Arterial distensibility in patients with ruptured and unruptured intracranial aneurysms: Is it a predisposing factor for rupture risk?

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Background: A risk factor assessment that reliably predicts whether patients are predisposed to intracranial aneurysm (IA) rupture has yet to be formulated. As such, the clinical management of unruptured IA remains unclear. Our aim was to determine whether impaired arterial distensibility and hypertrophic remodeling might be indicators of risk for IA rupture.

Material/Methods: The study population (n=49) was selected from consecutive admissions for either unruptured IA (n=23) or ruptured IA (n=26) from January to December 2010. Hemodynamic measures were taken from every patient, including systolic and diastolic blood pressure using a sphygmomanometer. Unruptured IA and ruptured IA characteristics, including aneurysmal shape, size, angle, aspect ratio, and bottleneck factor, were measured and calculated from transverse brain CT angiography images. With ultrasound, the right common carotid artery intima-media thickness was measured, as well as the lumen diameter during systole and diastole. Arterial wall strain, distensibility, stiffness index, and elastic modulus were calculated and compared between patients with unruptured IAs and ruptured IAs. A p-value less than 0.05 was considered statistically significant.

Results: General demographic data did not differ between patients with unruptured IAs and ruptured IAs. Greater mean intima-media thickness (p=0.013), mean stiffness index (p=0.044), and mean elastic modulus (p=0.026) were observed for patients with ruptured IAs. Moreover, mean strain (p=0.013) and mean distensibility (p=0.024) were decreased in patients with ruptured IAs.

Conclusions: Patients with ruptured IAs demonstrated decreased arterial distensibility and increased intima-media thickness at the level of the carotid arteries. By measuring these parameters via ultrasound, it may be possible to predict whether patients with existing IAs might rupture and hemorrhage into the subarachnoid space.

Key words: ruptured • intracranial aneurysm • predisposing factors • elasticity • carotid intima-media thickness • ultrasound

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Background

Population-based and autopsy studies report that the incidence of intracranial aneurysms (IAs) may be as high as 10% and peaks in the sixth decade of life. Females with a family history of IA are especially at risk [1–3]. Subarachnoid hemorrhages (SAHs) due to ruptured IAs account for 10% and 40% of deaths before hospitalization and after a 1-month hospital stay, respectively [1,4]. More than 35% of patients with SAH develop major neurological deficits preceding hospital discharge, even if they demonstrated favorable Glasgow Coma Scores [5–8]. Although it is easier to detect unruptured IAs with various imaging modalities, it is difficult to predict if or when they will rupture, which poses a dilemma for both patients and physicians [9–11].

Acquired and hereditary risk factors contribute to the multifactorial etiology of unruptured IA, including sex, hypertension, atherosclerosis, alcohol consumption, and smoking [12]. Parameters utilized for rupture assessment include aneurysm size, shape, and location, in addition to angle and flow hemodynamics [13–18]. Cumulative arterial wall deterioration as a result of constant remodeling characterized by degeneration and inflammatory cell infiltration lead to IA rupture and subsequent SAH [19,20]. Altered arterial wall elastic properties and hypertrophic remodeling might predispose IAs to rupture [21–23]. Arterial wall elasticity and intima-media thickness can be estimated non-invasively via ultrasound to indirectly evaluate arterial wall strength [24–26]. We hypothesized that hypertrophic intimal remodeling and impaired elastic properties detected in the right carotid artery might co-occur with IA rupture and thus may predict an impending IA rupture.

Material and Methods

A total of 49 patients consecutively admitted with a diagnosis of IA (n=23) or ruptured IA (n=26) between January and December 2010 were included in this study. Study subjects were screened and removed from the study if they qualified for the following exclusion criteria: history of stroke, heart failure, sepsis, atherosclerosis, alcohol consumption, and smoking [12]. Ultrasound examinations were performed for patients with ruptured IAs within the first 3 days of rupture to avoid SAH induced vasospasm and following DSA. Specifically, the Aplio XG scanner equipped with a 10 MHz linear array transducer (Toshiba Medical Systems, Tokyo, Japan) was used. A pulse repetition frequency of 3 kHz with an automatic cutoff filter ranging from 1 to 3 kHz was utilized. M-mode ultrasound was performed at a speed of 50 mm/sec.

The right common carotid artery (CCA) was examined while the patient assumed the supine position with slight head elevation. The transducer was positioned parallel to the CCA such that the lumen’s diameter was maximized in the longitudinal plane. Maximum (Dmax) and minimum (Dmin) internal lumen diameters were measured at 1 to 2 cm proximal to the CCA bifurcation in magnified M-mode during systole and diastole. Intima-media thickness measurements were taken at this same location, but were derived in B-mode.

Elastic properties

Arterial elastic properties, including distensibility, strain, stiffness index, and elastic modulus, were measured to determine the stress on the right CCA wall during systole and diastole [27,28]. Strain was defined as the percent change in CCA artery lumen diameter during systole and diastole. The following calculations were performed to determine the aforementioned measures:

\[
\text{Strain} = \frac{(D_{\text{max}} - D_{\text{min}})}{D_{\text{min}}};
\]

\[
\text{Distensibility} = \frac{[(D_{\text{max}} - D_{\text{min}}) + (D_{\text{max}} - D_{\text{min}})]}{(BP_{\text{max}} - BP_{\text{min}})};
\]

\[
\text{Stiffness index} = \ln \left( \frac{BP_{\text{max}} + BP_{\text{min}}}{(D_{\text{max}} - D_{\text{min}}) + D_{\text{max}}} \right);
\]

\[
\text{Elastic modulus} = \frac{(BP_{\text{max}} - BP_{\text{min}})}{(D_{\text{max}} - D_{\text{min}}) + D_{\text{min}}}.\]

Statistics

Statistical Package for the Social Sciences for Windows (SPSS ver. 18, Chicago, IL, USA) software was used to analyze all data. Descriptive parameters were expressed as the mean ± the standard deviation or via percentages. Variations between groups were compared with the Mann-Whitney U test. Correlation analyses were performed with the Spearman test. A p-value less than 0.05 was considered significant. The right CCA internal diameter was measured by an expert, blinded observer (A.D.). To evaluate inter-observer reliability, minimum
and maximum CCA internal diameter and distensibility were also calculated by a second observer (M.I.). An inter-class correlation coefficient (ICC) above 0.72 was considered sufficient.

Results

A comparison between unruptured IA and ruptured IA groups in terms of demographics and aneurysm characteristics is provided in Table 1. There were no differences in age, sex, and heart rate between groups. Patients with unruptured IA had a mean age of 47.1±12.0 years, with ages that ranged from 26 to 68 years. Patients with ruptured IA had a mean age of 48.6±11.5 years, ranging from 31 to 67 years. Unruptured IA and ruptured IA characteristics included shape, size, angle, aspect ratio, and bottleneck factor. For the entire study population, unruptured IA and ruptured IA locations included the internal carotid artery (ICA) in 14% of cases, the anterior communicating artery (ACoA) in 20% of cases, the middle cerebral artery (MCA) in 41% of cases, and the vertebral and basilar arteries (V-B) in 25% of cases (Figures 1 and 2).

The unruptured IA group exhibited a decreased mean CCA intima-media thickness at 0.52±0.12 cm vs. 0.61±0.13 cm for the ruptured IA group (p=0.013). However, the unruptured IA group exhibited increased mean CCA lumen diameter change (ΔD) at 0.7±0.1 cm as compared to 0.5±0.1 cm for the ruptured IA group (p=0.04) (Figures 3 and 4). Mean CCA stiffness index was greater for the ruptured IA group at 6.0±0.5 vs. 6.7±0.5 for the IA group (p=0.044). This was also true for the mean CCA elastic modulus, as this measure was higher for the ruptured IA group at 0.9±0.3 compared to the IA group at 0.7±0.2 (p=0.026). Mean CCA strain was decreased for the ruptured IA group at 6.1±1.7 vs. 8.1±1.9 for the IA group (p=0.013). This same trend was observed for mean CCA distensibility, as the ruptured IA group mean value was lower at 1.8±0.4 than the IA group at 2.3±0.5 (p=0.024). Table 2 illustrates a comparison of all these calculated mean values between groups.

Discussion

The risk of rupture per year for patients with asymptomatic IAs has been reported at 0.05% [8]. In population-based studies, the prevalence of IAs ranged widely, from 0.2% to 10% [2,10]. As such, much research has been devoted to studying IAs and the factors that facilitate rupture. Reduced arterial elasticity was observed in patients with ruptured IAs in a recent ex vivo study [11]. The relationship between arterial wall distensibility and stress is still a matter of debate [29,30]. Patients with IA rupture exhibit decreased arterial wall distensibility compared to those with unruptured IAs [11,25].
is widely accepted, even though one ex vivo study asserted the opposite upon measuring arterial wall distensibility in the anterior cerebral, radial, and dorsalis pedis arteries. Moreover, arterial distensibility measurements have been commonly performed on the CCA [29,31]. In agreement with most studies, it is preferred to perform investigations on arterial wall distensibility in vivo. Therefore, we designed an in vivo study using measurements from the right CCA, such that our outcomes might aid in advancing the clinical management of patients with unruptured IA.

Numerous studies have been performed that focused on parameters predicting rupture, such as aneurysm location, size, shape, and angle [14–18]. IAs with an irregular shape and multilobular contours are associated with increased focal stress and distensibility [32,33]. Elliptical IAs are more prone to rupture than spherical IAs [34,35]. Decreased bottleneck and aspect ratios are also correlated with increased rupture risk [14,17]. However, once rupture has occurred, spherical aneurysms become more oval-shaped; thus, an aneurysm’s elliptical quality may not be distinctive of increased rupture risk [4]. A recent study based on biomechanical models of rupture reported that rupture risk is associated with increased aneurysm size [11]. The cutoff value for increased rupture risk was determined to be 10 mm; however, the vast majority of IAs reported in other studies range between 5 to 9 mm [8,36]. Because of the high prevalence of IAs less than 10 mm in diameter, it is important to use criteria other than size to determine rupture risk [33]. It has been postulated that rupture occurs in small-sized IAs if they rapidly expand [4]. However, surgical interventions are not indicated for small IAs, since the rupture risk is relatively low [10,37].

Recent studies have emphasized that the pathophysiology of IA rupture could be evaluated biophysically [7,28]. An experimental study focusing on biomechanical alterations between unruptured IAs and ruptured IAs showed that patients with greater arterial wall rigidity were more prone to IA rupture [11]. Rigidity can be determined by the elastic properties of the arterial wall.
tissue, and a reduction in elasticity significantly contributes to the pathobiology of IA rupture [19,25]. Rupture risk for abdominal aortic aneurysms has also been evaluated in several studies [28,38]. It has been widely reported that arterial distensibility with comorbid vasculopathy predisposes patients to abdominal aortic aneurysm formation, dissection, and rupture.

Figure 3. Ultrasound imaging of the right CCA for same patient as in Figure 1. (A) M-mode, (B) Doppler, and (C) ultrasound images of the CCA. The large parallel white lines are the CCA wall, which moves as the heart beats. The black area between the large parallel lines represents the CCA lumen. Lumen diameter is indicated with the double-headed arrow. The dashed lines highlight the intima-media junction, and the small double-headed arrow (see inset) indicates the intima-media thickness.

Figure 4. Ultrasound imaging of the right CCA from the same patient in Figure 3. (A) M-mode, (B) Doppler, and (C) ultrasound images of the CCA. Lumen diameter is indicated with the double-headed arrows. The dashed lines highlight the intima-media junction, and the small double-headed arrow (inset) indicates the intima-media thickness.
These studies asserted that aneurysmal rupture occurred when wall tension exceeded the strength limit of the artery wall [40]. Another study evaluating the aneurysmal expansion limit demonstrated a correlation between the extent of distensibility and rupture [41,42]. Increased arterial wall stiffness, loss of elasticity, and decreased perivascular support might be associated with vasculopathies resulting from aging, essential hypertension, diabetes mellitus, and vasculitis [23,31,43–45]. Intimal remodeling and arterial stiffness might be associated with defects in elastin, collagen, and extracellular matrix [41,46]. Specifically, defective collagen contributes to arterial wall weakness due to decreased wall distensibility, which facilitates IA rupture [11,40]. Deficiencies in elastin are also correlated to intimal hypertrophy [26,27,47]. Aneurysmal growth and rupture has been associated with TNF-mediated inflammation [19]. In fact, patients with IA rupture exhibit exaggerated intimal hypertrophy [25,46,48]. Hemodynamic studies also highlight parameters that modulate aneurysmal wall rigidity, growth, and rupture [35,36,40]. Diminished arterial wall elasticity has been associated with a large discrepancy between diastolic and systolic BP (ΔP), which contributes to increased arterial resistance [38,40,43,49]. This phenomenon of continuous, increased mechanical loading augments IA wall stress, which facilitates IA fatigue and rupture [5,45]. Our results were in accordance with these data, as a high ΔP was associated with IA rupture.

Overall, our results are in parallel with most in vivo studies performed on the extracranial arteries. We found that patients with IA rupture exhibit impaired CCA elasticity and increased intima-media measurements might be associated with an increased likelihood of IA rupture, which may be helpful in decision-making for IA clinical management.

### Limitations

The study sample size was small, lacked a healthy control group, and no long-term follow-up was performed. However, all study subjects ultimately received surgical or interventional treatment.

### Conclusions and Future Perspectives

Our findings demonstrate that patients with ruptured IAs exhibit impaired CCA wall distensibility and increased intima-media thickness, which suggests hypertrophic remodeling. Thus, determining CCA distensibility and intima-media thickness might be useful in determining whether an IA may rupture in the future. To better determine whether CCA elastic properties predispose patients to IA rupture, a larger prospective study design might be more informative, as the development of rupture may be correlated with changes in these factors over time. It is our hope that developing a set of predictive parameters for IA rupture will guide clinical management so to prevent complications such as subarachnoid hemorrhage.

### Conflict of interest

We declare that we have no conflict of interest.

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### Table 2. Right CCA elastic properties comparison.

|                      | Unruptured IAs (n=23) | Ruptured IAs (n=26) | p-value |
|----------------------|-----------------------|---------------------|---------|
| IMT (mm)             | 0.52±0.12             | 0.61±0.13           | 0.013   |
| Dmax (mm)            | 6.9±0.4               | 7.1±0.3             | 0.14    |
| Dmin (mm)            | 6.2±0.3               | 6.6±0.2             | 0.08    |
| ΔD (mm)              | 0.7±0.1               | 0.5±0.1             | 0.04    |
| BPMax (mmHg)         | 117±6                 | 134±8               | 0.08    |
| BPMin (mmHg)         | 72±5                  | 83±8                | 0.09    |
| ΔP (mmHg)            | 45±4                  | 51±5                | 0.07    |
| Strain (%)           | 8.1±1.9               | 6.1±1.7             | 0.013   |
| Distension (×10⁻⁶ cm²/dyne) | 2.3±0.5           | 1.8±0.4             | 0.024   |
| Stiffness index      | 6.0±0.5               | 6.7±0.4             | 0.044   |
| Elastic modulus (×10⁻⁶ cm²/dyne) | 0.7±0.2           | 0.9±0.3             | 0.026   |

IAs – Intracranial aneurysms.
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