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Sex Differential in 15-Hydroxyprostaglandin Dehydrogenase Levels in the Lumen of Human Intracranial Aneurysms

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Background—Aspirin is a promising medical therapy for the prevention of intracranial aneurysm (IA) rupture. Recently, we found that men have a better response to aspirin than women. The purpose of this study was to determine whether a sex differential exists in the level of 15-hydroxyprostaglandin dehydrogenase (15-PGDH) in the lumen of human IAs.

Methods and Results—Consecutive patients undergoing coiling or stent-assisted coiling for a saccular IA at our institution were enrolled. Two samples (A and B) were collected from IA lumens, and the plasma level of 15-PGDH was measured using an ELISA-based method. The study included 38 patients, with 20 women and 18 men. Women and men were comparable on baseline characteristics. The mean plasma concentration of 15-PGDH did not differ statistically between sample A (62.8 ± 16.2 ng/mL) and sample B (61.8 ± 17.9 ng/mL; 95% confidence interval -6.6 to 9.4). The mean plasma concentration of 15-PGDH in IA lumens of samples A and B was significantly higher in men (73.8 ± 13.5 ng/mL) than women (49.6 ± 7.8 ng/mL; $P < 0.0001$).

Conclusions—Higher enzyme levels of 15-PGDH exist in the lumen of IAs of men compared with women. This observation could explain why aspirin confers better protection against IA rupture in men than in women. The susceptibility of an individual to aspirin may differ according to the level of 15-PGDH. (*J Am Heart Assoc.* 2017;6:e006639. DOI: 10.1161/JAHA.117.006639.)

Key Words: aneurysm • inflammation • sex

Prostaglandins are eicosanoids derived from arachidonic acid through the cyclooxygenase (COX) pathway and mediate several pathogenic mechanisms, including the inflammatory response.¹ COX-1 is expressed constitutively in most cells, whereas COX-2 is induced by inflammatory stimuli. Prostaglandin E₂, which plays an important role in the pathogenesis of intracranial aneurysms (IAs),² is produced by the sequential enzymatic activity of COX-1 or COX-2, followed by that

of prostaglandin E synthase. The levels of prostaglandin E₂ and other prostaglandins are regulated not only by their synthesis but also by their degradation. As such, 15-hydroxyprostaglandin dehydrogenase (15-PGDH) is the key enzyme responsible for the biological inactivation of prostaglandins by converting them to the corresponding 15-keto derivatives.¹ 15-PGDH is being increasingly recognized as a key protective enzyme in several inflammatory and neoplastic disease processes.^{3,4}

Our group and others have shown that different constituents of the inflammatory reaction play a major role in IA formation and rupture.^{5,6} We have also found, in both experimental and human studies, that aspirin, through its anti-inflammatory properties, decreases the risk of IA rupture.^{7–9} Furthermore, in a recent study, we reported that aspirin inhibits IA rupture more efficiently in men than women.¹⁰ The sex-differential action of aspirin was reproduced in mice, where higher levels of 15-PGDH were found in cerebral arteries of male mice compared with female mice. More important, the modulation of the activity of 15-PGDH resulted in the reversal of the sex-differential response in mice, indicating that this enzyme may play a role in mediating the protective effects of aspirin against IA rupture.¹⁰

In the present study, we aimed to determine whether a sex differential exists in the level of 15-PGDH in the lumen of human IAs.

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Clinical Perspective

What Is New?

- Men have higher levels of 15-hydroxyprostaglandin dehydrogenase, a key protective enzyme in inflammatory disorders, in the lumen of intracranial aneurysms than women.

What Are the Clinical Implications?

- Higher levels of 15-hydroxyprostaglandin dehydrogenase in men may explain why aspirin confers better protection against intracranial aneurysm rupture in men versus women.

Methods

Study Population

The study protocol was approved by the University of Iowa (Iowa City) Institutional Review Board, and enrolled subjects gave informed consent. Consecutive patients undergoing coiling or stent-assisted coiling for a saccular IA at the Department of Neurosurgery at the University of Iowa Hospitals and Clinics between January and June 2016 were enrolled. This included patients with unruptured aneurysms treated electively or those treated in the setting of subarachnoid hemorrhage. Patients with fusiform aneurysms, pseudoaneurysms, and extracranial aneurysms and those taking steroids or receiving immunosuppressant therapy were excluded.

Sampling

The technique for intraluminal blood sampling has been previously described.¹¹ Briefly, after femoral arterial access is obtained, a sheath is inserted and a guiding catheter is navigated into the target vessel. A microcatheter is then advanced over a micro-guide wire and positioned inside the aneurysm sac. Two samples (A and B) are collected from each aneurysm lumen before stent or coil deployment, with a total of 3 mL of blood. Blood is subsequently centrifuged, and the plasma is immediately stored at -80°C . The plasma concentration of 15-PGDH is measured in each sample using ELISA kits.

Statistical Analysis

Data are presented as mean and SD for continuous variables and as frequency for categorical variables. The equivalence test was conducted using 2 1-sided tests to confirm that the levels of 15-PGDH were similar between samples A and B. Subsequently, mean 15-PGDH concentrations in samples A+B were compared between men and women using a nonparametric test (Mann-Whitney *U* test) because levels of 15-PGDH were not normally distributed. Correlation between levels of

15-PGDH and age/aneurysm size was assessed using the Spearman correlation coefficient (*r*). $P \leq 0.05$ was considered statistically significant.

Results

The study included 38 patients, of which 20 were women and 18 were men. Age was 53.8 ± 13.0 years on average in the cohort. Mean aneurysm size was 8.6 ± 7.1 mm. Fourteen patients (37%) were treated in the setting of subarachnoid hemorrhage.

Women and men were comparable on baseline characteristics. Mean age was 54.0 ± 13.2 years in the female group and 53.5 ± 13.4 years in the male group ($P=0.9$). Mean aneurysm size was 9.6 ± 8.9 mm in women versus 7.4 ± 4.3 mm in men ($P=0.4$). Of 20 women, 7 (35%) and 7 of 18 men (39%) had ruptured aneurysms ($P=0.8$). Of 20 women, 2 (10%) were taking aspirin long-term versus 5 of 18 men (28%; $P=0.2$). The 2 groups did not differ on aneurysm location ($P=0.7$) (Table).

The mean plasma concentration of 15-PGDH was 62.8 ± 16.2 ng/mL in sample A and 61.8 ± 17.9 ng/mL in sample B. Using 2 1-sided tests, the concentrations of 15-PGDH in samples A and B were statistically similar (95% confidence interval, -6.6 to 9.4).

The mean plasma concentration of 15-PGDH in IA lumens of samples A and B was significantly higher in men (73.8 ± 13.5 ng/mL) than women (49.6 ± 7.8 ng/mL; $P < 0.0001$). There was no association between 15-PGDH levels and age ($r=0.13$; $P=0.4$) or aneurysm size ($r=-0.17$; $P=0.3$).

Discussion

The inflammatory process in arterial walls is the major force driving IA formation and rupture.⁵ This process involves

Table. Location of Treated Aneurysms

Location	Women	Men
Anterior communicating	4 (20)	7 (38.9)
Basilar	3 (15)	2 (11.1)
Middle cerebral	4 (20)	3 (16.7)
Posterior inferior cerebellar	1 (5)	2 (11.1)
Posterior communicating	2 (10)	2 (11.1)
Carotid terminus	2 (10)	1 (5.6)
Posterior cerebral	1 (5)	0
Carotid cavernous	2 (10)	0
Carotid ophthalmic	1 (5)	1 (5.6)
Total	20	18

several inflammatory cells and mediators, including macrophages, mast cells, lymphocytes, and various cytokines and chemokines.⁶ Although inflammation involves primarily the aneurysm wall, recent reports have demonstrated the ability to detect inflammatory changes in IA lumens.^{11,12} As such, our group has shown a local increase of the concentration of chemokines and chemoattractant cytokines in the lumen of human IAs compared with peripheral arterial blood, suggesting active recruitment of inflammatory cells into aneurysm walls.¹¹ In another study, there was a significant positive correlation between IA size and the plasma concentration of granulocyte-monocyte colony-stimulating factor in IA lumens.¹² It is, therefore, possible to study the inflammatory process in IAs by sampling blood safely from aneurysm lumens during endovascular treatment.

Aspirin has emerged as a potentially promising medical therapy to prevent IA rupture.^{7–9} The protective effects of aspirin were initially reported by Hasan et al¹³ in a nested case-control study from the ISUIA (International Study of Unruptured Intracranial Aneurysms), where frequent aspirin use (3× weekly to daily) was associated with a significant decrease in the risk of aneurysm rupture. The mechanism appears to involve the inhibition of COX-2, which is more prominently expressed in the wall of ruptured than unruptured human IAs.² As such, in a randomized study, aspirin therapy was associated with a significant decrease in the expression of inflammatory markers, including COX-2 in human IA walls compared with controls.⁸ A recent analysis of the ISUIA data revealed that aspirin decreased the risk of IA rupture more significantly in men than in women, suggesting a sex-differential response.¹⁰ Likewise, male mice taking aspirin had a lower rate of IA rupture and higher levels of 15-PGDH, a prostaglandin-degrading enzyme that physiologically antagonizes COX-2, than female mice taking aspirin. Interestingly, the addition of 15-PGDH agonist in female mice led to the reversal of the observed differential sex response to aspirin.¹⁰ These findings raised the question about whether women may have lower levels of 15-PGDH, an enzyme that may mediate the protective effects of aspirin against IA rupture.

The present study brings evidence that women do have remarkably lower enzyme levels of 15-PGDH in IA lumens than men. It may be possible that the susceptibility to aspirin may differ according to the level of 15-PGDH, which explains why men had better protection against IA rupture than women in ISUIA. This observation is similar to the protective effects of aspirin in colorectal cancer, where aspirin is associated with a lower incidence of colorectal cancers arising in association with high 15-PGDH expression, but not with low 15-PGDH expression.¹⁴ As such, 15-PGDH level in IA lumens and walls may serve as a biomarker that may predict stronger benefit from aspirin.

Limitations

We did not compare the levels of 15-PGDH in the walls of IAs between women and men. Such a study is underway, but we foresee several years of patient recruitment to gather a large enough sample because endovascular therapy is significantly more used than microsurgical clipping in most centers, including ours. Because of the small sample size of our study, we could not test the effect of long-term aspirin use on the levels of 15-PGDH. It would be interesting to longitudinally observe the risk of IA rupture in patients taking aspirin and correlate this with the intraluminal enzyme level of 15-PGDH.

Conclusions

The present study shows consistently higher enzyme levels of 15-PGDH in IA lumens of men compared with women. This observation could explain the sex-differential response to aspirin in preventing IA rupture. It may be possible that the susceptibility to aspirin may differ according to the level of 15-PGDH.

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Disclosures

None.

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