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A narrative review of intravascular catheters in therapeutic hypothermia

Yuan Gao[1,2], Ming Li[3], Miaowen Jiang[1,2], Yang Zhang[3,4], Xunming Ji[1,2,3,4]

[1]School of Instrumentation and Optoelectronic Engineering, Beihang University, [2]Research Institute for Frontier Science, Beihang University, [3]Department of China-America Institute of Neuroscience, Xuanwu Hospital, Capital Medical University, [4]Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China

Address for correspondence: Dr. Xunming Ji, School of Instrumentation and Optoelectronic Engineering, Beihang University, Beijing 100191, China. Research Institute for Frontier Science, Beihang University, Beijing 100191, China. Department of China-America Institute of Neuroscience, Xuanwu Hospital, Capital Medical University, Beijing 100053, China. Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing 100053, China. E-mail: jixm@ccmu.edu.cn

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Abstract:

Therapeutic hypothermia (TH) has been regarded as a promising neuroprotective method for acute ischemic stroke (AIS) for decades. During the development of TH, most researchers focused on improving hypothermic benefits by optimizing treatment processes and conditions. Intravenous thrombolysis and endovascular thrombectomy, for instance, have been introduced into AIS treatment. However, the lack of specialized intervention consumables, especially intervention catheter, led to inaccurate and uncontrolled hypothermic temperature, limited the efficacy of TH. In this review, intervention catheters as well as accessory equipment utilized in TH treatment has been summarized. Hopefully, this review may inspire the future development of TH specialized intervention catheter, enhance the outcome of TH, and neuroprotective efficacy in AIS.

Keywords:

Acute ischemic stroke, intervention catheter, medical consumable, neuroprotection, therapeutic hypothermia

Introduction

In 1987, Busto proposed initially that mild hypothermia (32°C–35°C) in the treatment of cerebral ischemia can significantly protect neurons.[1] Moreover, animal and human trials have been conducted since then, and the results have confirmed that mild hypothermia therapy can positively affect in terms of brain functional prognosis in accordance with the following mechanism (i.e., slowing down metabolism of brain, reducing intracranial pressure, and alleviating reperfusion injury and inhibition of apoptosis[2-6]). The neuroprotective effect of therapeutic hypothermia (TH) has already been confirmed in patients with cardiac arrest,[2,3] and it is considered a promising neuroprotective method.[7,8] However, the efficacy of TH in stroke patients is controversial. The reason of this controversy may be dependent on three problems as follows: (1) Lack of vascular recanalization; (2) unknown optimistic conditions of hypothermia; and (3) unneglectable side effects.[9] Extensive research has suggested that the protective effects of mild hypothermia therapy on the brain are significantly correlated with the range of hypothermia, cooling rate, lasting time, as well as the rate of rewarming.[9] Furthermore, most the above-mentioned parameters are affected significantly by the cooling method.

Mild hypothermia therapy comprises surface cooling and intravascular cooling.[10] Surface cooling has been criticized for its low cooling efficiency, inaccurate cooling region, lack of revascularization, as well as high side effects.[11,12] However, endovascular hypothermia has been arousing intense attention, and it is considered as a more promising clinical application of mild hypothermia therapy.[13] Endovascular hypothermia selects blood flow as the cooling agent, which is not consistent with surface cooling method that transfers heat through multiple tissues and bones.[14] By cooling brain-supplying blood, endovascular

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hypothermia can serve as a more direct method while avoiding the dissipation of cooling capacity. Endovascular hypothermia can fall into three types as follows:[14] (1) Autologous blood cooling; (2) cold saline infusion cooling; and (3) closed-loop cooling. The cooling effect of all endovascular hypothermia methods is notably dependent on interventional catheter. However, the previous summary of neuroprotection in mild hypothermia has primarily focused on the mechanisms and clinical trials of hypothermia.

Accordingly, this review highlights the interventional catheters of hypothermia therapy, i.e., one of the most crucial components of intravascular hypothermia. Starting from the structure of the catheters, this study is conducted to analyze and summarize the design concept, application scenario, and clinical use effect of the catheters. Based on the comparison of the advantages and disadvantages of the respective catheter cooling modes, we look forward to the future development trend of low-temperature catheters.

Endovascular Hypothermia Catheter Types

In endovascular hypothermia, a catheter is inserted percutaneously into a target vessel to cool the blood by infusing cold saline or infuse cooled blood directly. As blood with lower temperatures flows through the blood vessels, the cooling capacity will pass through the walls of the vessels into targeted tissues. Based on different cooling mechanisms, endovascular cooling can fall into liquid perfusion cooling (autologous blood cooling and cold saline infusion cooling) and heat exchange cooling (closed-loop cooling). Cold liquid perfusion method should inject cold saline into vessel and form diluted blood with lower temperature to deliver cooling capacity or perfuse autologous blood cooled *in vitro* directly. Consequently, conventional interventional catheter can be utilized to delivery cold liquid. However, there exists a high temperature gradient between cold saline and warm blood, thus resulting in severe heat transfer, which is manifested by the increased temperature of cold saline from 5.4°C to 25.2°C.[13] On that basis, thermal insulation performance takes on critical significance to cold liquid perfusion method, which is the major difference between conventional interventional catheter and hypothermia catheter.

Cold liquid perfusion catheter

Khione insulative catheter

FocalCool developed Khione, an insulation catheter for low-temperature perfusion, fully exploits selective brain cooling advantages, thus increasing the local cooling rate, controlling temperature precisely, and reducing core temperature drop led by heat loss of cooling infusion fluid. Khione insulative catheter (FocalCool, Mullica Hill, New Jersey, USA) made of thermal insulation materials is capable of reducing heat transfer through the wall of the catheter. It plays the role of guide catheter, percutaneously punctures the carotid artery, while uniting microcatheter XT-27 inserted into the internal carotid artery to infuse hypothermic saline.[15]

Caroff *et al*. proved the concept to validate the performance of low-temperature perfusion by adjusting the perfusion speed and time of hypothermic saline.[15] The researchers used the catheter to infuse the pig model with normal saline at 4.5°C at a rate of 20–40 ml/min. On that basis, the cooling rate can fluctuate in 0.4°C–5.9°C/min, with an average of 2.2°C ±2.5°C/min. After an average low temperature of 14.4 min, the lowest temperature reaches 23.8°C, whereas local intracranial hypothermia exerts a slight effect on the lateral brain tissue and core temperature. The core temperature declines by only 0.2°C on average, and the maximum temperature is reduced by 0.5°C. Moreover, as indicated by the search results, the situation (i.e., 22 ml/min for 25 min) is capable of most accurately achieving and maintaining the target temperature, 31°C–32°C while avoiding fluid infusion overload. Furthermore, the regional hypothermia trail is applied to a model of intracranial middle artery occlusion in a dog in the above-mentioned situation, and the infarction volume declines significantly (0.2 ± 0.2 cm^3 vs. 3.8 ± 1.0 m^3) as compared with the control group. Merrill *et al*. compared the thermal insulation effect of Khione with that of the conventional catheter under the identical hypothermic perfusion condition with the use of an *in vitro* model.[16]

Hybernia medical-insulated catheter

Choi *et al*. reported Hybernia Medical thermal insulation catheter, which was also developed using thermal insulation materials.[17,18] 4.5 F thermal insulation catheter with a temperature sensor and the tips linked to a controller of cooling liquid perfusion is capable of controlling the temperature of specific area accurately. The catheter was inserted into the carotid artery in pigs to explore its cooling rate, feasibility, and safety, with the saline of 0.1–70 ml/min for 2 h and the target temperature of 33°C (baseline 37.3°C ±0.9°C). As indicated by the result, the ipsilateral cerebral temperature can be cooled by 33°C usually through perfusion for 5 min (95% confidence interval 2.3°C–4.9 °C), and the temperature is notably lower than that of body temperature (35.8°C). The histopathologic observations suggested that mild hypothermia therapy induced by the Hybernia will not trigger cerebral ischemic or traumatic damage.

Heat exchange cooling catheter

Catheter with multiple balloons and thrombectomy

This catheter refers to a novel type of catheter innovatively applying induced hypothermia to thrombectomy.

Thrombectomy recanalization has been the most commonly used treatment for ischemic stroke patients, whereas ischemia reperfusion can cause additional injury, bleeding, and inflammatory responses, such that the prognosis and recovery of the patients can be affected.[19,20]

During treatment, the catheter is inserted from the femoral artery into the common carotid artery or proximal internal carotid artery. Cattaneo *et al*. obtained fluid hydrodynamics that under the identical heat transfer surface conditions. The four balloons in a tandem array are capable of achieving the most efficient heat transfer rate.[21] The wall of the balloon reaches 15 μm, the length of a single balloon is 20 mm, and the outer diameter reaches 4 mm. With the blood flow velocity set to 400 ml/min (conventional common carotid blood flow rate) and 250 ml/min (the flow rate of blocked middle cerebral artery), and the cooling fluid flow rate set to 100 ml/min at 10°C, the temperature can be lowered by 1.6°C and 2.2°C, respectively.

Moreover, they used sheep, an animal model, to verify the intracranial cooling effect of the catheter.[22] Researchers have placed the catheter into the common carotid artery of sheep, with circulated normal saline at 6°C for 180 min and monitored temperature of central vein, nasal cavity, intracranial frontal cortex, as well as temporal cortex. As indicated by the results, the maximum cranial temperature drop of the ipsilateral carotid artery with hypothermia reached 4.7°C; compared with the contralateral cranial temperature, its temperature declines faster and leads to lower temperature; the maximum temperature difference reaches 1.3°C and 1.4°C with body temperature.

The explanation for the above results is that the catheter is capable of cooling intracranial temperature selectively. The cranial temperature can be significantly cooled to 35°C in 30–40 min, and there exists a certain temperature difference with the body temperature, whereas the body temperature has declined to a certain degree. Thus, the side effects of systemic hypothermia (including shivering, myocardial irritability, and cardiac arrhythmia[23]) turn out to be inevitable since temperature gradient cannot be eliminated.

However, there is not a stroke model being adopted to verify the feasibility and effectiveness of the catheter in achieving hypothermia and thrombectomy. Furthermore, to be combined with thrombectomy, the catheter should be added with balloon to remove the broken blockages easily.

Intravascular temperature management™

Zoll developed four intravascular temperature management catheters (IVTM™), i.e., Cool Line®, Solex 7™, Icy® and Quattro®. Table 1 listed the performance of IVTM™. The above-mentioned products are intravenous catheters based on the principle of heat exchange. There are a wide variety of designs in accordance with the application requirements (e.g., insertion site, retention time, and cooling speed). The difference between intraarterial selective cooling and intravenous whole body cooling is the position of cooling, where the former places at artery supplying blood to target area and latter locates at inferior vena cava.[23]

The end of the catheter is connected to the Thermogard XP® device *in vitro*, and the body is bonded to a number of coaxial intercommunicating balloons. The closed circulation of cold saline in the balloon serves as the induced hypothermic medium. Besides providing cold saline and its fluid dynamics, the equipment can automatically regulate the temperature of circulating saline in accordance with the difference between the monitored human core temperature and the set target temperature to reach and stabilize the target temperature quickly.

The technique of the intravascular temperature management system is comparatively mature, and clinical trials have been reported extensively. Diringer *et al*. adopted the cool line catheter to protect the hypothermia brain in critical patients and neurosurgical patients (e.g., subarachnoid hemorrhage, cerebral trauma, intracranial hemorrhage, and ischemic stroke[24,25]). As revealed by existing results, this system can effectively reduce the core temperature of patients and notably eliminate the fever; its cooling rate is twice that of conventional hypothermia therapy, ice blanket, and antipyretic.

In addition, catheters, except for the effect of hypothermia therapy, are indistinguishable from common central venous catheters, thus conforming to the requirements of drug delivery, blood sampling, and blood flow

Table 1: List of biological intravascular temperature management series catheter of Zoll

	Cool line®	Solex 7™	Icy®	Quattro®
Balloon number	2	Snake-shaped	3	4
Length (cm)	22	25	38	45
Position	Subclavian vein, jugular vein, and femoral vein	Subclavian vein and jugular vein	Femoral vein	Femoral vein
Retention time (days)	4 or 7	4 or 7	4	4
Cooling power (W)	74	144	139	173

monitoring, without bringing additional risks of infection and bleeding. Fischer *et al*. have suggested that the intracranial temperature of most patients is nearly 0.1°C higher than the core temperature when the normal body temperature of patients with traumatic brain injury is maintained at 36.5°C by the Cool Line catheter system.[26] When employing the Icy catheter system for mild hypothermia therapy, researchers have always compared it with the conventional cool means (e.g., the superficial cool means). Their results have suggested that the rate of intravascular cooling can be faster, and the effect of maintaining low temperature becomes more stable. Under the same conditions, the cooling rate of Icy catheter can reach 1.46°C ± 0.42°C/h, whereas the conventional low temperature only reaches 0.18°C ± 0.2 °C/h. The probability of patients under the control of the Icy catheter deviating from the target hypothermia only reaches 3.2% in comparison with 69.8% with conventional cryogenic methods.[27] When the Quattro catheter system is adopted for mechanical thrombectomy and recanalization of acute ischemic stroke (AIS), a mild hypothermia of 33°C can be achieved in 65 min, such that hemorrhage after recanalization can be effectively prevented. Sonder *et al*. have compared the induced low temperature efficiency of Cool Line, Icy, and Quattro catheters.[28] The Quattro catheter is the fastest (3.12°C/h) and exhibits the optimal performance in maintaining low temperatures with 99.3% stability. This is because that with more balloons, catheter will have larger heat exchange area and lead to higher heat flow. Besides, Solex 7 catheter system has been rarely reported.

Furthermore, some clinical studies of cardiac arrest using Thermogard XP cryogenic catheter system have suggested that it can strongly induce hypothermia and maintain the stability of hypothermia, whereas no significant difference exists between its neuroprognostic effect and body surface hypothermia.

Accutrol™ catheter

Philips developed the InnerCoolRTx intravascular temperature control system, which matches to the Accutrol™ interventional catheter, i.e., the only heat-exchange cryogenic catheter with a temperature sensor on the market. The temperature sensor located at the top of the catheter is made of a thermistor. Not consistent with other devices that require additional temperature probes in the rectum, bladder, or ear, the catheter enables the system to directly obtain the blood temperature in the blood vessel without delay, such that the temperature control system can make timely responses and become more accountable to the induction and maintenance of hypothermia.

The equipment comprises three chambers. Different from the polymer material of conventional interventional catheter, the part inserted into the body is made of flexible metal, such that the heat exchange effect can be enhanced. The puncture operation of the catheter through the femoral vein to the inferior vena cava is identical to that of the central venous catheter. The catheter is connected to the InnerCoolRTx device, thus providing cold saline to flow through the catheter.

The metal part responsible for heat exchange covers a spiral groove, with an aim of increasing the contact area with blood and ultimately improving the cooling efficiency. The model of the catheter can be selected in accordance with the weight of the patient. There are external diameters of 9 F, 10.7 F, and 14 F. InnerCoolRTx intravascular temperature control system was first adopted to induce and maintain hypothermia and rewarming in intracranial aneurysms patients, and Steinberg *et al*. reported that it is effective in inducing hypothermia.[29]

Similarly, in 99% of intravascular hypothermia patients (cooling rate of 4.77°C/h), the core temperature was reduced to the target temperature of 33°C prior to the placement of the aneurysm clip, whereas only 20% of the low temperatures of the ice blanket reach the target. The same excellent hypothermia induction efficiency has been confirmed in the treatment of patients with AIS with mild hypothermia. Hemmen *et al*. investigated the feasibility and safety of using this system for hypothermia therapy in patients with AIS after t-PA thrombolysis, and no significant difference was reported in the prognosis between patients in the hypothermia group and those in the control group.[30]

The incidence of pneumonia was relatively high in the hypothermia group and the occurrence of pneumonia did not generate any significant side effects on the prognosis. Besides, the side effects and prevention of pneumonia should be investigated in depth. Flint *et al*. compared the induction of hypothermia between the Accutrol catheter system and surface hypothermia in patients who remained in a coma after resuscitation from cardiac arrest, whereas no significant difference was reported in the cooling rate.[31] However, an increased heart rate has been commonly reported in patients with superficial hypothermia, whereas this side effect is less common in patients with intravascular hypothermia. 14 F and 10.7 F Accutrol catheters can maintain the patients' low temperature of 33°C. To be specific, the 14 F catheter achieves a faster cooling rate of 1.84°C/h, whereas the 10.7 F catheter shows a cooling rate of 0.89°C/h.

The use of the InnerCoolRTx temperature control system has been reported more frequently over the past few years in patients with ST-segment elevation myocardial infarction. Götberg *et al*. combined InnerCool intravascular hypothermia with cryogenic solution injection to investigate the safety and feasibility of rapidly inducing hypothermia in patients before coronary intervention. Moreover, they explored the effect of sub-hypothermia on infarct volume and cardiac protection.[32,33] As indicated by the results, increased InnerCoolRTx vascular hypothermia does not extend the patients' window from hospital entry to coronary intervention compared with conventional procedures, and the core temperature of the patients stabilizes at 34.7°C before recanalization. As indicated by the magnetic resonance imaging (MRI) results after 3 days of interventional therapy, the myocardial infarction volume declines in the mild hypothermia group, which has a slight protective effect on the myocardium, whereas the difference is not significant compared with that in the normal temperature group.

Nevertheless, Christoph reported that the cryogenic treatment is not in the patients with myocardial salvage index and the clinical outcome after recanalization and 6 months after the cardiovascular magnetic resonance exert a significant positive effect on cardiac MRI results in 2019.[34]

The Accutrol™ cryogenic catheter system acts on the inferior vena cava. The cooling effect is systemic hypothermia, of which the side effects are less severe than surface hypothermia but are equally inevitable. Moreover, compared with Zoll's cryogenic catheter, Accutrol™ catheter cannot consider the functions of central venous catheter (e.g., drug administration and blood collection and monitoring), and accordingly, patients may need to open two interventional wound for hypothermia catheter and central venous catheter.

Setpoint catheter

Radiant Healthcare of Canada has developed a balloon cryogenic catheter, i.e., Setpoint catheter based on heat exchange. A spiral interlaced balloon at the start of the catheter serves as the heat exchange area and the balloon is closed and circulated in the inner part of the balloon for heat exchange between hypothermic saline and blood. The catheter refers to a three-lumen catheter, two of which serve as the normal saline channels, and the remaining one acts as a guidewire channel. When the catheter is punctured through the femoral vein to the inferior vena cava and reaches the septum, the guidewire is withdrawn and the inner cavity can act as a temperature probe channel. The diameter of the catheter without balloon dilatation reaches 9.2 F, and 8.25 mm after full dilatation with normal saline, accounting for 8%–10% of the cross section of the inferior vena cava; it does not cause clinically significant blood flow disorder.[35] The tube can be employed with different temperature control systems to achieve different cooling effects (e.g., The Radiant Reprieve™ system and Zoll Proteus™ system), which have been reported at a cooling rate of 3.3°C/h and 9.6°C/h, respectively.[36]

The catheter system has been first used in the mild hypothermia treatment of myocardial infarction in large animals. Dae *et al*. adopted this catheter to provide mild hypothermia protection for myocardial infarction reperfusion in pigs of the same weight as humans. As indicated by their results, this hypothermia method is capable of fully reducing cardiac temperature, effectively reducing myocardial infarction volume, providing solid cardiac protection, ensuring microvascular circulation, and maintaining cardiac output.[35] Dixon *et al*. employed the above-described cooling method as an adjunctive therapy for coronary intervention in patients with acute myocardial infarction.[37] The core temperature of the patients reaches an average of 33.2°C, and the blood temperature declines to 34.7°C when the myocardial infarction is recanalized. No blood flow disorder and no more cardiac side effects are reported, compared with conventional treatment. In the treatment of AIS, De Georgia *et al*. used the cryocatheter and Reprieve™ system to cool the patients to 33°C and maintain the temperature for 24 h.[38] Most patients could reach the target temperature after 77 min on average.

Nevertheless, compared with conventional treatment, mild hypothermia therapy does not show any significant advantages in clinical prognosis, for which implementation of hypothermia therapy may delay the prognosis progress. Over the past 2 years, Noc *et al*. and Keeble *et al*. investigated the cooling effect and prognosis improvement of the low-temperature catheter in combination with Zoll Proteus™ system in patients with ST-segment elevated myocardial infarction administrated with percutaneous coronary intervention.[36,39] As indicated by the results, the core temperature of the patients declines to 33.6°C after nearly 20 min of hypothermia, a faster rate of cooling than the InnerCool system, whereas coronary recanalization is delayed by 17 min due to related operations of hypothermia.[32,33] There exists a slight decrease in MI volume (16.7% vs. 23.8%) and a slight decrease in the incidence of microvascular obstruction compared with conventional treatment, whereas there is no difference with statistical significance.

Special interventional catheter for autologous blood extracorporeal circulation

CoolGuide

The CoolGuide catheter developed by FocalCool was initially developed to provide rapid local cardiac hypothermia protection for heart disease, especially myocardial infarction arising from coronary artery occlusion. The catheter covers a 3-lumen structure. The largest inner cavity serves as the blood cooling and delivery channel, and the two small wing-like lumens serve as the closed circulation low temperature normal saline channels to cool the blood passing through the large lumen. The catheter is made of braided composite structure. The inner core of the three lumen is made of polytetrafluoroethylene (PTFE) and the outer shell comprises stainless-steel braided layer and nylon material to ensure the operability of the catheter.

Merrill *et al*. primarily considered the relevant operations and the necessary equipment of percutaneous coronary intervention during the design of the cryogenic catheter, such that additional operations and care in cardiac hypothermia therapy can be avoided.[40]

The length of catheter reaches 115 cm, the outer diameter is 8 F determined in accordance with the conventional maximum guide catheter and the largest inner cavity is 5 F, as the passage of the dilated catheter or stent for angioplasty. Moreover, PTFE material ensures the lubricity when passing through. In the practical application, the catheter is punctured through the vascular sheath to the femoral artery to the coronary artery. Subsequently, the blood is extracted by a peristaltic pump from the guide sheath and then returned to the largest lumen of the CoolGuide catheter. Furthermore, normal saline at 4°C circulates to cool the blood at 45 ml/min. After long distance heat exchange, the blood temperature declines, and it is exported from the head to the target tissue.

The above result suggests that the cooling rate is largely dependent on the blood flow in the catheter by simulation *in vitro*. When it is 30 ml/min, the target cooling capacity of 20 W can be achieved. At the above-mentioned rate, myocardial tissue can be cooled by 3°C in 5 min in accordance with large pig tests. Subsequently, Thomas has improved the catheter and added three small holes with a diameter of 0.5 mm on the original basis, 30 cm away from the catheter head.[41] The holes are self-perfusion entrance where body temperature blood can flow into cooling lumen. Based on the difference in blood pressure between aorta and coronary artery, blood can spontaneously go into the catheter for cooling and infusion. Accordingly, blood circulation equipment (e.g., extracorporeal pump) can be decreased, and operational convenience can be increased. As indicated by the result of the large-scale swine experiment, although it was feasible to spontaneously circulate the blood by pressure difference, the pressure difference between the perfusion hole and the coronary artery only reaches 5–10 mmHg in practice. The simulation results *in vitro* suggest that the cooling efficiency only reaches 6 W, which cannot conform to the preset requirement of 20 W and should be optimized in depth.

TwinFlo

ThermopeutiX's TwinFlo catheter aims to achieve more precise, rapid, and deeper hypothermia therapy for protecting the brain in severe cases. It comprises two coaxial canaliculars.

The outer catheter is 14 F, and the percutaneous puncture reaches the aortic arch through the femoral artery in practice. The inner catheter with a double lumen is 9.5 F, and it is inserted into the carotid artery through 14 F catheter. The ends of the catheters cover different interfaces. The two interfaces of the outer catheter are adopted to connect the extracorporeal circulation pipeline and heparin dropping and flushing, respectively, when the autologous blood is extracted from the main cavity. One of the three interfaces of the inner catheter is employed to connect to cooled blood from the extracorporeal circulation line, and the other two are adopted to infuse the contrast agent and saline to dilate the balloon and monitor the pressure of blood perfusion. The extracorporeal circulation pipeline comprises conventional blood pumps, heat exchangers, and refrigerators to ensure the normal delivery and cooling of blood. The blood in the blood vessel is drawn from the gap between the outer catheter and the inner one. The balloon in the head of the inner one expands to block the carotid artery, and the cooling blood is introduced from the tip of the back of the balloon, such that the direct mixing of hypothermic blood and blood flow can be avoided, and the cooling efficiency can be increased. Moreover, TwinFlo catheter can be employed in conjunction with vascular thrombectomy, with the inner diameter of the balloon tube as 2 mm, such that the catheterization devices are enabled to be operated.[42] Mattingly *et al*. systematically investigated the selective cryogenic efficiency of TwinFlo using a swine infarction model.[43] Three hours after middle cerebral artery clogging of pigs with TwinFlo catheter intracranial partial reperfusion at low temperatures, the result indicated that the implementation of the experimental group on the same side of the brain temperature at low temperatures can decline to 26.5°C, the average 25.4 min to moderately low temperature (<30°C), the contralateral brain temperature reaches 31.6°C, and the core temperature is not reduced, whereas the temperature stabilizes in the safe range of 32°C–34°C. Despite the short duration of hypothermia, MRI results reveal a nearly 10-fold reduction in infarct volume and a 42% reduction in pathological infarct volume in the hypothermia group compared with the control group. TwinFlo catheters have been rarely employed in human clinical studies, and only two cases have been reported. Wang *et al*. provided extracorporeal membrane oxygenation (ECMO) treatment to patients with out-of-hospital cardiac arrest in combination with adjuvant therapy of intracranial selective hypothermia (27°C ±3°C) for 12 h using TwinFlo

Table 2: Comparison the structure, design concept, clinical application, advantages, and disadvantages of various catheters for intravascular hypothermia

Model	Structure	Design concept	Infusion rate (mL/min)	Position	Clinical application	Cooling rate	Advantages	Disadvantages
Khione insulative catheter	Single lumen	Cooling liquid perfusion with thermal insulation design	20~40	Common carotid artery	AIS	2.2°C±2.5°C/min	1. Excellent thermal insulation performance 2. Reduce systemic hypothermia side effects 3. Improve cooling efficiency	Prolonged application increases circulating volume, large wall thickness
Hybernia medical insulative catheter	Single lumen	Cooling liquid perfusion with thermal insulation design	0.1~70	Common carotid artery	AIS	0.8°C/min	1. Precise temperature control in the target area 2. Reduce systemic hypothermia side effects	Prolonged application increases circulating volume
Multi-balloon and thrombectomy cryogenic catheter	Three-lumen with multi-balloon	Closed-loop cooling	100	Common carotid artery	AIS	1.6°C–2.2°C/min	1. Excellent cooling efficiency 2. Expected to be achieved the combination of hypothermia and thrombectomy	Systemic hypothermia is unavoidable
IVTM™								
Cool line®	Two-balloon	Closed-loop cooling and heat exchange cooling	/	Subclavian vein, internal jugular vein, femoral vein	Subarachnoid hemorrhage, brain trauma, intracranial hemorrhage, and AIS	1.46°C±0.42°C/h	1. Fast cooling rate and the stable cooling effect 2. Consider the functions of central venous catheter such as drug administration, blood collection and monitoring	Systemic hypothermia is unavoidable
Solex 7™	Serpentine balloon			Subclavian vein, internal jugular vein				
Icy®	Three-balloon			Femoral Vein				
Quattro®	Four-balloon			Femoral Vein				
Accutrol™	Three-lumen	Heat exchange cryogenic conduit with temperature sensor	/	Femoral vein	Intracranial aneurysm, AIS and STEMI	4.77°C/h	1. Get the blood temperature directly in the blood vessel 2. Made of flexible metal can enhance the heat transfer effect	1. Systemic hypothermia are unavoidable 2. The functions of central venous catheter such as drug administration and monitoring are not considered
Setpoint	Three-lumen	Closed-loop cooling and heat exchange cooling	/	Femoral vein	Myocardial infarction and AIS	3.3°C/h (Radiant Reprieve™ system) 9.6°C/h (Zoll Proteus™ system)	Fast cooling rate and the stable cooling effect	Systemic hypothermia is unavoidable
Cool guide	Three-cavity with braided composite structure	Hypothermic perfusion of autologous blood	45	Femoral artery	Coronary heart disease	0.6°C/min	1. Accurate and rapid cooling 2. Avoid the side effects of systemic hypothermia	Cooling efficiency needs to be improved
TwinFlo/DuoFlo	Two coaxial canaliculars	Hypothermic perfusion of autologous blood	/	Femoral artery	Ischemic stroke	3.5°C/h	1. Accurate and rapid cooling 2. Avoid the side effects of systemic hypothermia	The effectiveness still needs to be further confirmed

AIS: Acute ischemic stroke, STEMI: ST-elevation myocardial infarction catheter, and the core temperature was maintained at 34°C.[44]

According to the condition of the patients, it was 8 min after he was reported with cardiac arrest before the ambulance arrived for cardiopulmonary resuscitation (CPR) *in vitro*. The medical staff did not start ECMO first aid till 44 min after the emergency of CPR. Under the above-mentioned circumstances, the patients have severe nerve injury, and it will take at least 2–3 weeks to recover. However, the recovery of the patients combined with hypothermia treatment is significantly better than expected. At the time of discharge 32 days after onset, the patients were evaluated to have no obvious nerve injury, and they can perform their professional work as usual 2 months later. Solar *et al*. reported the first human trial of TwinFlo catheter, in a 59-year-old patient with a large middle cerebral aneurysm that requires prolonged occlusion during surgical repair.[45] TwinFlo catheter was adopted to selectively cool the brain to a low temperature of 26°C while maintaining a normal core temperature (36.7°C). In terms of time, the total duration reaches 2 h, 65 min before arterial occlusion, 39 min after occlusion, and 16 min after ventilation. The patient recovered more quickly than expected without any neurological defects.

However, from the author's point of view, although the above two human clinical trials have achieved significantly positive neuroprognostic effects, they can only ensure the feasibility of intracranial selective cryogenic catheters at present, and their effectiveness still needs to be confirmed by a large number of clinical studies.

Cryogenic Catheters Comparison

A summary is supplied (e.g., the structure, position, design concept, advantages, and disadvantages of a wide variety of catheters for intravascular hypothermia) to gain more insights into the characteristic of hypothermia catheter mention in this article.

From Table 2, it is clear that hypothermia catheters on the market have common problems including inevitable systemic hypothermia, limited infusion volume (cold saline infusion), and low cooling efficiency. These issues impeded the clinical translation of TH.

Conclusion

Endovascular hypothermia, a very promising subcritical treatment modality, has been effective in clinical trials of neuro-cerebral protection, in which the catheter plays a key role. As concluded above, many researches had tried to manipulate different cooling methods and catheter constructions. However, for therapy operating at large temperature gradient and severe heat transfer, thermal insulation performance is a crucial criterion for catheter. Elevated thermal resistance is beneficial for not only the accuracy of temperature management, but reducing infusion rate. Some inspiring attempts had been made such as thermal insulation coatings without altering mechanical performance of catheter.[46]

For future development of novel intravascular catheters in hypothermia therapy, more efforts should be made in enhancing thermal insulation performance of catheter. In addition, future clinical trials need to further explore the safety and efficacy of intravascular hypothermic catheters and apply them to the most appropriate patients in clinical treatment to achieve optimal neuroprotection.

Author contributions

YG: Design, Literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation and manuscript editing; ML: Concepts, manuscript review and guarantor; MJ: Definition of intellectual content and manuscript editing; YZ: Definition of intellectual content, clinical studies and manuscript editing; XJ: Concepts, manuscript review and guarantor.

Ethics committee approval and declaration of Helsinki

Not applicable.

Patient consent

Not applicable.

Data availability statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

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Conflicts of interest

Dr. Xunming Ji is the Editor-in-Chief, Dr. Ming Li is an Editorial Board member of Brain Circulation. The article was subject to the journal's standard procedures, with peer review handled independently of them and their research groups.

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