

Research Advances in 4D-CTA for Rupture Risk Assessment of Intracranial Aneurysms

Ziyu Zhou, Zixuan Deng, Nan Li, Xiujuan Liu

Department of Radiology, Zhuhai Clinical Medical College of Jinan University (Zhuhai People's Hospital, The Affiliated Hospital of Beijing Institute of Technology), Zhuhai, China
Email: zzy06250925@163.com

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Abstract

Conventional imaging techniques can observe static morphological parameters, such as shape, location, and size, which are related to the rupture of aneurysms, but these parameters may be incomplete and controversial. Currently, dynamic four-dimensional CT angiography (4D-CTA) has been widely used in cerebrovascular imaging. Compared with other traditional imaging methods, 4D-CTA has a higher temporal resolution. By visualizing aneurysm wall motion and blood flow, dynamic morphological parameters can be observed, such as irregular pulsation and morphological change rate, so as to more accurately assess the rupture risk of intracranial aneurysms. This article reviews the progress of the application of 4D-CTA in assessing the risk of ruptured intracranial aneurysms.

Keywords

Intracranial Aneurysm, Rupture Risk Assessment of, 4D-CTA

1. Introduction

Intracranial aneurysms (IAs) are focal pathological dilations of the intracranial arteries. They generally occur in individuals aged 40 to 60, with a prevalence of approximately 3% to 5% [1]. Most patients with IAs remain asymptomatic until rupture. However, unruptured IAs are associated with an annual rupture risk of approximately 1%, which can result in aneurysmal subarachnoid hemorrhage (SAH). Furthermore, aneurysm ruptures are the leading cause of spontaneous SAH [2], accounting for 70% to 85% of cases annually. Approximately 27% of patients with SAH may die within one year [3]. The management of IAs, whether through surgical clipping or endovascular treatment, carries a potential complication and mortality rate of around 2% to 5% [4]. Therefore, the selection between

aggressive surgical intervention and conservative treatment for unruptured intracranial aneurysms (UIAs) remains a subject of ongoing debate. Accurately identifying the UIAs with high rupture risk is essential to resolving this controversy.

The most common locations of IAs are the turning points of the Willis circle and the bifurcations of the middle cerebral artery. This is due to the fact that these vascular regions are exposed to continuous and intense blood flow impingement, making them more susceptible to aneurysm formation and eventual rupture. This observation highlights the critical role of hemodynamics in aneurysm formation and rupture. The hemodynamics largely depend on morphological changes in the aneurysm sac and the parent artery [5]-[8]. Therefore, appropriate morphological parameters that describe the geometric features of IA can reflect its hemodynamic characteristics and predict rupture risk. While traditional imaging techniques are valuable in characterizing morphological parameters, they primarily provide static parameters, such as shape, location, and size, which lack temporal dimensions and are associated with rupture risk [9] [10]. However, the blood flow in IAs, similar to the parent artery, is pulsatile, leading to dynamic morphological changes rather than a fixed, static form [11]. Consequently, these static morphological parameters are insufficient for comprehensive rupture risk assessment and remain controversial [12].

Compared to traditional two- and three-dimensional vascular imaging techniques, dynamic four-dimensional computed tomography angiography (4D-CTA) offers superior temporal resolution in cerebrovascular imaging. This technique enables visualization of wall motion and hemodynamics, thereby providing critical information for a more accurate assessment of IA rupture risk. Consequently, 4D-CTA serves as a valuable reference for determining optimal treatment timing and strategies for IAs. This article reviews recent advances in the application of 4D-CTA for assessing rupture risk, highlighting its application and clinical value.

2. Concept and Imaging Schemes

4D-CTA is an advanced imaging technique that builds upon conventional Computed Tomography Angiography (CTA) by incorporating a temporal dimension. Multiple-phase recording of contrast agent flow into and out of the vessels allows for the acquisition and visualization of hemodynamic characteristics of the cerebral vasculature over time. In addition to the information provided by conventional CTA, 4D-CTA offers dynamic observation of cerebral vessels and vascular lesions [13], addressing the limitations of three-dimensional CTA in temporal resolution.

In 4D-CTA, a single scan provides cranial CT, dynamic CTA, and whole-brain CT perfusion (CTP) images, enabling dynamic subtraction of cerebral vessels across the entire brain along the temporal axis [14]. Current practice typically involves the use of a 320-row CT scanner, which can complete a full-brain scan in a single rotation of the X-ray tube without requiring patient movement [15]. Electrocardiogram (ECG) gating, originally used in coronary CTA to reduce motion

artifacts caused by cardiac pulsations, can also synchronize scans with the cardiac cycle. This enables the dynamic visualization of vascular structures throughout the cardiac cycle. When applied to IAs, ECG-gated 4D-CTA uses a coronary CTA scanning protocol to acquire volumetric data for a single R-R interval, which is then reconstructed in increments of 5% time intervals. This results in 20 data sets, generating dynamic images corresponding to each R-R interval, and producing continuous, time-sequenced images of the IAs [16]. The resulting datasets are transferred to an offline workstation for further analysis and reconstruction, allowing for comprehensive dynamic imaging of the IAs.

3. Dynamic Morphometric Indicators of Risk of Rupture of Intracranial Aneurysms Assessed by 4D-CTA

The morphology of an IA is dynamically influenced by pulsatile blood flow resulting from cardiac contraction and relaxation. Throughout the cardiac cycle, the aneurysm wall exhibits cyclic deformation. Due to the structural heterogeneity of the aneurysm wall, its motion patterns can range from global expansion to localized irregular pulsations [17]. Dynamic morphologic indices of 4D-CTA for assessing the rupture risk of IAs include irregular pulsations and the rate of morphology change, both of which reflect dynamic alterations in IAs. These aspects are discussed in detail below.

3.1. Irregular Pulsations

4D-CTA enables the evaluation of aneurysm wall motion and facilitates the identification of focal, irregular, and discrete pulsations, thereby improving the accuracy of rupture risk assessment. Regarding the definition of irregular pulsation, Hayakawa *et al.* [18] proposed that a pulsation point is identified when a bleb-like undulation or a small sharp protrusion is observed at the same location on the IA wall over at least three consecutive frames. Subsequently, Zhang *et al.* [19] provided a more refined interpretation, defining an irregular pulsation as a focal protrusion of 1 mm or greater observed in at least three consecutive frames. In these studies, the identification of irregular pulsations relied on manual evaluation, which tends to be subjective. To address this limitation, Xie *et al.* [20] [21] introduced a method based on displacement and strain to automatically identify and quantify irregular pulsations in IAs, offering a more standardized definition for clinical work.

In the early 21st century, Kato *et al.* [22] observed blebs in 10 cases of IAs using 4D-CTA. They measured the displacement of the bleb during each pulsation and hypothesized that the point of maximal amplitude of abnormal pulsation observed within the cardiac cycle might represent a potential rupture site. Pathological examination of these cases showed 100% positive results, with hematoxylin and eosin staining revealing the partial or complete absence of the smooth muscle in the medial layer and internal elastic lamina of the aneurysm wall. A sudden reduction

in collagen at the bleb site suggested imminent rupture. This study provided pathological evidence supporting the use of 4D-CTA in assessing IAs rupture risk.

On the other hand, the ability of 4D-CTA to assess IAs rupture risk has also been confirmed during surgical procedures. Hayakawa *et al.* [18] defined pulsation points as irregular, small, bubble-like fluctuations or minor protrusions observed at the same location of the aneurysm wall in at least three consecutive frames. Pulsations were observed in four cases, specifically at the dome of the bleb. Two patients underwent clipping, and the rupture sites identified during surgery corresponded precisely with the pulsation points observed on 4D-CTA. Ishida *et al.* [23] identified pulsatile blebs on preoperative 4D-CTA in two patients with SAH, which were subsequently confirmed as rupture sites during surgery. These studies suggest that pulsatile blebs detected on 4D-CTA can predict rupture points, thereby identifying IAs with high rupture risk.

Pulsations observed on 4D-CTA can reflect structural weak points in the aneurysm wall, potentially attributed to the fact that IA pulsations reflect structural weaknesses in the aneurysm wall [24]. These dynamic wall motions are associated with localized thinning of the wall, progressive aneurysm growth, and ultimately, rupture. Longitudinal studies have linked pulsation to aneurysm growth, confirming their association with rupture risk. Ishida *et al.* [23] reported aneurysm growth in two cases over an average follow-up of 12.5 months (range 3 to 18 months), with highly irregular pulsations at the dome on 4D-CTA. Similarly, Krings *et al.* [25] found that pulsation sites identified through 4D-CTA with ECG gating corresponded to regions of aneurysm growth during follow-up. Hayakawa *et al.* [26] conducted a study with an average follow-up period of 453.07 days (range 137 to 1236 days), finding that aneurysms with pulsations detected by 4D-CTA were more likely to show shape changes during follow-up ($P = 0.04$). Gu *et al.* [11] retrospectively analyzed 168 cases of IAs using 4D-CTA and found that 5 out of 16 aneurysms with pulsation points showed growth during follow-up, compared to only 1 out of 43 without pulsation points. The annual rupture rate for growing UIAs is approximately 10 times higher than for non-growing ones [27]. Therefore, these findings suggest that irregular pulsations observed on 4D-CTA may assist in identifying IAs with a higher rupture risk.

The significant correlation between the occurrence of pulsations and rupture of IAs has been further confirmed through statistical analysis of large case series. Gu *et al.* [11] demonstrated, through multivariable regression analysis in a retrospective study of 168 cases, that the occurrence of pulsations is an independent predictor of rupture in asymptomatic IAs. Zhou *et al.* [28], in a prospective study of 217 small IAs (<7 mm), found that irregular pulsations were independently associated with aneurysm rupture ($p = 0.003$). Therefore, irregular pulsations may be regarded as a supplementary risk factor for predicting the rupture risk of intracranial aneurysms.

Besides, irregular pulsations can be considered an additional risk factor for predicting aneurysm rupture. Zhou *et al.* [28] also identified that traditional rupture-

related features, such as aneurysm irregularity and size ratio, were independent predictors of irregular pulsations, indicating a correlation between these factors. Zhang *et al.* [19] observed that IAs with irregular pulsations had significantly larger volumes and more irregular shapes. Cui *et al.* [29] used 4D-CTA imaging reconstruction to predict irregular pulsations in elderly patients with IAs. Their study identified a larger size ratio, posterior circulation aneurysms, and the presence of sub-dome aneurysms as independent predictors of irregular pulsations. The aforementioned studies have demonstrated a significant correlation between irregular pulsations and other well-established risk factors for rupture.

Zhang *et al.* [30] conducted a large cohort study of 305 patients with IAs using 4D-CTA and demonstrated that irregular pulsations were independently associated with aneurysm symptoms and rupture status. Typical symptoms included headaches with severe acute onset and oculomotor nerve palsy resulting from local mass effects. Zhang *et al.* [19] further analyzed 117 cases of IAs using 4D-CTA and found that aneurysms with irregular pulsations had more than six times the rupture risk at 1 and 5 years compared to those without irregular pulsations. They proposed that 4D-CTA detection of irregular pulsations could improve the management of UIAs. For example, a 5- or 6-mm UIA would typically be monitored with follow-up imaging after routine rupture risk assessment. However, if irregular pulsations were considered a risk factor in this assessment, neurosurgeons might recommend prophylactic treatment rather than opting for observation. Furthermore, further research in patients with multiple intracranial aneurysms suggests that irregular pulsations may be useful for identifying the causative aneurysm in cases of rupture and SAH. In conclusion, combining irregular pulsations with other traditional factors may improve the accuracy of rupture risk prediction for UIAs.

In summary, irregular pulsations may serve as a supplementary indicator for predicting the risk rupture of IAs. Integrating such dynamic features with established risk factors—including aneurysm size, morphology, and location—can enhance the accuracy of rupture risk stratification, thereby improving conventional IA management strategies and offering substantial clinical relevance.

3.2. Rate of Morphological Change

Blood flow between IAs and parent arteries is continuous, resulting in morphological changes of IAs during each cardiac cycle, which can be dynamically observed using 4D-CTA. Since changes in aneurysm volume are directly related to the pulsatile motion of the aneurysm wall, assessing cyclic volume variations approximates evaluating the pulsatile motion of the aneurysm wall [14]. Kuroda *et al.* [31] used 4D-CTA to quantify the volume changes of UIAs during the cardiac cycle, they defined the following parameters: expansion volume, which represents the difference between the maximum and minimum volumes of aneurysm or parent artery within one cardiac cycle; and expansion rate, defined as the ratio of the expansion volume to the minimum volume, reflecting the dilation extent of aneu-

rysm or parent artery. Kuroda *et al.* assessed the relationship between IAs and the motion of normal intracranial arteries during one cardiac cycle. Although no significant differences were found, subtle variations were noted. This suggested that the integrity of the aneurysmal wall may be comparable to that of normal vascular walls. Wang *et al.* [32] demonstrated that the rate of morphological change in aneurysms during the cardiac cycle was significantly higher in the rupture group than in the non-rupture group ($P < 0.05$). The rate of change for individual morphological features was calculated as the difference between the maximum and minimum values, divided by the average value across ten phases. The change rate of dome height and aneurysm volume were identified as independent factors associated with aneurysm rupture ($P < 0.05$). A negative correlation was observed between the change rate of dome height and aneurysm rupture, while a positive correlation was observed between the rate of volume change and rupture. The change rates of dome height and aneurysm volume reflect the extent of morphological variations during the cardiac cycle, potentially altering hemodynamics and contributing to the formation, growth, and rupture of IAs. Chen *et al.* [17] further investigated the correlation between morphological changes and irregular pulsations, revealing that IAs exhibiting irregular pulsations demonstrated more pronounced changes in aneurysm size, height, volume, aspect ratio, size ratio, and nonsphericity index. These studies suggest that the rate of morphological changes detected by 4D-CTA in IAs may be a potential clinical indicator for aneurysm rupture risk.

4. Current Status of 4D CTA-Based Image Post-Processing Research

4D-CTA provides high spatial resolution, enabling morphological assessments comparable to those obtained by digital subtraction angiography (DSA) [33]. Consequently, 4D-CTA allows for post-processing operations, including the construction of computational fluid dynamics (CFD) models and deep learning models. These approaches enable the computation of advanced hemodynamic parameters, thereby facilitating hemodynamic analysis based on 4D-CTA.

Cancelliere *et al.* [34] demonstrated that models segmented from 4D-CTA and three-dimensional rotational angiography (3D-RA) data showed consistency in both geometric and hemodynamic outcomes. This finding indicates that CFD models based on 4D-CTA can generate reliable geometric and hemodynamic data within intracranial circulation, confirming the feasibility of 4D-CTA as a dependable data source for CFD analysis. Chen *et al.* [35] utilized 4D-CTA data to establish CFD models to further quantify key hemodynamic parameters, including wall shear stress (WSS), oscillatory shear index (OSI), and relative residence time (RRT). Their analysis revealed that IAs exhibiting irregular pulsations underwent more significant changes in size, volume, OSI, and RRT, suggesting that such aneurysms may experience a more unstable hemodynamic environment throughout the cardiac cycle, leading to an increased rupture risk in areas of irregular pulsa-

tion. This study enhances the understanding of the potential hemodynamic mechanisms underlying the dynamic changes in IAs during the cardiac cycle.

One limitation of traditional CFD modeling is the assumption of a rigid wall. In contrast, 4D-CTA enables the observation of aneurysm wall motion. Shimodoumae *et al.* [36] applied the motion captured from the images as a boundary condition for the wall surface and compared it with rigid-boundary models to investigate the relationship between wall displacement and hemodynamic factors. This finding highlights the complementary value of the dynamic data provided by 4D-CTA for CFD simulation studies, as it allows researchers to investigate the effect of realistic wall deformation on hemodynamics.

Additionally, the multi-phase 4D-CTA introduces a new dimension for deep learning model development. Wang *et al.* [37] designed a multi-phase fusion deep learning model utilizing 4D-CTA images as raw data, incorporating automatic phase selection. When compared to algorithms using single-phase CTA, multi-phase analysis demonstrated higher sensitivity in determining the presence or absence of aneurysm rupture.

In summary, integrating dynamic information from 4D-CTA images into CFD or deep learning analyses allows for a more accurate identification of unstable hemodynamic states or rupture status in IAs. This holds significant value for clinical risk assessment and pathophysiological research.

5. Comparison, Limitations and Future Directions

4D-CTA, four-dimensional flow magnetic resonance imaging (4D Flow MRI), and high-resolution vessel wall imaging (HR-VWI) each contribute to the rupture risk assessment of IAs from distinct perspectives. The strength of 4D-CTA is its exceptional spatiotemporal resolution and rapid scanning speed, enabling precise capture of dynamic changes in IAs throughout the cardiac cycle. There is no radiation during the scanning process of 4D Flow MRI. This modality enables the visualization of blood flow patterns and direct measurement of blood velocity. This allows for the acquisition of precise, advanced hemodynamic parameters. Its main limitations include longer scan times and lower spatial resolution. In contrast, HR-VWI focuses on imaging the vessel wall itself. By directly visualizing features such as wall enhancement and thickening, it assesses inflammatory activity and structural integrity. This technique also faces the challenge of longer scan times.

Studies on 4D-CTA also present certain limitations. Motion artifacts primarily arise from involuntary slight head movements of patients during scanning, leading to misalignment of images across different time phases and affecting the evaluation of subtle pulsations in aneurysms. The observed pulsatile changes may be artifacts. It is because pulsatile changes may be produced by motion or other factors. Therefore, careful differentiation and identification of true pulsatile changes in the aneurysm wall, driven by hemodynamic factors, are crucial when interpreting 4D-CTA results [24]. Dynamic imaging requires multiple scans, resulting in a

cumulative radiation dose higher than that of conventional CTA. Another limitation is the small sample size of current studies. Future prospective research with larger patient cohorts and longer follow-up periods is required to elucidate the role of dynamic morphological indicators observed by 4D-CTA in assessing aneurysm rupture risk.

6. Conclusion

Leveraging its capability for four-dimensional visualization of IAs, 4D-CTA has emerged as a valuable complement to conventional two- and three-dimensional imaging modalities in cerebrovascular practice. By capturing dynamic morphological parameters—such as irregular pulsations and morphological change rates—as well as real-time hemodynamic information within the aneurysm, and integrating these dynamic parameters into existing static risk assessment models represented by the PHASES score, this technique enhances the accuracy of IA rupture risk assessment. Furthermore, it contributes to improved routine clinical management of IAs and holds considerable research significance.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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