Vessel centerline reconstruction from non-isocentric and non-orthogonal paired monoplane angiographic images

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Supplement

S.1 Experiment with In Vitro Phantom Models

First, phantom models were filled with radio-opaque contrast dye at a clinical concentration (contrast dye: saline = 1:1). Then, after confirming that isocenters were coincident from any projection angles, angiographic images were acquired at 30 frames/s while varying the projection angle to create a range of angles between paired images from 20° to 130°. This range was selected based on the clinical datasets. To create a non-isocentric pair of images, the imaging table was moved in the horizontal plane to the maximum distance that the entire phantom model can be visualized without changing the magnification. Angiographic images were acquired again from various projection angles similar to the ones for isocentric images. All the angiographic images were obtained with Innova 2100 (GE Healthcare, Cleveland, OH) at CBSET, Inc. (Lexington, MA) and stored in the DICOM format with all the imaging parameters. The movement of the table was also recorded in the DICOM header. The resolutions of all angiographic images were 0.35 mm/pixel ± 0.04 mm/pixel.

S.2 Experiment with In Vivo Animal Models

Twelve coronary arteries (five right coronary arteries (RCA), four left anterior descending arteries (LAD), and three left circumflex arteries (LCX)) from five Yorkshire swine (40-50 kg)
were imaged *in vivo*. After anesthetizing the swine and accessing the coronary artery, heparin (50-200 U/kg) was administered so as to maintain an activated clotting time greater than 275 s. Coronary arteries were selectively cannulated with a 7F guide catheter (JL 3.5 VISTA BRITE TIP® Guiding Catheter, Cordis Corporation, Dublin, OH) under fluoroscopic guidance. Several angiographic images were obtained and the arterial diameters were measured by quantitative coronary angiography analysis (2.84 mm ± 0.17 mm). Bare metal stents (3.0 mm × 17 mm) were implanted in the targeted arteries with standard procedures. The inflation pressure of the balloon catheter was selected to achieve balloon:artery ratios of 1-1.1 to ensure minimal injury and to be in line with the current clinical practice guidelines. Post-implantation angiographic images were acquired in isocentered alignment and from two different views at a rate of 30 frames/s with radio-opaque contrast dye injection through the guide catheter. The radio-opaque contrast dye was diluted the same as that for clinical usage (contrast dye: saline = 1:1).

Additional angiographic images were acquired with specific conditions for validation. We examined the effects of cardiac cycle time and ECG-gating, angle between paired images (imaging angle difference) from 20° to 130°, and isocentricity and non-isocentricity. The non-isocentric paired images were acquired by moving the imaging table from the first image acquisition to the second one, and this movement was also recorded in the DICOM header.

All animal studies were performed at GLP AAALAC accredited animal facility (CBSET, Inc,
Lexington, MA) according to the US Department of Agriculture Animal Welfare Act and with the guidelines described in the Guide for Care and Use of Laboratory Animals. All angiographic images were taken with Innova 2100 (GE Healthcare, Cleveland, OH) and stored in the DICOM format with all the imaging parameters, including the position of the angiography system and the magnification of the images. The resolution was 0.35 mm/pixel ± 0.04 mm/pixel.

S.3 Vessel Centerline Reconstruction from Isocentric Pair of Angiographic Images

End-diastolic images were selected manually for preclinical and clinical datasets. The sensitivity of manual selection was confirmed with a subset of ECG-gated angiographic images *in vivo*. The selected images from two views were imported (Figure S1a) and contrast was adjusted to enhance vessel structure delineation (Figure S1b). Then, the images were thresholded manually to obtain binary images that showed only the stented artery and the side branch with approximately 5 mm margins at both proximal and distal ends. Sobel edge detection was applied, and the insides of the detected edges were filled morphologically (Figure S1c). The filled images were skeletonized to yield candidate centerline projections. The edges of the skeletonized results, where spurious nodes were created, were eliminated (Figure S1d). From these candidates, the potential corresponding pairs between two projected curves were selected based on the vertical distance from the bifurcation between the stented artery and the
side branch. Then, the absolute corresponding pairs were identified (Figure S1c) by applying epipolar constraints (22) three times due to the different lengths of the stented artery and the side branch: (i) only for the stented artery (blue line in Fig. 1d and e), (ii) only for the side branch (red line in Fig. 1d and e), and (iii) for all the identified points in (i) and (ii). Random sample consensus (RANSAC) method was used for (i) and (ii), and least trimmed squares (LTS) method was used for (iii). RANSAC method is appropriate for (i) and (ii) since the distance threshold between the point and epipolar line can be set, while LTS method is appropriate for (iii) because this method enables setting the minimum percentage of inliers, which allows including as many pairs as possible that fall within corresponding pairs determined at (i) and (ii).

Vessel centerlines were reconstructed in 3D from the corresponding pairs using projection matrix \( P \) (Fig. 1f). This projection matrix \( P \) was derived mathematically from the stereoscopic theory (1) that describes the relationship between the actual 3D geometry \((x, y, z)\) and the projected 2D geometry \((u, v) = (r_y/r_x, r_y/r_u)\) based on the rotation and the magnification of the angiographic system (Eqs. S1-S4). All the information on rotations and magnifications were extracted from the DICOM header. Then, the reconstructed 3D points were smoothed with cubic smoothing spline function (2). The smoothing parameter was determined experimentally to minimize the error between the 2D points that were used for reconstruction and the 3D-to-2D
back-projection. Finally, the vessel centerlines were transferred rigidly so that the bifurcation
was coincident to the origin (0, 0, 0). The reconstructions were performed from all imaging
angle differences in vitro and in vivo, and from four different cardiac phases, i.e., end-diastole,
middle-systole, end-systole, and middle-diastole, in vivo. All the processes were executed
within MATLAB environment.

\[
\begin{bmatrix}
  r_x & r_y & r_z \\
\end{bmatrix} = P \begin{bmatrix}
  x & y & z & 1 \\
\end{bmatrix}^T \tag{S1}
\]

\[
P = \begin{bmatrix}
  -S_{ID} \cdot U / IS & 0 & U / 2 \\
  0 & S_{ID} \cdot V / IS & V / 2 \\
  0 & 0 & 1
\end{bmatrix} \begin{bmatrix}
  R_{3d} \cdot R_{5d} & 0 \\
  0 & -S_{OD}
\end{bmatrix} \tag{S2}
\]

\[
R_{3d} = \begin{bmatrix}
  \cos \theta & 0 & -\sin \theta \\
  0 & 1 & 0 \\
  \sin \theta & 0 & \cos \theta
\end{bmatrix} \tag{S3}
\]

\[
R_{5d} = uu^T + \cos \phi \begin{bmatrix}
  1 & 0 & 0 \\
  0 & 1 & 0 \\
  0 & 0 & 1
\end{bmatrix} - uu^T + \sin \phi \begin{bmatrix}
  0 & -u_x & u_y \\
  u_x & 0 & -u_z \\
  -u_y & u_z & 0
\end{bmatrix} \tag{S4}
\]

where

\[
u = R_{5d}^T \begin{bmatrix}
  0 \\
  0
\end{bmatrix}
\]

\[
U, V: \text{dimension of the image in pixels}
\]

\[
\text{S}_{ID}: \text{distance between X-ray source and image intensifier}
\]

\[
\text{S}_{OD}: \text{distance between X-ray source and object}
\]

\[
\theta: \text{Primary angle (LAO/RAO, positive in LAO)}
\]

\[
\phi: \text{Secondary angle (Cranial/Caudal, positive in Cranial)}
\]
Figure S1 Steps of vessel centerline reconstruction

The images from two views are selected (a), and thresholded manually to create the binary images (b). Then, the edge was detected, and the inside is filled morphologically (c) and skeletonized (d). After that, the corresponding pairs in both images were identified by applying epipolar constraints (e), and the initial vessel centerline was reconstructed using stereoscopic relations (f).
S.4 Vessel Centerline Reconstruction from Computed Tomography Angiographic Images

The coronary arteries were reconstructed from the CTA images with ScanIP (Simpleware Ltd., United Kingdom). Images were first segmented to extract the coronary arteries and the neighboring tissue in each frame. The extracted structures were then interpolated in the longitudinal direction (proximal to distal direction). After that, the neighboring tissue was deleted manually and the surface of the coronary arteries was smoothed by applying a Gaussian smoothing filter. Finally, the vessel centerline was extracted by skeletonizing the surface structure of the coronary arteries. The length of the reconstructed vessel centerline between two side branches was compared for our newly developed coronary angiography-based method and a clinically available CTA-based method.

References

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Vessel Centerline Reconstruction from Non-isocentric and Non-orthogonal Paired Monoplane Angiographic Images

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ABSTRACT

Purpose

Three-dimensional reconstruction of a vessel centerline from paired planar coronary angiographic images is critical to reconstruct the complex three-dimensional structure of the coronary artery lumen and the relative positioning of implanted devices. In this study, a new vessel centerline reconstruction method that can utilize non-isocentric and non-orthogonal pairs of angiographic images was developed and tested.

Methods

Our new method was developed in in vitro phantom models of bifurcated coronary artery with and without stent, and then tested in in vivo swine models (twelve coronary arteries). This method was also validated using data from five patients.

Results

Our new method demonstrated high accuracy (root mean square error = 0.27 mm or 0.76 pixel), and high reproducibility across a broad imaging angle (20° to 130°) and between different cardiac cycles in vitro and in vivo. Use of this method demonstrated that the vessel centerline in the stented segment did not deform significantly over a cardiac cycle in vivo. In addition, the total movement of the isocenter in each image could be accurately estimated in vitro and in vivo. The performance of this new method for patient data was similar to that for in vitro phantom models and in vivo animal models.

Conclusions

We developed a vessel centerline reconstruction method for non-isocentric and non-orthogonal angiographic images. It demonstrated high accuracy and good
reproducibility in vitro, in vivo, and in clinical setting, suggesting that our new method is clinically applicable despite the small sample size of clinical data.

**KEYWORDS**

Coronary angiography, Image reconstruction, Reconstruction algorithm, Stereoscopic theory

**INTRODUCTION**

Coronary angiography is the mainstay imaging modality to assess extent of atherosclerotic disease and effects of catheter-based intervention [1-3]. Angiography defines the silhouette of the coronary artery lumen in the 2D projected plane [1-3]. The arterial lumen’s structure can be reconstructed via 3D vessel centerline analysis from paired planar angiographic images [4-10,1]. Moreover, by fusing intravascular images, which capture the cross-sectional plane of the coronary arteries, onto the vessel centerline in lieu of the imaging catheter path, we can analyze both lumen and stent simultaneously [11-15]. Thus, 3D reconstruction of the vessel centerline from paired planar angiographic images has great potential of clinical utility, and many vessel centerline reconstruction methods have therefore been proposed. However, clinical adoption of them has been limited due to their image requirements. Most of the state-of-the-art methods have been validated for isocentric (i.e., no machine-origin isocenter offset [4-10,1] or no movement of object center from image to image [6,5,13]) and orthogonal pairs of angiographic images [14,16,15], which is difficult to satisfy in actual clinical settings. In addition, influence on 3D structural reconstruction by fusing angiography and intravascular imaging has been unclear because the morphology change of vessel centerline has not been evaluated. Current fusion techniques assume no change in centerline morphology despite the facts that angiographic images and intravascular images are acquired at different timings (i.e., at different cardiac cycles) and that, within a cardiac cycle, cardiac motion may affect the morphology of coronary arteries.

In this study, we developed a new vessel centerline reconstruction method that overcame these spatial and temporal alignment challenges using static phantom models and in vivo swine models. We tested the precision and limitations of our method by evaluating the reproducibility of vessel centerline reconstruction across variable imaging angle differences and for images from different phases of the cardiac cycle. We also evaluated deformation of the vessel centerline over a cardiac cycle
cycle to understand the potential influence of cardiac motion on 3D structural reconstruction. We finally validated this method using datasets that were obtained from patients in real-world clinical scenarios to test its clinical applicability.

MATERIALS AND METHODS

In Vitro Static Phantom Models

Two static phantom models that we previously developed [17] were used. Their geometries are similar to those of human coronary arteries and their mechanical properties are matched to those of human native coronary arteries. A 3.0 mm × 17 mm bare metal stent was implanted in one of them. Isocentric and non-isocentric pairs of angiographic images were acquired for each phantom model with the angle between the paired images of 20°-130° (Supplement S.1). Non-isocentric paired images were created by moving the imaging table after the first image was captured and before the second image was captured.

In Vivo Animal Models

All animal studies were performed at an AAALAC accredited animal facility (CBSET, Inc., Lexington, MA) according to the US Department of Agriculture Animal Welfare Act and within the guidelines described in the Guide for Care and Use of Laboratory Animals.

Twelve coronary arteries (five right coronary arteries (RCA), four left anterior descending arteries (LAD), and three left circumflex arteries (LCX)) from five Yorkshire swine (40-50 kg) were imaged in vivo. After implanting bare metal stents (3.0 mm × 17 mm) to the targeted vessels (Supplement S.2), angiographic images were acquired in the same manner as the one with the phantom models. Some of the angiographic images were acquired with ECG monitoring.

Clinical Datasets

Clinical data was obtained from six patients who underwent coronary stent implantation. This data contained computed tomography angiographic (CTA) images at pre-implantation and coronary angiographic images at pre- and post-implantation. The retrospective use of the angiographic and CTA images was approved by
the Ethics Committee at University of Sao Paulo Medical School.

**Vessel Centerline Reconstruction**

Vessel centerline was reconstructed in 3D from corresponding pairs of 2D projected points using projection matrix $P$. This projection matrix $P$ was derived mathematically from stereoscopic theory [18]. This theory describes the relationship between the actual 3D geometry $(x, y, z)$ and the projected 2D geometry $(u,v) = \left( \frac{r}{r_u}, \frac{r}{r_v} \right)$ based on the rotation and the magnification of the angiographic system (Eqs. 1-3), all of which were obtained from the DICOM header. The corresponding pairs of 2D points were determined with Epipolar constraints [18] from the centerline candidate points that were yielded from the angiographic images from two views (Supplement S.3). Then, the reconstructed 3D points were smoothed by applying cubic smoothing spline function [19]. The smoothing parameter was determined experimentally (Supplement S.3). Finally, the vessel centerlines were transferred rigidly so that the bifurcation of the stented artery and the nearby side branch was coincident to the origin $(0, 0, 0)$. The reconstructions were performed from all imaging angle differences in vitro and in vivo, and from four different cardiac phases, i.e., end-diastole, middle-systole, end-systole, and middle-diastole, in vivo. All the processes were executed within MATLAB environment.

**Implementation of Algorithm for Non-isocentric Paired Images**

To make the developed vessel centerline reconstruction method applicable to non-isocentric pairs of images, an algorithm was implemented based on Yang, et al.’s method [7]. First, a corresponding anatomical landmark, e.g., bifurcation point, was selected manually in both images. Then, one of the images was moved to align the vertical location of the manually selected landmark. This initial 3D centerline geometry was back-projected to the 2D space by considering the total movements of the isocenter in each image, $m_1$ and $m_2$ (Eqs. 1 and 2, Fig. 1). $m_1$ and $m_2$ were then found by minimizing the optimization function (Eq. 3) described by the sum of point transfer error (distance between the original 2D points extracted from angiographic images and the corresponding 3D-to-2D back-projected points) and directional vector transfer error (distance between the original 2D direction vectors and the projected 3D directional vectors). Levenberg-Marquardt
(LM) nonlinear optimization algorithm was used for this minimization [7].

\[
\begin{align*}
  u_{i,j} &= P_1(X_i + m_1) \\
  u_{2,j} &= P_1(X_i + m_2)
\end{align*}
\]

where \((k = 1, 2)\)

\[
m_k = m_{k_isocenter_offset} + m_{m_table/object}
\]

\[
P = \begin{bmatrix}
  -S I D_k \cdot U / IS_k & s_k & U / 2 \\
  0 & S I D_\ell \cdot V / IS_\ell & V / 2 \\
  0 & 0 & 1
\end{bmatrix} 
\]

\[
f(m_1, s_1, m_2, s_2) = \sum_{j=1}^n \left[ (u_{i,j} - P_1(X_i + m_1))^2 + (u_{2,j} - P_2(X_j + m_2))^2 \right] 
\]

\[
+ w \sum_{j=1}^n \left[ \frac{u_{i,j} - u_{1,j-1}}{||u_{i,j} - u_{1,j-1}||} - \frac{P_1(X_j + m_1) - P_1(X_{j-1} + m_1)}{||P_1(X_j + m_1) - P_1(X_{j-1} + m_1)||} \right]^2 
\]

\[
+ \frac{u_{2,j} - u_{2,j-1}}{||u_{2,j} - u_{2,j-1}||} - \frac{P_2(X_j + m_2) - P_2(X_{j-1} + m_2)}{||P_2(X_j + m_2) - P_2(X_{j-1} + m_2)||} \right]^2
\]

Finally, using this optimal \(m_1\) and \(m_2\), the 3D centerline geometry was updated. The updated centerline was smoothed and transferred rigidly as explained in the previous section.

**Vessel Centerline Registration**

After reconstructing the vessel centerlines from various imaging angle differences either with or without table movement and/or from different cardiac cycles or cardiac phases, the centerlines from the same vessel were registered to the centerline that was reconstructed from a pair of isocentric and orthogonal angiographic images by rotating rigidly to minimize the distance between two landmarks, Landmarks 1 and 2 (Fig. 2).
Method Validation

The implemented algorithm for a non-isocentric pair of images was first validated by (i) comparing the static error, i.e., difference between the reconstructed geometry and the actual geometry, before and after implementing the algorithm in in vitro, and (ii) comparing the estimated movement to the actual movement in in vitro and in vivo.

Then, the entire vessel centerline reconstruction method was validated in vitro and in vivo. The reconstructed geometries of both the non-stented and the stented phantom models, from various imaging angle differences (20°-130°), were compared to the actual geometry in terms of lengths and bifurcation angle. The vessel centerline reconstructed with our method was compared to the centerline reconstructed with Bourantas, et al.’s method [12], which does not use the projection matrix, from the same in vivo angiographic images.

Reproducibility of the centerline reconstruction was evaluated across the imaging angle differences and between different cardiac cycles using two sets of angiographic images: isocentric images whose imaging angle differences varied from 50° to 130° (N = 48; 4 vessels, 12 patterns of imaging angle difference/vessel) and non-isocentric images whose imaging angle differences varied from 20° to 130° (N=64; 2 vessels, 16 patterns of imaging angle difference/vessel, 2 movement patterns/imaging angle difference). After registering all the vessel centerlines to that obtained from isocentric and orthogonal paired images or from end-diastolic phase images of an earlier cardiac cycle, the reproducibilities were evaluated in terms of: (i) the difference in the stented segment length between two side branches, (ii) the distance between Landmarks 1, (iii) the difference in the maximum curvature of the stented segment, (iv) the error of the bifurcation angle, (v) the distance between Landmarks 2, and (vi) the angle between Landmarks 2 ((ii)-(vi) for isocentric images, and (i)-(iii) and (v) for non-isocentric images). The maximum curvature in the stented segment was determined from the change in the tangent vector $\mathbf{T}$ along the curve $s$, i.e., the reconstructed vessel centerline of the stented segment, or

$$\kappa_{\text{max}} = \max\left(\frac{dT(s)}{ds}\right)$$

(4)
where $\kappa_{\text{max}} = 0$ designates a straight line, and as $\kappa_{\text{max}}$ approaches 1, the curvature closely represents that of a unit sphere.

**Vessel Centerline Deformation over a Cardiac Cycle**

Deformation of the vessel centerline was evaluated by assessing the same metrics as in the previous section for four different cardiac phases, i.e., end-diastole, mid-systole, end-systole, and mid-diastole, based on the result from the end-diastolic images.

**Clinical Applicability**

To evaluate clinical applicability, the reconstructed vessel centerlines with our method were first compared to those from CTA images (Supplement S.4) in terms of the length between two side branches (4 LAD, 3 LCX). Then, the reproducibility of vessel centerline between different cardiac cycles and the deformation of the vessel centerline over a cardiac cycle were evaluated (1 RCA, 5 LAD, 2 LCX) and compared to those results in the preclinical setting.

**RESULTS**

**Validation of Implemented Algorithm**

The implemented algorithm for non-isocentric paired angiographic images was first validated by evaluating the optimization function (Eq. 3). Larger static errors were observed in 62.5% of cases for the non-stented phantom model and 48.5% of cases for the stented phantom model when the directional vector transfer error was not used. This is because the 3D-to-2D projected geometry may not be parallel to the extracted 2D geometry when the directional transfer error is not considered, although the point transfer error is minimal and the same between with and without the directional vector transfer error. This result suggests that the existence of the directional vector transfer error enables the reconstruction of more precise vessel centerlines from non-isocentric paired images.

Secondly, the movement estimated with this optimization function, which is the sum of the machine-origin isocenter offset and the table and/or object movement, was compared to the actual movement. If the machine-origin isocenter offset can be assumed to be small, the estimated movement should be close to the actual
movement of the table since the phantom models are static. Indeed the differences were small (Table 1, N=32 for each phantom model), though as the isocenter offset was not available, these differences cannot be compared directly to the machine-origin isocenter offset. Nonetheless, these differences were less than 1% of the distance between X-ray source and the intensifier: 0.19% ± 0.10% for the non-stented model and 0.33% ± 0.09% for the stented model.

The same comparison was performed for preclinical data obtained from in vivo swine (Table 1; N = 64 in total, N = 32 for LAD and N=32 for LCX). The absolute differences and the errors are similar to the in vitro results (Table 1). Slight differences between in vitro and in vivo results are likely caused by movement of the object, i.e., the swine itself. Since the swine is anesthetized during the procedure, the object movement is expected to be minimal, which is consistent with these findings. Similar to the static phantom model result, these differences represent less than 1% of the distance between the X-ray source and the intensifier: 0.23% ± 0.10% for LAD and 0.34% ± 0.13% for LCX. In addition,

Finally, to evaluate the effectiveness of the algorithm, the 3D-to-2D back-projected distance error after applying the algorithm was compared to that before applying the algorithm. The 3D-to-2D back-projected distance error was evaluated with Eq. 5 using the distances of each 2D point that was used for reconstruction.

$$\text{error} = \sqrt{\frac{\sum_{i=1}^{n} (\text{distance})^2}{n}}$$  \hspace{1cm} (5)

The error improved by approximately 35-fold in vitro and by approximately 30-fold in vivo by applying this algorithm (Table 2). In addition, the in vitro error after applying this algorithm was similar to that of Yang, et al.’s method (1.30 pixels) [7]. Moreover, the in vivo errors were similar to or only slightly larger than the in vitro errors.

**Static Errors of Length and Bifurcation Angle**

Our method produced similar centerline geometries to the actual geometry for all imaging angle differences (20°-130°) in both the non-stented and the stented phantom models for both isocentric pairs (without table movement) and non-isocentric pairs (with table movement) (Fig. 3). The static errors of the length and the bifurcation angle (N=32) were summarized in Table 3. These errors were independent of imaging angle differences. These results demonstrate that our method has a high reproducibility across various imaging angle differences (20°-130°).
**Comparison to State-of-the-art Method**

Our method yielded a similar shape in the stented segment to the state-of-the-art method (Fig. 4). The root mean square error between these two vessel centerline in the stented segment was 0.27 mm or 0.76 pixels, similar to or smaller than the error with Yang et al.’s method (0.26 mm or 1.3 pixels [7], 0.367 mm on average [20]).

**Reproducibility of Vessel Centerline Reconstruction**

The reconstructed vessel centerlines from various imaging angle differences and from different cardiac cycles were similar to each other especially in the stented segment (Figs. 5 and 6a). Although the difference in the stented segment length between two side branches was bigger than that of the stented phantom model, these two values have similar magnitude when compared to the based length or the actual length (8.8% ± 5.9% for imaging angle difference and 7.9% ± 4.3% for different cardiac cycles vs. 4.4% ± 4.0%), suggesting that the performance is similar between in vitro and in vivo (Tables 4 and 5). In addition, for both different imaging angles and different cardiac cycles, the distances between Landmarks 1 were smaller than the static error of length in both isocentric and non-isocentric paired angiographic images, and the difference in the maximum curvature of the stented segment was small (Tables 4 and 5). These results suggest a robust reproducibility of our method for various imaging angle differences and from different cardiac cycles. On the other hand, the difference in the bifurcation angle was bigger than that in the stented phantom model (Tables 4 and 5). This is likely due to the twisting of the side branch over time as cardiac motion is torsional and not planar and as the side branch does not have any constraints to its movement, unlike the relatively rigid stented segment. The facts that the distance between Landmarks 2 is bigger than the static error of length and that the angle between Landmarks 2 is widely varied support the presence of twisting (Tables 4 and 5).

**Deformation of Vessel Centerline over a Cardiac Cycle**

The difference in the stented segment length between two side branches was larger than the static error of length, but the distances between Landmarks 1 were
smaller than the static error of length and the distance from the intersection of the stented segment and the nearest side branch in both isocentric and non-isocentric pairs of images (Table 5). The difference in the maximum curvature of the stented segment was small (Table 5). In addition, all the results were similar to the reproducibility results (Tables 4 and 5). These findings suggest that the vessel centerline in the stented segment does not deform significantly over a cardiac cycle (Fig. 7a). On the contrary, the difference in bifurcation angle was bigger than the static error, and the distance between the pair of Landmarks 2 was also bigger than the root mean square error. Considering that both of them and the angle between the pair of Landmarks 2 were similar to the results of reproducibility between different cardiac cycles, the twisting of the side branch over time likely causes these results.

**Clinical Applicability**

CTA is a clinically-used imaging modality to reconstruct the structure of the lumen [3,21]. Although its sensitivity for detecting coronary arteries is not as high as that of coronary angiography, the 3D structures of the coronary arteries can be reconstructed with sufficient accuracy to evaluate its dimension [3,21]. Our method yielded similar vessel centerlines to those from the CTA images for all seven vessels (Fig. 8). The difference between the two methods in estimating vessel centerline length between two side branches was 7.2% ± 5.5%, which is smaller than the static error of length. The reconstructed vessel centerlines had similar shapes, especially in the stented segment, from two different cardiac cycles (Fig. 6b) and from four different cardiac phases (Fig. 7b) for all three patients. The results of reproducibility and deformation were similar to those in the preclinical setting (Table 5).

**DISCUSSIONS**

**Advantages of Our Newly Developed Method**

Our new vessel centerline reconstruction method is significant and potentially clinically valuable as: (i) it can handle non-isocentric and non-orthogonal paired angiographic images, (ii) it has high reproducibility across imaging angle differences (20°-130°) and for different cardiac cycles, specifically in the stented segment, (iii) it is robust to cardiac motion, and (iv) it can estimate accurately the total isocenter movement in each image.
Most state-of-the-art methods, including those available in commercial software, have not been validated for non-isocentric and/or non-orthogonal paired angiographic images and cannot account for differences in cardiac timing or displacement. Tu, et al.’s method [11] can handle non-orthogonal pairs if the imaging angle difference is at least 25° and ignores skew, while our method can handle paired images with at least 20° of imaging angle difference. Unlike Yang, et al.’s method [7,20], our method can estimate the total isocenter movement and skew in each image. Moreover, this method can reconstruct the vessel centerline even with vascular foreshortening at extreme imaging angle.

The accuracy of this new method is comparable to that of the state-of-the-art methods. This method yielded a vessel centerline in the stented segment similar to that yielded by the currently available method [12] with the root mean square error between two vessel centerlines similar to that with Yang, et al.’s method [7,20] in in vivo preclinical setting. Moreover, our method can yield similar vessel centerlines, even in relatively tortuous artery, e.g., RCA and LCX, compared to the vessel centerline that was reconstructed from CTA images, which is a clinically available method. Importantly, the error in vessel centerline reconstruction with this method in the clinical setting was similar to that in the preclinical setting, which suggests that this method is sufficiently robust even when the imaging environment cannot be recorded precisely and when the underlying disease may affect the image acquisition.

**Influence on 3D Structural Reconstruction**

There are two intravascular imaging modalities: intravascular ultrasound and optical coherence tomography (OCT). Because of higher in-plane resolution [22,11], 3D reconstruction of lumen and stent via angiography-OCT fusion could be more precise. However, since OCT images of the stented segment are acquired over approximately a single cardiac cycle due to the fast pullback speed of OCT [14], the deformation of the vessel centerline may affect the accuracy of 3D reconstruction. The vessel centerline reconstructed with our method did not deform significantly in the stented segment. This suggests that the usage of the vessel centerline that is reconstructed with our method can minimize the influence on angiography-OCT fusion, leading to more accurate reconstruction of lumen and stent in 3D space.
Study Limitations

The robust, consistent, and reproducible results across models (in vitro, in vivo swine, and in vivo human) were obtained using a small sample size in the clinical setting. Further analysis with a large sample size is required. In addition, this method has been tested in stented segments. Thus, further investigation on the non-stented segment and improvement is necessary to make this method applicable from native vessel to stented segment.

CONCLUSIONS

We developed a vessel centerline reconstruction method using stereoscopic theory to enable use of non-isocentric and non-orthogonal angiographic images. This method demonstrated high accuracy and good reproducibility in various angles between paired images and in different cardiac cycles. We demonstrated that the vessel centerline of the stented segment did not deform greatly within a cardiac cycle. All of these features were retained in the clinical setting. Although the clinical sample size is small (five patients), these results suggest that our new method is applicable to the actual clinical data.

SUPPLEMENTARY DATA

The detail description of experiments with phantom models and animal model, and vessel centerline reconstruction from isocentric pair of angiographic images and from CTA images are available in supplement.

References
Table captions:

Table 1 Comparison between actual movement and estimated movement.

<table>
<thead>
<tr>
<th></th>
<th>Actual movement</th>
<th>Estimated movement</th>
<th>Difference</th>
<th>Error</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phantom model (in vitro)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-stented</td>
<td>25.5 mm</td>
<td>23.5 ± 1.2 mm</td>
<td>2.0 ± 1.1 mm</td>
<td>8.0 ± 4.3%</td>
</tr>
<tr>
<td></td>
<td>Stented</td>
<td>Preclinical data (\textit{in vivo})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
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<td>----------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>35.2 mm</td>
<td>LAD 23.8 mm</td>
<td>26.2 ± 1.0 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31.6 ± 1.0 mm</td>
<td>2.4 ± 1.0 mm</td>
<td>10.1 ± 4.1 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.6 ± 1.0 mm</td>
<td>15.1 ± 5.3 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.4 ± 2.8 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35.2 mm</td>
<td>LCX 23.8 mm</td>
<td>27.4 ± 1.3 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31.6 ± 1.0 mm</td>
<td>3.6 ± 1.3 mm</td>
<td>15.1 ± 5.3 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.4 ± 2.8 %</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All the values were represented as mean ± standard deviation.

**Table 2** 3D-to-2D back-projected distance error before and after applying an algorithm

<table>
<thead>
<tr>
<th></th>
<th>Before applying</th>
<th>After applying</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phantom model (\textit{in vitro})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-stented</td>
<td>18.1 mm, 46.2 pixel</td>
<td>0.458 mm, 1.17 pixel</td>
</tr>
<tr>
<td>Stented</td>
<td>25.4 mm, 65.0 pixel</td>
<td>0.768 mm, 1.97 pixel</td>
</tr>
<tr>
<td>Preclinical data (\textit{in vivo})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>16.9 mm, 50.0 pixel</td>
<td>0.778 mm, 2.30 pixel</td>
</tr>
<tr>
<td>LCX</td>
<td>16.7 mm, 49.4 pixel</td>
<td>0.437 mm, 1.29 pixel</td>
</tr>
</tbody>
</table>

* All the values were represented as mean ± standard deviation.

**Table 3** Static errors of length and bifurcation angle

<table>
<thead>
<tr>
<th></th>
<th>Isocentric pair</th>
<th>Non-isocentric pair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Non-stented  1.9 mm ± 1.4 mm  1.7 mm ± 1.4 mm
Stented  1.8 mm ± 1.5 mm  1.8 mm ± 1.6 mm

Bifurcation angle
Non-stented  2.6° ± 1.7°  2.6° ± 2.0°
Stented  1.5° ± 0.9°  0.9° ± 0.9°

* All the values were represented as mean ± standard deviation (N=32).

Table 4 Reproducibility of vessel centerline reconstruction across various imaging angle differences (in vitro phantom models)

<table>
<thead>
<tr>
<th></th>
<th>Difference in stented segment length</th>
<th>Distance between pair of Landmark 1</th>
<th>Distance between pair of Landmark 2</th>
<th>Difference in bifurcation angle</th>
<th>Angle between pair of Landmark 2</th>
<th>Difference in maximum curvature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isocentric images</td>
<td>(0.11±0.10) mm (0.39±0.34) pixel</td>
<td>(0.83±0.58) mm (2.90±2.01) pixel</td>
<td>13.7°±10.8°</td>
<td>24.3°±17.4°</td>
<td>0.11±0.09</td>
<td></td>
</tr>
<tr>
<td>Non-isocentric images</td>
<td>(3.3±2.2) mm (9.8±6.4) pixel</td>
<td>(0.46±0.28) mm (1.37±0.82) pixel</td>
<td>(0.38±0.47) mm (1.12±1.38) pixel</td>
<td>10.9°±16.6°</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* All the values were represented as mean ± standard deviation.

Table 5 Evaluation results with in vivo preclinical data and clinical data. Reproducibility of vessel centerline reconstruction between different cardiac cycles and deformation of vessel centerline over a cardiac cycle were evaluated with both data.
<table>
<thead>
<tr>
<th></th>
<th>Difference in stented segment length</th>
<th>Distance between pair of Landmark 1</th>
<th>Distance between pair of Landmark 2</th>
<th>Difference in bifurcation angle</th>
<th>Angle between pair of Landmark 2</th>
<th>Difference in maximum curvature</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reproducibility</strong></td>
<td></td>
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<tr>
<td><em>in vivo</em> preclinical data,</td>
<td></td>
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</tr>
<tr>
<td>Isocentric images</td>
<td>(0.06±0.07) mm</td>
<td>(0.40±0.13) mm</td>
<td>9.7°±5.9°</td>
<td>11.6°±3.8°</td>
<td>0.065±0.029</td>
<td></td>
</tr>
<tr>
<td><em>in vivo</em> preclinical data,</td>
<td>(3.0±1.6) mm</td>
<td>(0.30±0.13) mm</td>
<td>3.6°±2.8°</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-isocentric images</td>
<td>(8.8±4.7) pixel</td>
<td>(0.89±0.38) pixel</td>
<td>7.0°±2.2°</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical data</td>
<td>(2.9±1.4) mm</td>
<td>(0.12±0.05) mm</td>
<td>0.23±0.15 mm</td>
<td>11.6°±3.8°</td>
<td>0.065±0.029</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(8.4±4.0) pixel</td>
<td>(0.36±0.16) pixel</td>
<td>(0.73±0.20) pixel</td>
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<tr>
<td><strong>Deformation</strong></td>
<td></td>
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<tr>
<td><em>in vivo</em> preclinical data,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isocentric images</td>
<td>(0.42 ±0.54) mm</td>
<td>(0.49±0.38) mm</td>
<td>13.7°±10.9°</td>
<td>14.0°±11.1°</td>
<td>0.072±0.061</td>
<td></td>
</tr>
<tr>
<td><em>in vivo</em> preclinical data,</td>
<td>(4.3±1.7) mm</td>
<td>(0.33±0.21) mm</td>
<td>7.1°±6.0°</td>
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<tr>
<td>Non-isocentric images</td>
<td>(12.7±4.9) pixel</td>
<td>(0.97±0.61) pixel</td>
<td>(1.11±0.87) pixel</td>
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<tr>
<td>Clinical data</td>
<td>(3.2±2.1) mm</td>
<td>(0.64±1.38) mm</td>
<td>(0.38±0.34) mm</td>
<td>10.5°±9.9°</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(9.3±6.1) pixel</td>
<td>(1.87±3.75) pixel</td>
<td>(1.10±1.00) pixel</td>
<td></td>
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</tr>
</tbody>
</table>

* All the values were represented as mean ± standard deviation.
Fig. 1 Potential causes of the isocenter movement.

(a) Machine-origin isocenter offset: The angiography system itself has an isocenter offset when it is rotated. This offset appears in each image as the difference between the center of view and the projected origin.

(b) Movement of the object center: During the procedure, the center of the object may move because physicians may move the table and/or patients themselves may move.

Fig. 2 Algorithm for vessel centerline registration.

First, two landmarks, Landmark 1 and 2 were set (a). Then, the secondary geometry (dotted line) was rotated about the origin until the distance between corresponding Landmarks 1 was minimized (b). Next, a vector through the origin and Landmark 1 was defined. Finally, the secondary geometry was rotated again about this vector until the distance between corresponding Landmarks 2 was minimized (c).
Fig. 3 Phantom models and reconstructed centerline geometries.

All the centerlines reconstructed from various imaging angle differences (20°-130°) were similar in lengths and bifurcation angle to the actual geometry in both non-stented and stented phantom models.

Fig. 4 Comparison between our vessel centerline reconstruction method and the state-of-the-art method.

The vessel centerline reconstructed with our method had a quite similar shape to that obtained with Bourantas et al.’s method in the stented segment.
**Fig. 5** Reproducibility across various imaging angle differences ($20^\circ$-$130^\circ$).

All the vessel centerlines from non-orthogonal pairs of angiographic images ($20^\circ$-$130^\circ$) were aligned well to the centerline from an orthogonal pair of angiographic images.

**Fig. 6** Reconstructed vessel centerlines from two different cardiac cycles: (A) pre-clinical results, (B) one patient result.

The vessel centerlines that were reconstructed from two different cardiac cycles had quite similar shapes, especially in the stented segment, in both pre-clinical and clinical settings. Blue and red lines represent the vessel centerlines from two different cardiac cycles.
Fig. 7 Deformation of the vessel centerline over a cardiac cycle: (A) pre-clinical results, (B) one patient result.

The vessel centerline did not deform significantly within the stented segment in both pre-clinical and clinical settings. Blue, red, green, and black lines represent the vessel centerlines at end-diastolic, mid-systolic, end-systolic, and mid-diastolic phases, respectively.

Fig. 8 Reconstructed vessel centerlines with CTA-based method (a) and with our method (b) (one patient result).