Local Hyperthermia Enhances Thrombosis in Aneurysms Containing Platinum Coils

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Summary

Despite recent technical advances in embolization of cerebral aneurysms with platinum coils, some aneurysms eventually resulted in incomplete packing with remnant neck or dome filling. Such a situation with a remaining inflow zone may pose a risk of rupture and subsequent regrowth. Metals characteristically generate heat under high-frequency alternating magnetic fields (AMF). We used this property to induce local hyperthermia and promote thrombogenesis in incompletely packed aneurysms.

Glass model aneurysms packed with coils were subjected to AMF to investigate the correlation between weight of platinum and temperature elevation and the correlation between flow rates of water through the model and temperature elevation. Next, activated coagulation time (ACT) of blood obtained from dogs was studied at various temperatures. Finally, side-wall aneurysms created in the canine carotid artery using a venous patch were packed with platinum coils. Change in temperature and angiographic changes were investigated after AMF application.

In the glass model, the weight of platinum was correlated with elevation of temperature, and a negative logarithmic correlation was evident between flow rate and elevation of temperature. Elevation of blood sample temperature tended to

shorten ACT. In canine carotid aneurysms, elevation of intra-aneurysmal temperature was confirmed and sufficient elevation of temperature was found to promote angiographically evident thrombogenesis of the remnant space after AMF application.

Local hyperthermia may be useful in completing luminal obliteration of aneurysms after coil embolization. It may particularly be useful for ruptured aneurysms to prevent the early rerupture.

Introduction

Guglielmi detachable coils (GDC) were introduced 1990 to occlude cerebral aneurysms via an endovascular approach¹. These devices consist of a platinum coil connected to a guide-wire by an uninsulated junction². Recent technical developments in the GDC system have enabled the interventional neuroradiologist to improve anatomic and clinical outcomes³. Although the safety of this system and its efficacy in preventing early aneurysmal rebleeding have been documented, recent studies have indicated that both clinical and angiographic results may be less satisfactory when the GDC method is applied to wide-necked or giant aneurysms⁴, with aneurysmal rebleeding rates of 33% in these subgroups⁵.

Thrombus formation in the remaining unoc-

cluded space in the coil-packed aneurysm should help to prevent rupture. Magnetic materials such as metals characteristically generate heat application of alternating magnetic fields (AMF). This method has been applied to hyperthermia therapy for malignant tumors⁶. We hypothesized that platinum coils can also generate heat in the course of eddy current loss of magnetic substance with high-frequency AMF. Such intra-aneurysmal hyperthermia could be used to promote thrombogenesis in the remnant space of incompletely packed aneurysms. In this study we investigated whether AMF application to coil-packed aneurysms could cause local hyperthermia and promote thrombogenesis as an adjunct to coil embolization.

Material and Methods

Study in a glass model

A glass model was used to investigate the correlations between aggregate weight of platinum and elevation of temperature, and between the flow rate of water through the model and elevation of temperature.

Spheric pouches ranging from 6 to 10 mm in diameter were created on one side of glass tubes originally 3 mm in diameter to simulate aneurysms. These pouches were packed densely with platinum coils (GDC). An optical fiber probe (fiber optic thermometer probe, FX-9020; Anritsu Meter, Tokyo) was inserted through a small hole in the pouch. The magnetic field used in this study, measuring 88.9 kHz and 380 Oe, was created by a horizontal coil (inner diameter, 25 cm, length, 25 cm) with a transistor inverter (Dai-ichi High Frequency, Tokyo). As water at 37°C was circulated continuously, the coil-packed glass model aneurysm was placed at the center of the horizontal coil for AMF application.

The temperature of models packed with various aggregate weights of platinum coils was measured using the optical fiber probe. Exposure time was ten minutes and the flow rate of circulating water was 180 ml/min. Then, to investigate the correlation between flow rate and elevation of temperature, coil weight was kept constant and water flow rate during application to AMF was varied from 0 to 360 ml/min. Each investigation was repeated three times and the mean value plotted with standard deviation.

Thrombogenicity of heat

To investigate the correlation between blood temperature and thrombogenicity, activated coagulation time (ACT) at various temperatures was studied in canine blood. Four mongrel dogs used for this study, each weighing approximately 12 kg, were treated according to a protocol approved by the Nagoya University Animal Care Committee. The dogs were anesthetized with ketamine hydrochloride (3 mg/kg I.M.) and pentobarbital (5 mg/kg I.V.). The animals were intubated and allowed to breathe room air spontaneously. Anesthesia was maintained with additional doses of pentobarbital as required.

Two milliliters of blood were drawn from the femoral artery via a 4-F. sheath. Immediately the sample was placed in a homiothermal pool at various elevated temperatures for 30s. After heating, the temperature of the blood was measured by an optical fiber probe, and simultaneously the blood was placed in a Hemochron test tube (FTCA 510; International Technidyne Corporation, New Jersey) and ACT was determined using a coagulation counter (HEMOCHRON 401; International Technidyne Corporation, New Jersey). Blood samples were harvested 15 to 20 times from each dog. The same investigator performed all blood collections and measurements of ACT to minimize inter-operator variability. The sample temperature was salometrically stabilized at 37°C during ACT determination. The influence of the cooling effects was neglected because the coagulation cascade was already accelerated during the heated time.

Creation of experimental aneurysms in vivo

Ten side-wall aneurysms were created using a venous patch in the carotid arteries of nine mongrel dogs weighing 9 to 12 kg, by partial modification of a previously described procedure⁷. Diameters of aneurysms varied from 7 mm to 15 mm. The surgical procedure was performed under sterile conditions with the aid of an operating microscope.

A 6-cm midline skin incision was made in the neck, and the common carotid artery and external jugular vein were isolated. The jugular vein was ligated proximally and distally and then excised. A microtube to measure hyperthermia (THERMOTRON, CEC-350; Hakko Electronics, Nagano, Japan) was inserted into the excised vein through one end and fixed in place

Figure 1 Side-wall aneurysm created using a venous patch in the carotid artery of a dog. A microtube was inserted into this aneurysm, through the tube, an optical fiber probe was placed in the aneurysm to measure temperature.

Table 1 Summary of in vivo experiment

Aneurysm n.	size of aneurysm (mm)	Type of GDC and length (cm)	Weight of platinum (g)	Elevation of temperature (°C)	Angiographic change
1	7 x 6 x 5	GDC 10.39	0.25	1.1	No change
2	11 x 6 x 6	GDC 10.46	0.29	2.2	No change
3	9 x 8 x 6	GDC 18.28	0.33	1.2	No change
4	14 x 8 x 6	GDC 18.30	0.35	1.4	No change
5	10 x 9 x 6	GDC 18.51	0.6	4.1	No change
6	15 x 10 x 8	GDC 18.46	0.54	2.1	Total occlusion before heating
7	15 x 10 x 8	GDC 18.68	0.8	3.8	Total occlusion before heating
8	11 x 7 x 6	GDC 18.50	0.59	4	Promotion of thrombosis
9	15 x 8 x 7	GDC 18.56	0.66	4.8	Promotion of thrombosis
10	12 x 8 x 6	GDC 18.92	0.92	4.8	Promotion of thrombosis
<i>Guglielmi detachable coil (GDC) 18 and GDC 10 weighed 0.0118 g and 0.0063 g respectively, per 1 cm.</i>

Figure 2 Correlation between weight of platinum and elevation of temperature in a glass model aneurysm. Circulation flow rate was 180 ml/min, and exposure to magnetic fields was for 10 min.

by a nylon suture. After vascular clamps were placed on the carotid artery both proximally and distally, a four to eight mm elliptical defect was made in the carotid artery. The external jugular vein was incised longitudinally, and an appropriate length was anastomosed side-to-side to the carotid artery, using a 8-0 nylon suture. When the vascular clamps were removed, an aneurysm-like projection thus extended from the lateral aspect of the carotid artery (figure 1). The aneurysms were partially packed with platinum coils (GDC) using an intravascular microcatheter technique. Continuing patency of the experimental aneurysms and lack of change of the remaining luminal space were confirmed by repeating the angiogram one hour after ruling out spontaneous thrombosis.

Exposure to AMF

Dogs were repositioned to place the aneurysm at the center of the horizontal coil. An

Figure 4 Correlation between blood temperature in vitro and activated coagulation time (ACT).

Figure 3 Correlation between flow rate and elevation of temperature in glass models. Closed circles, squares, triangles, open circles indicate data for weights of platinum of 0.880 g, 0.440 g, 0.240 g, 0.055 g, respectively.

optical fiber probe was inserted in the aneurysm through the microtube, and the aneurysms were exposed to AMF for ten minutes. During this procedure the temperature of the aneurysms and surrounding tissue were measured continuously. Immediately after AMF application, angiography was performed for comparison with the angiogram obtained before AMF application, particularly with respect to the inflow zone of the aneurysms. The follow-up angiography was taken two hours after these procedures to check the stability of the intra-aneurysmal thrombus.

Statistical analysis

StatView 4.1 statistical software (Abacus Concepts) was used for all analyses. Correlations between weight of platinum and elevation of temperature and between blood temperature and ACT were calculated with the Pearson test. All parametric values are expressed as means $\pm$ SD, and with p values. The difference in temperature between groups with and without successful promotion of thrombogenesis by AMF application was compared with Student's t test. A value of $p < 0.05$ was considered to indicate significance.

Result

Evaluation using the glass model

Correlation between weight of platinum and elevation of temperature in glass model aneurysms is shown in figure 2. The temperature of glass model aneurysms packed with platinum coils rose dramatically within the first ten min-

utes, after which elevation of temperature became slower. We therefore determined that with an exposure time of ten minutes the temperature reached a plateau (data not shown). When the flow rate of circulating water was kept at 180 ml/minutes and AMF exposure time was kept at ten min, temperature increased in direct proportion to changes in the weight of platinum between 0 and 0.88 g.

The correlation between circulating water flow rate and elevation of temperature is shown in figure 3. Weights of platinum tested were 0.055, 0.24, 0.44, and 0.88 g. A negative logarithmic correlation was seen between flow and temperature for every weight of platinum examined.

Thrombogenicity of heat

Correlation between blood temperature and ACT was investigated in blood samples from four dogs. The data are shown in figure 4. As blood temperature was varied from 34°C to

Figure 5 Correlation between weight of platinum and elevation of temperature in canine carotid aneurysms. Exposure to magnetic fields was for 10 min. Temperature of surrounding tissue was measured simultaneously. Open circles indicate temperature of canine carotid aneurysms, closed circles indicate temperature of surrounding tissue.

48°C, ACT changed in nearly inverse proportion, suggesting a greater tendency to coagulate at elevated temperatures.

Figure 6 Angiograms of experimental aneurysm 9. A) Before exposure to magnetic field. Contrast medium enters the aneurysm (arrow). B) Immediately after exposure. Contrast medium does not enter into the aneurysm (arrow), suggesting promotion of thrombogenesis.

Figure 7 Angiograms of experimental aneurysm 3. A) Before exposure to magnetic field. The aneurysm was partially occluded. B) Immediately after exposure, showing no further change.

Radiologic evaluation of the animal model

Ten aneurysms were created in nine dogs. A summary of this experiment appears in table 1. Weights of GDC 18 and GDC 10 were deter-

Figure 8 Difference in elevation of temperature between aneurysms with successful thrombogenesis and failure despite magnetic field exposure. Elevation of temperature in the effective group ($4.53 \pm 0.46^{\circ}\text{C}$) was significantly higher ($*p < 0.05$) than in the group with failure ($2.00 \pm 1.25^{\circ}\text{C}$).

mined to be 0.0118 g and 0.0063 g per cm of length, respectively. Aggregate weight of platinum placed in the experimental aneurysms varied from 0.25 g to 0.92 g. Two aneurysms were found to be totally occluded before exposure to AMF. Temperatures in aneurysms rose between 1.2°C and 4.8°C , and while temperatures in surrounding tissues rose between 0.4°C and 1.8°C . Correlation between weight of platinum and elevation of temperature and surrounding tissue is shown in figure 5. Temperatures of coil-packed aneurysms rose in proportion to the weight of platinum. In contrast, temperature changes in surrounding tissue were significantly smaller, and elevation was not proportional to the weight of platinum. Because the coil complex did not always distribute uniformly inside the aneurysms, and the value of the investigation point of surrounding tissues could be affected by heat distribution of the adjacent aneurysmal wall.

The remnant aneurysmal space of three aneurysms disappeared in the post-AMF angio-

gram, suggesting promotion of thrombogenesis by AMF (figure 6). Five aneurysms showed no angiographic change between pre- and post-AMF states (figure 7). These angiographic findings did not change in the follow-up angiogram. The difference in elevation of temperature between groups with and without successful promotion of thrombogenesis by AMF application is shown in figure 8. Elevation of temperature of the effective group was $4.53 \pm 0.46^\circ\text{C}$ while that in the ineffective group was $2.00 \pm 1.25^\circ\text{C}$, representing a significant difference. At least 4°C elevation was required to promote thrombogenesis of coil packed aneurysms.

Discussion

Recent advances in coil embolization techniques, including the introduction of GDCs, have dramatically increased the clinical use of coil packing of intracranial aneurysms⁸. Outcome generally has been favorable except in patients with large or giant aneurysms⁹. In such aneurysms, coils are subject to compaction and displacement toward the dome, presumably by continuous impact with the pulsatile blood flow, a such compaction is associated with an increased risk of eventual rerupture^{5,10,11,12}.

GDC are fashioned from platinum, which is largely inert biologically. This property may explain the paucity of fibrosis when large aneurysms are embolized¹³. Several promising modifications of the GDC have been shown to enhance intra-aneurysmal fibrosis in animal models. Such modifications include addition of collagen coating, inclusion of collagen filaments, and implantation of various extracellular matrix proteins¹⁴⁻¹⁷. All of these modifications involve boarding additional materials to the platinum coil.

Promotion of thrombus formation in the remnant space in the coil-packed aneurysms should decrease the likelihood of rupture. Guglielmi et Al pointed out that with passage of positive current, the uninsulated part of the stainless steel introducer wire is dissolved, electrolytically, with the aim of detaching the platinum coil within a clotted aneurysm^{1,18}. However, Horwitz et Al reported that immediate thrombosis may not be as common as expected after initial placement of the GDC and application of current to detach the coil within the fundus¹⁹.

In various attempts to treat aneurysms, stereotactic methods involving electrical or magnetic induction of thrombosis were studied²⁰⁻²². These methods proved to be impractical and complicated. Our own group previously developed an electrocoagulation coil to activate thrombosis²³. In that study, the perivascular temperature rose to 80°C and coagulative necrosis of the aneurysm wall occurred, causing penetration. A temperature below 60°C surrounding the coil proved necessary for safe and effective thrombosis.

Systemic hyperthermia is well known to cause coagulopathy, and consumption coagulopathy is an important factor in the pathophysiology of heat stroke²⁴. In such states thrombin initially is generated via the intrinsic clotting pathway. Fibrin formation is accelerated during systemic hyperthermia from 41 to 42°C , resulting in thrombosis²⁴⁻²⁶. Moreover, platelet activation occurs in vivo, as evidenced by very early increases in platelet-specific proteins during systemic hyperthermia²⁴. As ACT measures the reaction of fresh whole blood with a given surface substrate, this test is sensitive to abnormalities in the intrinsic and common pathways²⁷. Between 34 and 48°C , we found that elevation of blood temperature tended to shorten ACT, suggesting activation of coagulation by heat.

Hyperthermia has been considered a promising approach to cancer therapy²⁸ and a few researchers have been investigating magnetic particles as conveyers of heat^{29,30} upon exposure to high-frequency AMF. Unlike chemotherapy and radiotherapy, local hyperthermia has few side effects³¹. Clinical studies performed so far have shown that interstitial brain hyperthermia is feasible, and that the degree of toxicity is acceptable assuming careful control of heating and limitation of target volume⁶.

Platinum apparently generates heat by eddy current loss of magnetic substance in high-frequency AMF. In glass models, we confirmed a direct correlation between weight of platinum and elevation of temperature. However, platinum generated less heat than iron might and elevation of temperature was impaired by the cooling effect of blood.

In our animal model, local hyperthermia was successfully achieved. Effective thrombogenesis was observed in aneurysms showing more than 4°C elevation of intra-aneurysmal temper-

ature in a 380-Oe magnetic field. And this effect maintained at least for two hours. To obtain this temperature, an aggregate of at least 0.7 g of platinum coils should be placed in the aneurysm. Thus hyperthermia may be useful for large or giant aneurysms, which may show less than satisfactory results with the GDC method^{11,32}.

In our study, elevation of temperature in canine carotid aneurysms was relatively low because platinum is only weakly magnetic, and a cooling effect occurs in the inflow zone. To achieve more effective local hyperthermia and thrombogenesis, we might attempt to use stronger magnetic materials or a more powerful magnetic generator. A risk of distal embolization may occur if the thrombus extends to the parent artery, but such thrombogenesis might be minimized by the cooling effect of blood flow. A balloon remodeling technique³³ may be useful for protecting the parent artery from the migration of thrombus and increasing thrombogenicity in the aneurysm by removing the cooling effect. Additionally, the present experiment involved mongrel dogs. The platelet cascade and the coagulation cascade differ between animal species, dogs show more coagulation activity than human beings, while activity in guinea pigs is more closely equivalent to that in humans³⁴. In this study we achieved effective thrombogenesis in dogs, but guinea pig experiments to clarify the threshold and safety level will be needed before clinical investigation. Al-

though this study clarified the acute thrombogenic effect by local hyperthermia, the fibrinolytic process should be considered in the chronic stage in further studies. This method will be applicable for embolization using a temperature-dependent drug delivery system or thermo-sensitive embolic materials³⁵ or delivered with a heat-induced drug delivery system. It may be another methodological option to boost the coil embolization effect as well as recently invented biofunctional coils³⁶.

Conclusions

Elevation of temperature in experimental aneurysms embolized with platinum coils was confirmed after application of high-frequency AMF. This study clarified the intra-aneurysmal thermal circumstances by externally loaded heat energy. AMF induced hyperthermia is surely less invasive than internal transplantation of heat source and direct heating with surgical intervention. Focal elevation of temperature promotes thrombogenesis *in vitro* and also in animals demonstrated by angiography. Coil-induced hyperthermia may enhance the effectiveness of GDC embolization, especially for large or giant aneurysms with incomplete packing by coils, and particularly may be useful for acute ruptured lesions to prevent early rerupture. The externally induced local hyperthermia will become more effective using stronger magnetic or thermosensitive materials.

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