the normal population. The middle row (B) shows the template heart color according to sheet angle [degrees] for the failing population. The bottom row (C) shows the statistical difference between the normal and failing population. The color cyan represents no difference and the color blue represents a statistical difference at (p<0.01).

**Figure 7:** Shown is an illustration of sheet remodeling that accounts for reduction in wall thickness. Shown in (a) are normal sheet orientation and (b) altered sheet orientation. The sheets become more vertical (less radial) and hence the wall becomes thinner.
Figure 1

A

B

C

Image Population of Hearts

Select Arbitrary Template

Map Template to Each Heart

Compute Mean Displacement from Maps

Mean Displacement Equal Zero?

No

Deform Template with Mean Displacement

Yes

Template Represents Mean Geometry
Figure 2
Figure 3
Figure 4

Normal

\[ -\alpha_n \rightarrow \text{Atlas} \rightarrow +\alpha_n \]

Failing

\[ -\alpha_f \rightarrow \text{Atlas} \rightarrow +\alpha_f \]
Figure 5
Figure 6
Figure 7
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<td>37±7†</td>
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<td>41±8†</td>
<td>32±5*†</td>
<td>29±6*†</td>
<td>41±20</td>
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Table 1
References


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