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## **Creation of Large Elastase-Induced Aneurysms: Presurgical Arterial Remodeling Using Arteriovenous Fistulas**

Y. Ding, D. Dai, R. Kadirvel, D.A. Lewis and D.F. Kallmes

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ORIGINAL  
RESEARCH

Y. Ding  
D. Dai  
R. Kadirvel  
D.A. Lewis  
D.F. Kallmes



# Creation of Large Elastase-Induced Aneurysms: Presurgical Arterial Remodeling Using Arteriovenous Fistulas

**BACKGROUND AND PURPOSE:** The size of elastase-induced aneurysms created in the usual way is relatively small. Our aim was to determine whether creation of a carotid-jugular AVF to induce remodeling of the RCCA results in larger elastase-induced aneurysms in rabbits.

**MATERIALS AND METHODS:** RCCA right-jugular AVFs were created in 6 New Zealand white rabbits (group 1), followed by elastase-induced aneurysm creation 4 weeks later. Follow-up DSA was performed to assess AVF patency and aneurysm sizes. Six other elastase-induced aneurysms created in the usual way were used as controls (group 2). The diameters of the RCCA and LCCA in group 1 and aneurysm sizes in both groups were measured from DSA images and compared by using the Student *t* test.

**RESULTS:** The patency of AVFs in group 1 was confirmed in all 6 (100%) cases. The mean RCCA diameter in group 1 was larger than that in the contralateral LCCA ( $3.6 \pm 0.7$  mm versus  $2.0 \pm 0.1$  mm, range, 1.8–2.2 mm,  $P < .01$ ). The mean aneurysm neck diameter, width, and height for group 1 was larger than those of group 2 ( $4.6 \pm 0.9$  mm versus  $3.5 \pm 0.7$  mm,  $P < .05$ ;  $4.7 \pm 1.1$  mm versus  $3.4 \pm 0.5$  mm,  $P < .05$ ;  $13.8 \pm 3.2$  mm versus  $8.1 \pm 1.3$  mm,  $P < .05$ , respectively). Aneurysm volume for group 1 was significantly larger than that of group 2 ( $273 \pm 172$  mm $^3$  versus  $77 \pm 32$  mm $^3$ ,  $P < .05$ ).

**CONCLUSIONS:** Carotid-jugular AVFs result in RCCA remodeling that yields relatively larger elastase-induced aneurysms.

**ABBREVIATIONS:** AVF = arteriovenous fistula; DSA = digital subtraction angiography; IADSA = intra-arterial DSA; IVDSA = intravenous DSA; LCCA = left common carotid artery; RCCA = right common carotid artery; REJV = right external jugular vein

The elastase-induced aneurysm model in rabbits has been widely used in basic and preclinical research, especially in the evaluation of neuroendovascular devices.<sup>1–14</sup> The advantage of this model is that it closely simulates the morphology and hemodynamics of human intracranial aneurysms.<sup>1,10</sup> However, unlike surgically created aneurysm models, the maximum size of the rabbit elastase-induced-model aneurysm is relatively small.<sup>15–17</sup> As such, the model does not show high rates of recurrence after coil embolization, which would be a desirable trait for testing new endovascular devices.<sup>11,18,19</sup>

Various modifications have been made to the elastase aneurysm model to alter its size and morphology, including such aspects as the location of the carotid artery ligation.<sup>20–25</sup> Although not previously applied in aneurysm research, surgically created AVFs have been used to stimulate arterial remodeling in animal models.<sup>26</sup> Such remodeling acts in response to elevated arterial flow, with well-defined molecular signaling pathways<sup>27,28</sup> and resultant chronic enlargement of the arterial diameter.

We hypothesized that the size of elastase-induced aneu-

rysms in rabbits could be increased if such aneurysms were created in the setting of a chronic AVF, which would act to remodel and enlarge the carotid artery before elastase injury and aneurysm creation. In the current study, we report our preliminary experience with elastase aneurysm creation following AVF creation to determine whether resultant aneurysms are larger in the setting of successful patent AVFs compared with aneurysms created in the usual way.<sup>1</sup>

## Materials and Methods

### *Creation of Carotid-Jugular AVF*

Following approval from our Institutional Animal Care and Use Committee, carotid-jugular AVFs were created in 6 New Zealand white rabbits (group 1). The RCCA and REJV were exposed and dissected. An arteriotomy of the RCCA was performed, and aneurysm clips were used to temporally occlude the proximal and distal side of the arteriotomy. The REJV was cut into 2 segments; the proximal side of the REJV was used for end-to-side anastomosis to the RCCA by using a 7–0 Prolene suture (Ethicon, Cincinnati, Ohio). The distal RCCA was permanently ligated by using 4–0 silk. An end-to-side anastomosis of the REJV and RCCA was performed, and the AVF was created. Animals were allowed to recover and were maintained for at least 4 weeks before aneurysm creation.

### *Aneurysm Creation*

In the same subjects detailed above, elastase-induced saccular aneurysms were created. IVDSA was performed before aneurysm creation to evaluate the patency of the AVF and to determine the diameters of the carotid arteries by using procedures described previously by our

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From the Neuroradiology Research Laboratory, Department of Radiology, Mayo Clinic, Rochester, Minnesota.

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Please address correspondence to David F. Kallmes, MD, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: kallmes.david@mayo.edu

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Sizes of aneurysms created after AVF establishment				
Rabbit No.	Time between 2 Procedures (weeks)	Neck (mm)	Width (mm)	Height (mm)
1	4	3.5	4.2	11.2
2	4	5.4	5.4	16.1
3	4	4.1	3.8	14.8
4	4	5.5	6.4	16.8
5	4	4	3.4	8.6
6	5	5.3	5.2	15

group.<sup>29</sup> Briefly, 7 mL of iodinated contrast material (iohexol, Omnipaque 300; GE Healthcare, Milwaukee, Wisconsin) was injected into the left ear-vein catheter at approximately 2 mL/s during DSA; the x-ray exposure rate was 2 frames per second. The diameters of the RCCA and control LCCA 4 weeks after AVF creation were determined in comparison with external sizing devices. Following IVDSA, aneurysms were created.

Detailed procedures for aneurysm creation have been described previously.<sup>1</sup> Briefly, anesthesia was induced with an intramuscular injection of ketamine, xylazine, and acepromazine (75, 5, and 1 mg/kg, respectively). Using a sterile technique, we re-exposed and isolated the RCCA. The AVF was disconnected at the surgical anastomotic site. A 1- to 2-mm bevelled arteriotomy was made, and a 5F vascular sheath (Cordis Endovascular, Miami Lakes, Florida) was advanced retrograde in the RCCA to a point approximately 3 cm cephalad to the origin of RCCA. A roadmap image (Advantx, GE Healthcare) was obtained by injection of contrast through the sheath retrograde in the RCCA, to identify the junction between the RCCA and the subclavian and brachiocephalic arteries. A 3F Fogarty balloon (Baxter Healthcare, Irvine, California) was advanced through the sheath to the level of the origin of the RCCA with fluoroscopic guidance and was inflated with iodinated contrast material.

Porcine elastase (5.23 µm/mgP, 40.1 mgP/mL, approximately 200 U/mL; Worthington Biochemical, Lakewood, New Jersey) was incubated within the lumen of the common carotid artery above the inflated balloon for 20 minutes; then, the catheter, balloon, and sheath were removed, and the RCCA was ligated below the sheath entry site. Six aneurysms (group 2) were randomly selected from 22 elastase-induced aneurysms we created before in the usual manner<sup>1</sup> without a fistula. Ligation positions of the RCCA in groups 1 and 2 were similar, approximately 3 cm cephalad to the origin of the RCCA. Our previous experience indicated that a ligation position of the RCCA of <1 cm will impact the aneurysm height and volume.<sup>25</sup> A ligation position of

>3 cm will not impact aneurysm height and volume by itself, so the aneurysm height in those 2 groups is comparable.

### Imaging Follow-Up

Three weeks after aneurysm creation, the width, height, and neck diameters of the aneurysm cavities were determined with IVDSA by using the same external sizing device as a reference. IADSA was performed in group 2 three weeks after aneurysm creation. Details of the IADSA procedure were demonstrated previously.<sup>29</sup> The aneurysm volume was calculated as

$$\text{Volume} = 3.14 (\text{width}/2)^2(\text{height}).$$

The diameter of the RCCA at initial follow-up, immediately before aneurysm-creation surgery, was compared with that of the LCCA in group 1; and the aneurysm dimensions 3 weeks following aneurysm creation were compared between groups by using the Student *t* test.

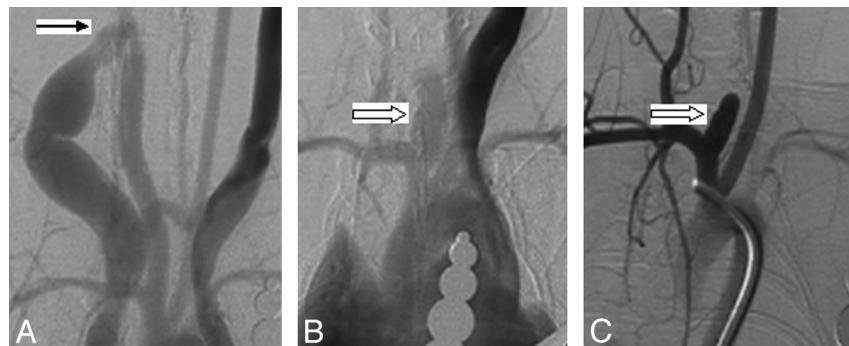
### Results

Six (100%) AVFs remained patent in group 1. The times between the 2 procedures (AVF and aneurysm creation) and aneurysm sizes are shown in the Table. The mean RCCA diameter ( $3.6 \pm 0.7$  mm, from 2.6 to 4.2 mm) was larger than that of the contralateral LCCA ( $2.0 \pm 0.1$  mm, from 1.8 to 2.2 mm) at initial follow-up in group 1 ( $P < .01$ ) (Fig 1A).

The mean aneurysm neck diameter for group 1 ( $4.6 \pm 0.9$  mm, from 3.5 to 5.5 mm) was larger than that of group 2 ( $3.5 \pm 0.7$  mm, from 2.5 to 4.3 mm) ( $P < .05$ ). Differences in aneurysm width between group 1 ( $4.7 \pm 1.1$  mm, from 3.4 to 6.4 mm) and group 2 ( $3.4 \pm 0.5$  mm, from 2.9 to 4.3 mm) were also significant ( $P < .05$ ). Mean aneurysm height was greater in group 1 ( $13.8 \pm 3.2$  mm, from 8.6 to 16.8 mm) compared with group 2 ( $8.1 \pm 1.3$  mm, from 6.4 to 9.5 mm) ( $P < .05$ ). Aneurysm volume in group 1 ( $273 \pm 172$  mm<sup>3</sup>, from 77 to 369 mm<sup>3</sup>) was significantly larger than that of group 2 (77 ± 32 mm<sup>3</sup>, from 44 to 138 mm<sup>3</sup>) ( $P < .05$ ) (Fig 1B, -C).

### Discussion

The elastase aneurysm is widely applied for both basic research and testing of neuroendovascular devices.<sup>30-34</sup> Unlike vein pouch models, in which large-diameter veins can be harvested to create large aneurysms, the ultimate size of the elastase-induced-model aneurysms likely is limited by the initial size of the RCCA.<sup>1,35-37</sup> In an attempt to increase the size of elastase-



**Fig 1.** *A*, Anteroposterior IVDSA image 4 weeks following AVF creation but immediately before aneurysm-creation surgery. Both the RCCA and the REJV are shown, indicating a patent AVF (arrow) and a larger RCCA compared with the LCCA. *B*, IVDSA image 3 weeks following aneurysm-creation surgery in the same animal as in *A*, demonstrating a relatively large aneurysm cavity (block arrow). Aneurysm dimensions were 6.4 mm in width and 16.8 mm in height with a neck measuring 5.5 mm. *C*, IADSA image 3 weeks following aneurysm creation in group 2, demonstrating a small aneurysm (block arrow). Aneurysm sizes of the neck, width, and height were 3.4, 3.6, and 8.4 mm, respectively.

induced aneurysms, we induced arterial remodeling by using chronic AVF before aneurysm-creation surgery. We have demonstrated positive remodeling in patent AVF cases, indicating, as expected, that chronic elevation of flow results in arterial luminal enlargement.

Previous studies have shown that elastase aneurysm dimensions can be modified by using specific surgical techniques. For example, the aneurysm neck can be controlled by adjusting the position of the inflated balloon during elastase incubation,<sup>20,23</sup> and the aneurysm height can be controlled by adjusting the position of the ligation of the RCCA.<sup>25</sup> Other researchers also reported that the aneurysm height can be controlled by adjusting the position of the sheath in the RCCA.<sup>21</sup> The current work expands our knowledge regarding optimal methods for elastase-induced aneurysm creation by suggesting that larger aneurysms can be induced following chronic AVF creation.

This study has several limitations. First, a small number of subjects was included. Second, no test of the impact of the aneurysms induced after AVF creation on the frequency of recurrences was performed in the current study. We acknowledge these limitations and are continuing to validate this model.

## Conclusions

Patent carotid-jugular AVFs result in RCCA remodeling that yields relatively large elastase-induced aneurysms.

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