Published in final edited form as:

Ann Thorac Surg. 2012 April ; 93(4): 1223–1227. doi:10.1016/j.athoracsur.2011.12.058.

Hypothermia Severely Effects Performance of Nitinol-Based Endovascular Grafts In Vitro

Michael P. Robich, MD, MSPH, Robert Hagberg, MD, Marc L. Schermerhorn, MD, Frank B. Pomposelli, MD, Michael C. Nilson, Michelle L. Gendron, Frank W. Sellke, MD, and Roberto Rodriguez, MD

Department of Surgery, Division of Cardiac Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; Department of Surgery, Division of Cardiothoracic Surgery, Warren Alpert School of Medicine, Brown University, Providence, Rhode Island; Department of Surgery, Division of Vascular Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; W.L. Gore & Associates Inc, Flagstaff, Arizona; Department of Surgery, Division of Cardiothoracic Surgery, Jefferson Medical College, Wynnewood, Pennsylvania

Abstract

Background—Nitinol is an alloy that serves as the base for numerous medical devices, including the GORE TAG Thoracic Endoprosthesis (W.L. Gore & Associates, Flagstaff, AZ) thoracic aortic graft device. Given the increasing use of therapeutic hypothermia used during the placement these devices and in post– cardiac arrest situations, we sought to understand the impact of hypothermia on this device.

Methods—Five 34-mm TAG devices were deployed in a temperature-controlled chamber at 20°C, 25°C, 30°C, 35°, and 37°C (25 total devices). A halographic measurement device was used to measure radial expansive force and normalized to the force at 37°C. Three 34-mm TAG devices were similarly deployed in a temperature-controlled water bath at each of the above temperatures. A laser micrometer was utilized to measure deployed diameter.

Results—A statistically significant decrease in expansive force at 20°C, 25°C, and 30°C of 65%, 46%, and 6%, respectively, was noted. A statistically significant decrease in radial diameter at 20°C and 25°C of 17% and 11%, respectively, was noted. Although a 9% difference was noted at 30°C, it was not significant.

Conclusions—The nitinol-based TAG device shows marked decreases in radial expansive force and deployed diameter at temperatures at or below 30°C. Surgeons should be aware of the potential implications of placing nitinol-based endoprostheses in hypothermic conditions. In addition, all health care providers should be aware of the changes that occur in nitinol-based endoprostheses during therapeutic hypothermia.

Endovascular repair of thoracic and abdominal aortic aneurysms as well as other aortic pathologies has redefined the management of these entities. A number of randomized clinical trials have confirmed the safety and short-term efficacy of endovascular aortic abdominal aneurysm repair and thoracic endovascular aneurysm repair [1, 2]. For these reasons, endovascular repair has become common, and more than 70% of abdominal aortic

aneurysms are now repaired in this manner [3]. Two recent studies by Sachs and colleagues [4, 5] examining the Nationwide Inpatient Sample have shown that 31% of ruptured abdominal aortic aneurysms and 32% of type B aortic dissections are managed by endovascular methods. Additionally, the technology is being more widely utilized in traumatic aortic injury, penetrating aortic ulcers, and intramural aortic hematomas [6, 7].

Many endovascular grafts, and one percutaneous aortic valve (Medtronic CoreValve), are made of nitinol, named for the Nickel Titanium Naval Ordnance Laboratory, where it was discovered. This nickel titanium alloy has the unique property of shape memory. Nitinol undergoes a martensite (easily deformed) to austenite (high strength) transition as it is exposed to increasing temperature, leading to a marked increase in strength and a return to a previously established shape, and results in gentle outward pressure with high resistance to inward pressure and high crush resistance [8]. Therefore, the device can be deformed at room temperature to maintain a low profile for insertion through a vascular sheath, and upon deployment, the prosthesis will expand to its designed preset dimensions and remain fixed and durable at body temperature.

Therapeutic hypothermia involves cooling the body below 35°C in a controlled setting to slow metabolism and decrease ischemic injury to organs. Therapeutic hypothermia has long been used in cardiac surgery as part of cardiopulmonary bypass and deep hypothermic circulatory arrest (DHCA), which involves cooling to 20°C or less [9]. Recently, the indications for therapeutic hypothermia have expanded outside of the operating room, and it is now utilized for a number of clinical situations including post-cardiac arrest, cerebrovascular accident, and traumatic brain injury [10–12].

The properties of nitinol in hypothermic conditions raise two main concerns. First, as complex hybrid aortic arch repairs become more common, surgeons must be aware of the implications of placing an endovascular prosthesis during hypothermia and DHCA. Second, as the use of nitinol-based endovascular prostheses increases and the indications for therapeutic hypothermia increase, it is likely to become more common for patients with previously placed endovascular grafts to undergo total body cooling. At this time, there has not been a description, either experimental or clinical, of the potential risks or management of patients with nitinol-based endovascular grafts requiring therapeutic hypothermia. In this study, we examined the properties of nitinol endovascular grafts at different temperatures in vitro. We hypothesized that use of nitinol-based endovascular grafts at temperatures commonly achieved in therapeutic hypothermic conditions will change the properties of the alloy and lead to altered expansion and deployment diameter.

Material and Methods

For these in vitro studies, the self-expanding GORE TAG Thoracic Endoprosthesis (W. L. Gore & Associates, Flagstaff, AZ) was studied (Fig 1). We first examined the radial expansion force created by the self-expanding device at different temperatures. We then tested the actual diameter of the device when deployed at different temperatures.

Determination of Radial Expansion Force

A 34 mm × 15 cm GORE TAG Thoracic Endoprosthesis was placed in a closed, temperature-controlled air chamber and allowed to equilibrate for 5 minutes before testing. Radial force was determined by the “loop method,” as previously described [13]. Briefly, the undeployed TAG device was placed inside a Mylar (DuPont Teijin Films US, Chester, VA) loop with one end of the loop fixed to the test fixture and another end connected to a force actuator. The Mylar loop is now a constraint against the self-expanding nitinol stent. The Mylar loop experiences a radial expansion force that is transferred to the load cell as a

pulling force. This simulates deployment of the device within the aorta at recommended size by the manufacturer, and allows for assessment of the force generated by the expanding nitinol at a designated temperature. Five TAG devices were tested at each temperature setting. Five measurements were taken for each device at each temperature level. A new device was utilized for each temperature level, and a total of 25 devices were used for this experiment. The experiment was carried out with temperature set points of 20°C, 25°C, 30°C, 35°C, and 37°C. We then calculated the percent reduction in the average expansion force for each temperature set point as follows:

$$\text{Example of calculation at } 20^{\circ}\text{C}: (\text{Force}_{37^{\circ}\text{C}} - \text{Force}_{20^{\circ}\text{C}}) / \text{Force}_{37^{\circ}\text{C}} \times 100\%$$

Deployed Diameter at Various Temperatures

For these experiments, 34 mm × 15 cm GORE TAG Thoracic Endoprosthesis devices were placed in a temperature-controlled water bath. The device was allowed to equilibrate for 1 minute. The device was then deployed in the water bath at varying temperatures. The experiment was carried out with temperature set points of 20°C, 25°C, 30°C, 35°C, and 37°C. The TAG device was removed from the water bath, and immediately the diameter of the proximal end at two locations was measured twice using the LaserMike (Beta LaserMike, Dayton, OH), a halographic measurement device. This laser scanning micrometer is a precision measurement instrument and has a repeatability of ± 0.000030 inches. The test was repeated with two more devices at each temperature set point (total of 10 devices). Data are presented as mean ± SD. All data were analyzed using two-way, repeated measures analysis of variance with a Tukey-Kramer post-hoc test (JMP; SAS Institute, Cary, NC). Probability values less than 0.05 were considered significant.

Results

The radial force experiment examines the ability of the stent to expand and interface with the aortic wall creating enough force to prevent migration of the stent graft. The values of force generated for each temperature set point were plotted on a graph (Fig 2). The results of the radial force experiment demonstrated that there was no difference in force generated at 35°C as compared with the 37°C group (0.8% ± 0.6% reduction; $p = 0.15$). However, at 30°C, 25°C, and 20°C, there was a significant and linear decrease in the amount of radial force generated by the expanding nitinol stent. The average reduction in expansion force at 30°C was 6% ± 0.2%; at 25°C it was 46% ± 14.9%, and at 20°C, it was 186 ± 60.8% ($p < 0.001$ for each comparison).

Measurement of the deployed diameter examines the ability of the stent graft to reach the predetermined size. For this series, the diameter achieved for each temperature point was plotted on a graph (Fig 3). In the deployed diameter experiment, there was a significant reduction in the endoprosthesis diameter at 25°C and 20°C as compared to 37°C. The mean reduction in diameter was 11% (31.167 ± 0.603 mm) at 25°C and 17% (29.053 ± 0.603 mm) at 20°C ($p < 0.001$ for both). There was no difference in TAG device diameter at 35°C (34.600 ± 0.100 mm; $p = 0.45$) and 30°C (35.533 ± 0.702 mm; $p = 0.07$).

Comment

In this study, we investigated the effects of hypothermic temperatures on the radial expansion forces and deployed diameter of self-expanding nitinol thoracic endoprostheses. The results demonstrated that lower temperatures significantly altered the properties of these TAG devices in vitro. This may have important clinical implications related to potential graft deformation and migration.

Overall, endovascular repair of thoracic and abdominal aortic pathology has been shown to decrease perioperative morbidity, mortality, and length of stay, as well as to increase the likelihood of discharge to home [14]. Endovascular repair is now being offered to patients with ruptured aneurysms, and similar improvements in outcomes have been described [3]. Additionally, elderly patients—including octogenarians and nonagenarians—are now increasingly being considered for aneurysm repair, further increasing the number of eligible patients [15]. Percutaneous aortic valve replacement has been shown to be equivalent to surgical aortic valve replacement in terms of survival in very high risk patients at 1 year and better than standard medical therapy for patients deemed nonconventional surgical candidates [16]. The long-term durability of the CoreValve prosthesis as well as the Edwards Sapien device (which is not nitinol based) has yet to be determined.

Concurrently, the indications for therapeutic hypothermia are also expanding. The use of medical cooling was first introduced in the 1950s, but fell out of favor as implementation was difficult and the benefits were not clear. However, in the early 2000s, evidence began to accumulate showing benefits of moderate hypothermia (28°C to 32°C) in certain clinical situations [10, 17, 18]. Currently, the International Liaison Committee on Resuscitation and the American Heart Association have made the following recommendation: “Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was ventricular fibrillation” [19]. Other indications include traumatic brain injury, spinal cord injury, ischemic stroke, and neurogenic fever [20–22]. Use of moderate cooling in patients with nitinol-based stent grafts may increase the risk for stent migration, leading to occlusion of branch vessels or development of an endovascular leak. A high index of suspicion for graft complications is needed in patients who demonstrate signs of mesenteric, renal, or lower extremity ischemia, as this may indicate that the stent has migrated. In the absence of more robust data, we recommend imaging by computed tomographic angiography in all patients subjected to hypothermia to ensure the aneurysm is still excluded and no migration has occurred even if there are no signs of ischemia.

Consideration should be given to potential complications when inducing DHCA in patients with previously placed nitinol grafts or when placing these devices in the setting of deep hypothermia. Based on recommended sizes for TAG devices and data from the current study, potential technical failure can be extrapolated (Table 1). As an example, a 34mm graft can reshape down to 28 mm at 20°C, with a 186% decrease in radial expansion force. One manuscript described a method for prewarming the graft to 48°C in a sterile water bath before insertion [23]. Further study of this interesting approach is needed. The GORE TAG Thoracic Endoprosthesis device was approved by the US Food and Drug Administration in 2005. Two subsequent self-expanding endovascular grafts have been approved for use, one of which is constructed of stainless steel. These devices will not be affected by use during hypothermia and, therefore, may be preferred for this technique.

Additionally, thoracic stent grafts with proximal hooks may be less prone to migration, as will endovascular grafts that are sewn in proximally (eg, the “frozen elephant trunk” procedure). That could potentially prevent migration of the stent graft. A recent report by Roselli and associates [24] described 38 patients undergoing antegrade placement of both nitinol and stainless steel thoracic endovascular grafts, with 52% being placed under DHCA. Sixteen were placed by direct implantation into the aorta and sutured in place proximally. During a mean follow-up period of 8 months, they did not describe any complications related to migration of the devices after placement under hypothermia. There were 10 endovascular leaks in 9 patients (2 type I, 8 type II), and 3 required late reinterventions. Which type of endovascular grafts were involved with endovascular leaks was not

described, however [24]. Finally, there may be a role for intravascular ultrasonography to confirm apposition of the stent to the aortic wall [25].

Studies using clinically relevant models are needed to understand the effects of temperature on self-expanding nitinol stents. One method to accomplish this is a porcine model. Long-term animal studies could be utilized to study tissue ingrowth and the effects of hypothermia on devices that have been in place over extended periods of time. Another potential model involves human cadavers. In a recent report, a technique to attain circulation for the purpose of preclinical testing of endovascular devices in cadavers was described using a roller pump is used to create pulsatile flow through the aorta [26]. In this model, the aorta is cannulated in the proximal ascending and distal descending thoracic aorta and clamped. In any model, it would be important to evaluate the apposition of the stent to the aorta at varying temperatures. Measurement of a friction coefficient created by the stent graft could be used to predict migration potential. Use of these techniques may help define the properties of nitinol in hypothermic conditions.

Study Limitations

This was an in vitro study, and it is not clear that the results will translate in vivo. There are passive and active biologic processes that would likely influence the results. For example, over time, tissue ingrowth may stabilize the graft, making “remote” hypothermia safe. Another example would involve implantation of the percutaneous aortic valve into a deformed calcified annulus, which would likely make migration less likely due to the jagged edges of retained calcium projecting into the interstices of the device [27]. Further, angulation of the aorta and presence of branched endovascular grafts may act to alter the risk of migration as well. At this time, we have no evidence that therapeutic hypothermia is leading to complications in patients, as we have seen none reported in the literature. We believe this study provides preliminary data to stimulate future studies.

In conclusion, nitinol-based endovascular grafts and percutaneous valves will continue to be important for the management of aortic disease and aortic valve stenosis owing to ease of deployment and advantageous alloy properties. Based on these in vitro data, it appears hypothermia severely affects performance of nitinol-based endovascular grafts. Further study is needed to determine if these changes in expansion characteristics lead to clinical complications. However, surgeons and other health care professionals should be aware of the potential for migration of these devices. At this time, we recommend imaging the graft after therapeutic hypothermia in patients with existing prostheses or when placed under DHCA, and consideration should be given to using stainless steel endovascular grafts in this setting.

Acknowledgments

Funding and materials for this project were provided by W.L. Gore & Associates. The authors had full control of the data and preparation of the manuscript. Funding for this project was provided by the National Heart, Lung, and Blood Institute (RO1HL46716, RO1HL69024, and RO1HL85647 to F.W.S; and 5T32-HL0074 to M.P.R), and by the Irving Bard Memorial Fellowship (to M.P.R).

References

1. Lederle FA, Freischlag JA, Kyriakides TC, et al. Outcomes following endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. *JAMA*. 2009; 302:1535–42. [PubMed: 19826022]
2. Prinssen M, Verhoeven EL, Buth J, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. *N Engl J Med*. 2004; 351:1607–18. [PubMed: 15483279]

3. Giles KA, Pomposelli F, Hamdan A, Wyers M, Jhaveri A, Schermerhorn ML. Decrease in total aneurysm-related deaths in the era of endovascular aneurysm repair. *J Vasc Surg.* 2009; 49:543–51. [PubMed: 19135843]
4. Sachs T, Pomposelli F, Hagberg R, et al. Open and endovascular repair of type B aortic dissection in the Nationwide Inpatient Sample. *J Vasc Surg.* 2010; 52:860–6. [PubMed: 20619592]
5. Sachs T, Schermerhorn M, Pomposelli F, Cotterill P, O'Malley J, Landon B. Resident and fellow experiences after the introduction of endovascular aneurysm repair for abdominal aortic aneurysm. *J Vasc Surg.* 2011; 54:881–8. [PubMed: 21620615]
6. Coady MA, Ikonomidis JS, Cheung AT, et al. Surgical management of descending thoracic aortic disease: open and endovascular approaches: a scientific statement from the American Heart Association. *Circulation.* 2010; 121:2780–804. [PubMed: 20530003]
7. Conrad MF, Ergul EA, Patel VI, Paruchuri V, Kwolek CJ, Cambria RP. Management of diseases of the descending thoracic aorta in the endovascular era: a Medicare population study. *Ann Surg.* 2010; 252:603–10. [PubMed: 20881766]
8. Stoeckel D, Pelton A, Duerig T. Self-expanding nitinol stents: material and design considerations. *Eur Radiol.* 2004; 14:292–301. [PubMed: 12955452]
9. Apostolakis E, Akinosoglou K. The methodologies of hypothermic circulatory arrest and of antegrade and retrograde cerebral perfusion for aortic arch surgery. *Ann Thorac Cardiovasc Surg.* 2008; 14:138–48. [PubMed: 18577891]
10. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med.* 2002; 346:557–63. [PubMed: 11856794]
11. Arrich J, Holzer M, Herkner H, Mullner M. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev.* 2009:CD004128. [PubMed: 19821320]
12. Polderman KH. Application of therapeutic hypothermia in the ICU: opportunities and pitfalls of a promising treatment modality. Part 1: indications and evidence. *Intensive Care Med.* 2004; 30:556–75. [PubMed: 14767591]
13. Kleinstreuer C, Li Z, Basciano CA, Seelecke S, Farber MA. Computational mechanics of nitinol stent grafts. *J Biomech.* 2008; 41:2370–8. [PubMed: 18644312]
14. Schermerhorn ML, O'Malley AJ, Jhaveri A, Cotterill P, Pomposelli F, Landon BE. Endovascular vs. open repair of abdominal aortic aneurysms in the Medicare population. *N Engl J Med.* 2008; 358:464–74. [PubMed: 18234751]
15. Prenner SB, Turnbull IC, Malik R, et al. Outcome of elective endovascular abdominal aortic aneurysm repair in octogenarians and nonagenarians. *J Vasc Surg.* 2010; 51:1354–9. [PubMed: 20347545]
16. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010; 363:1597–607. [PubMed: 20961243]
17. The Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* 2002; 346:549–56. [PubMed: 11856793]
18. Mooney MR, Unger BT, Boland LL, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest: evaluation of a regional system to increase access to cooling. *Circulation.* 2010; 124:206–14. [PubMed: 21747066]
19. Nolan JP, Morley PT, Vanden Hoek TL, et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation. *Circulation.* 2003; 108:118–21. [PubMed: 12847056]
20. Fox JL, Vu EN, Doyle-Waters M, Brubacher JR, Abu-Laban R, Hu Z. Prophylactic hypothermia for traumatic brain injury: a quantitative systematic review. *Can J Emerg Med.* 2010; 12:355–64.
21. Mummaneni PV. Use of systemic hypothermia for patients with spinal cord injury. *Neurosurgery.* 2010; 66:E1217. [PubMed: 20495399]
22. Macleod MR, Petersson J, Norrving B, et al. Hypothermia for stroke: call to action 2010. *Int J Stroke.* 2010; 5:489–92. [PubMed: 21086713]
23. Lin PH, Dardik A, Coselli JS. A simple technique to facilitate antegrade thoracic endograft deployment using a hybrid elephant trunk procedure under hypothermic circulatory arrest. *J Endovasc Ther.* 2007; 14:669–71. [PubMed: 17924732]

24. Roselli EE, Soltesz EG, Mastracci T, Svensson LG, Lytle BW. Antegrade delivery of stent grafts to treat complex thoracic aortic disease. *Ann Thorac Surg.* 2010; 90:539–46. [PubMed: 20667347]
25. Pearce BJ, Jordan WD. Using IVUS during EVAR and TE-VAR: improving patient outcomes. *Semin Vasc Surg.* 2009; 22:172–80. [PubMed: 19765528]
26. Arbatli H, Cikirikcioglu M, Pektok E, et al. Dynamic human cadaver model for testing the feasibility of new endovascular techniques and tools. *Ann Vasc Surg.* 2010; 24:419–22. [PubMed: 19619977]
27. Shin CK, Rodino W, Kirwin JD, et al. Histology and electron microscopy of explanted bifurcated endovascular aortic grafts: evidence of early incorporation and healing. *J Endovasc Surg.* 1999; 6:246–50. [PubMed: 10495152]

Fig 1.

The self-expanding GORE TAG Thoracic Endoprosthesis devices used in this study are pictured: (A) A 34-mm TAG device in a silicone tube at 80% device diameter, and (B) a 34-mm TAG device fully deployed.

Fig 2.

Percent reduction in radial expansion force of TAG device at 80% device diameter. At lower temperatures, the force generated was significantly decreased. * $p < 0.0001$. Dots represent data points, green triangles represent the data population (horizontal lines represent quintiles). The Tukey-Kramer analysis (red and gray circles) indicate statistical differences in the population.

Fig 3.

Deployed diameter of TAG device. At the lower temperature set points, the diameter of the device was significantly decreased. * $p < 0.0001$. Dots represent data points, green triangles represent the data population (horizontal lines represent quintiles). The Tukey-Kramer analysis (red and gray circles) indicate statistical differences in the population.

Table 1

Recommended Sizes for GORE TAG Devices

Intended AorticInner Diameter (mm)	Endoprosthesis Diameter (mm)	Endoprosthesis Length (mm)
23–24	26	10
24–26	28	10/15
26–29	31	10/15
29–32	34	10/15/20
32–34	37	10/15/20
34–37	40	10/15/20