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Deep Hypothermic Circulatory Arrest Effectively Preserves Neurocognitive Function

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Katherine Hsin-Yu Chau

2014

Abstract

DEEP HYPOTHERMIC CIRCULATORY ARREST EFFECTIVELY PRESERVES NEUROCOGNITIVE FUNCTION.
Katherine H. Chau, Tamir Friedman, Maryann Tranquilli, John A. Elefteriades. Section of Cardiothoracic Surgery, Yale University School of Medicine, New Haven, CT.

Few (conflicting) studies have quantitatively assessed neurocognitive effects of deep hypothermic circulatory arrest (DHCA), and even fewer have looked at the long-term effects of DHCA. In this study, we aim to determine if DHCA negatively affects neurocognitive function and if so, are the effects long-term. We assess neurocognitive function quantitatively before and after DHCA and also in comparison with non-DHCA patients. 62 aortic surgical patients underwent a battery of neuropsychometric tests, both pre and post-operatively, evaluating multiple aspects of memory, processing speed, executive function, and global cognition. 33 patients did not require DHCA, and 29 underwent DHCA as the sole means of cerebral protection. Of these, 19 patients who tested positive for cognitive deficits, 8 of whom underwent DHCA and 11 who did not, were followed long-term with an additional testing months to years post-operatively. "Neurocognitive deficit" was defined as greater than 20% decline in two or more cognitive areas. Pre and post-operative test scores, as well as incidence of "neurocognitive deficit", were compared within each group (post versus pre-operatively), and between the non-DHCA and DHCA groups. There were no significant differences in the post versus pre-operative scores in any cognitive area tested between DHCA and non-DHCA groups. There was also no difference between the two groups in incidence of "neurocognitive deficit": 13 non-DHCA, 11 DHCA ($p = 1.00$). In addition, there was no correlation between time under DHCA and incidence of "neurocognitive deficit". Within both groups, there was a mild decline in memory in the areas of acquisition, retention,

and delayed recall. Within the DHCA group, recognition was also affected. Time under DHCA up to 40 minutes was also found to be safe neurocognitively. Of the 24 patients that who incurred a "neurocognitive deficit," 19 participated in further follow-up, and of these, 4 DHCA and 2 non-DHCA patients had persistent memory deficits ($p = 0.32$). There was also no statistically significant difference in duration under DHCA between those who did or did not recover from their deficits ($p = 0.56$). DHCA patients who did have persistent memory deficits tended to have additional aspects of memory become affected when tested at further follow-up. There was a statistically significant difference in age, above or below 70 years old, between patients whose memory deficits persisted or recovered ($p < 0.001$). While cardiac surgery had some effects on memory, overall neurocognitive function was well preserved and did not differ between DHCA and non-DHCA patients. DHCA does not affect whether or not memory deficits incurred post-operatively persist, but in those patients who underwent DHCA whose memory deficits did persist, those deficits tended to affect additional memory aspects that on previous testing had not been affected. What does affect the temporal nature of memory deficits is age, with patients over the age of 70 having a higher incidence of persistent long-term memory deficits. This study provides strong evidence that straight DHCA effectively preserves neurocognitive function.

Acknowledgements

I would like to express my utmost gratitude to Dr. John A. Elefteriades who has provided invaluable support and guidance since the very beginning of this study, and without whom I would never have been able to carry this out.

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Introduction

Deep hypothermic circulatory arrest (DHCA) is a cerebral protection strategy that has been an integral part of cardiac and aortic surgery for decades. It has been especially important in advancing the feasibility of aortic arch operations, which entail unique challenges. At our institution, we have found DHCA to be a safe and effective cerebral protection method, and we employ DHCA in the vast majority of procedures involving the aortic arch. However, while we favor the use of DHCA, that is not the case at other institutions. A recent survey finds a variety of methods applied at expert institutions (1). While the benefits of DHCA are well established, potential shortcomings have been under debate—specifically if there are any negative effects on neurocognition and also how long can a patient be safely under DHCA.

Thoracic Aortic Aneurysms

Approximately 10.4 per 100,000 people in the United States develop a thoracic aortic aneurysm (TAA) each year (2). TAA is a silent, but lethal, disease, with 95% of TAAs being asymptomatic before an acute event, such as dissection or rupture, occurs (3). Aortic aneurysms (both abdominal and thoracic) represent the 15th leading cause of death in individuals older than 55 years, and the 19th leading cause of death in individuals of all ages—so that aortic aneurysms cause more deaths in the United States than human immunodeficiency virus (HIV) (4).

Natural History and Progression. The aneurysmal thoracic aorta grows in a generally indolent manner, increasing by about 1 mm each year. The average ascending aneurysmal aorta expands by 0.10 cm annually, with the descending thoracic aneurysmal aorta expanding at a slightly faster rate of 0.29 cm each year (5). Aneurysms with larger diameters, however, tend to expand more rapidly. The annual growth rate for a 4.0 cm ascending TAA, for example, is 0.10 cm, while the annual growth rate for an 8.0 cm ascending TAA is 0.19 cm (6). The relationship between annual growth rate and aneurysm size is depicted in Figure 1. Dissected aortas also tend to grow more rapidly than non-dissected aortas (6).

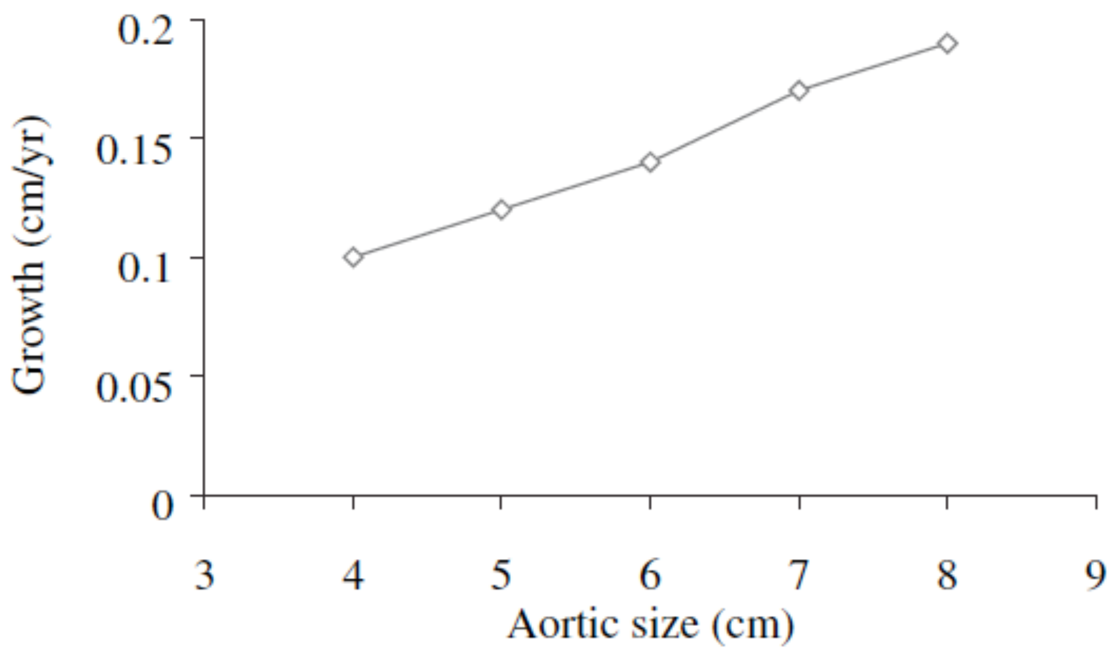

Figure 1. Absolute change in growth as a function of aortic size. Reprinted with permission from Coady et al (6).

There are subgroups of TAA patients in whom aneurysm growth rate is faster, and regular monitoring of aneurysm size is therefore even more crucial in avoiding potentially fatal complications such as dissection and rupture. One such subgroup is patients with familial TAAs. These patients' TAAs grow at 0.21 cm/year (combined ascending and descending TAA) compared with patients with sporadic TAAs (7). Loeys-

Dietz syndrome patients grow at an especially rapid rate, with their TAAs sometimes growing faster than 1.0 cm/year (7, 8).

Size of Aneurysm. In monitoring and managing TAAs, size has become the most important parameter to follow. In our Yale studies, we showed that the risk of natural complications, such as dissection or rupture or death, increases as TAAs get larger. In fact, we have been able to produce calculations of the annual risk of complications based solely on TAA size (Table 1) (9). Figure 2 graphically highlights the increase in risk of complications that corresponds with increasing TAA size.

Table 1. *Annual Risk of Complications Based on Thoracic Aortic Aneurysm Size*

	Annual Risk (%)			
Aortic Size	Rupture	Dissection	Death	Rupture/Dissection/ Death
> 3.5 cm	0.0	2.2	5.9	7.2
> 4.0 cm	0.3	1.5	4.6	5.3
> 5.0 cm	1.7	2.5	4.8	6.5
> 6.0 cm	3.6	3.7	10.8	14.1

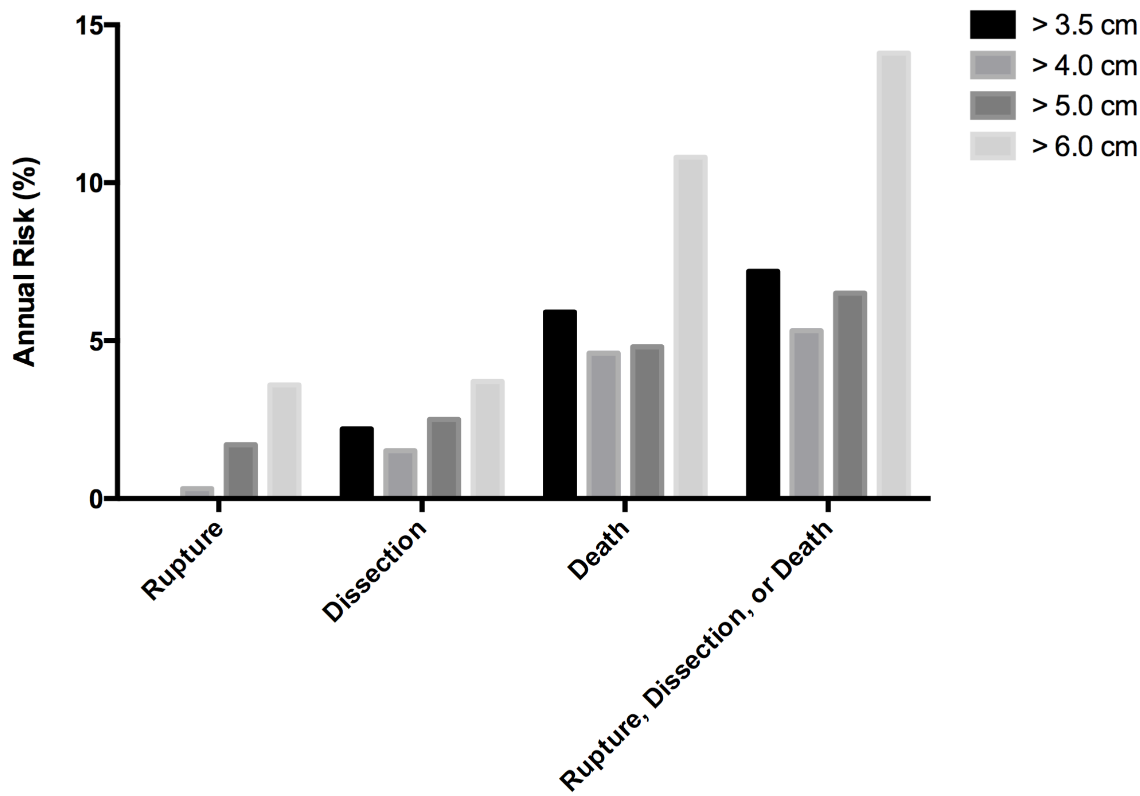

Figure 2. Annual risk of complications based on thoracic aortic aneurysm size.

Aortic dissection and rupture have approximately the same annual incidence of 3.5 per 100,000 patients (10). Once dissection or rupture occurs, short-term and long-term outcomes diminish rapidly. Data from the International Registry of Acute Aortic Dissection (IRAD) show that overall in-hospital mortality for acute thoracic aortic dissection is 27.4%. In-hospital mortality for acute type A dissections is about 35% (26% in patients undergoing surgical repair and 58% in patients managed non-surgically due to age or comorbidities) (11). In-hospital mortality for acute type B dissections is somewhat better at 12% (29%, 11%, and 10% for patients receiving surgical, endovascular, and medical management, respectively) (12).

Patients who have had dissected aortas have a severely compromised long-term outlook, as nearly 40% will suffer a fatal aortic rupture or require additional intervention (13). This is because, as mentioned above, previously dissected aortas expand at an accelerated rate (6).

The prognosis for TAA rupture is even worse than dissection. Johannson et al found that only 41% of patients with TAA rupture reach a hospital alive (14). For those patients lucky enough to make it to a hospital alive, the peri-operative mortality for surgical repair of the ruptured descending aorta is 28.6% and 23.4% for endovascular repair (15).

Our graphs and nomograms allow physicians to form a reasonable estimate of a specific patient's risk of dissection, rupture, or death from the TAA for each future year of life if the aorta is not resected; this permits an evidence based decision on management of the TAA.

Indications for Surgery. Our Yale studies have shown that once the aortic aneurysm has grown to a certain size, there is a dramatic increase in the risk of acute complications (rupture and dissection). In ascending aortic aneurysms, that "hinge point" is 6.0 cm, and in descending aortic aneurysms, the "hinge point" is 7.0 cm, as can be seen in Figure 3 (5).

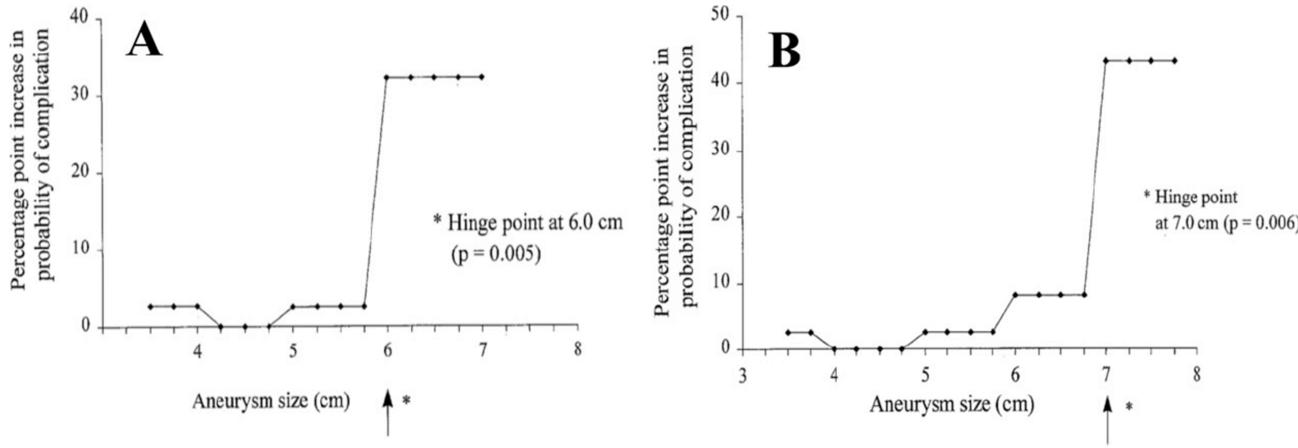

Figure 3. Effect of aortic aneurysm size on cumulative, lifetime incidence of complications for the (A) ascending and (B) descending aorta. Reproduced with permission from Coady et al (5).

It is important to note, however, that by the time the ascending aortic aneurysm reaches 6.0 cm, 31% of patients have already suffered a dissection or rupture of the aneurysm. By the time the descending aortic aneurysm reaches its “hinge point” of 7.0 cm, 43% of patients have already suffered a dissection or rupture (9). A surgeon should therefore *not* wait until the aorta grows to its “hinge point” for intervention. Intervention should be made before the “hinge point” is reached. Elective surgical treatment of TAAs (very safe) is also highly beneficial to the patient over emergency surgical intervention (very dangerous). The 5-year survival rate after elective extirpation of a TAA is approximately 85%, achieving a survival curve approaching that of the healthy, age-matched population. The 5-year survival rate after emergency surgical intervention, on the other hand, is only 37% (Figure 4) (16).

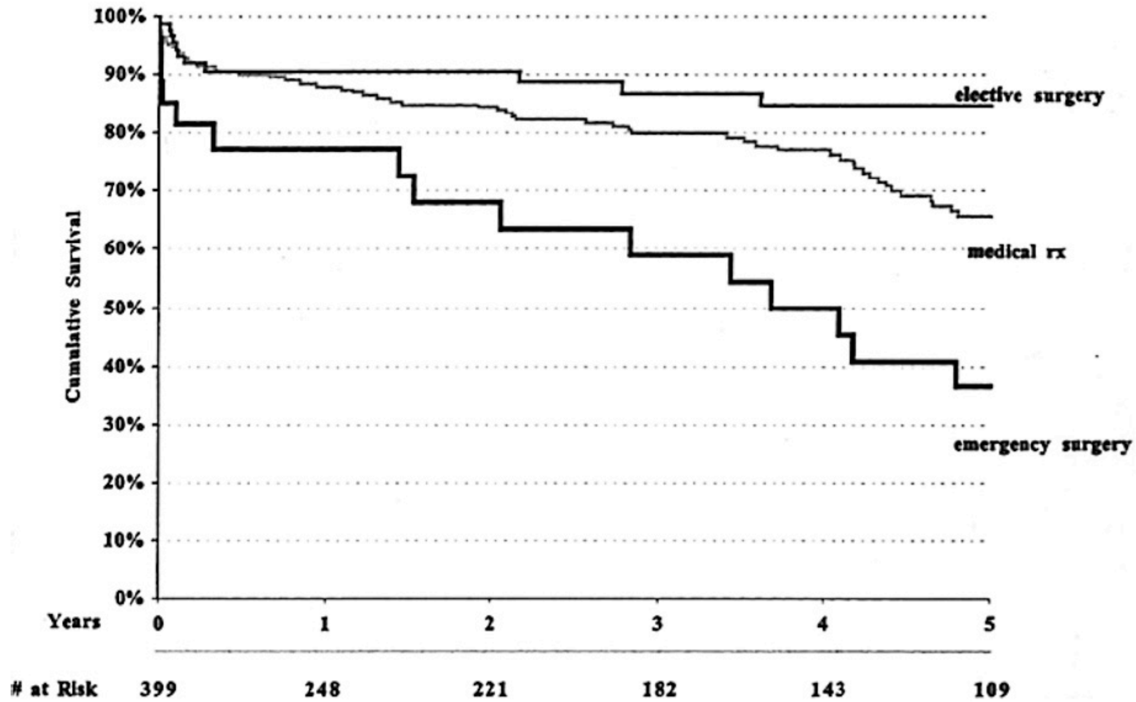

Figure 4. Kaplan-Meier survival curves after elective surgery, medical management, and emergency surgery for thoracic aortic aneurysms. Reproduced with permission from Davies et al (16).

Surgical intervention before the "hinge point" aortic size is reached is therefore highly desirable, if possible. Our evidence-based recommendations for surgical intervention based on size are summarized in Table 2 (17, 18).

Table 2. *Thoracic Aortic Aneurysm Size Criteria for Elective Surgical Intervention*

	Non-Marfan's	Marfan's or Familial	Bicuspid Aortic Valve
Ascending	5.5 cm	5.0 cm	5.0 cm
Descending	6.5 cm	6.0 cm	N/A[a]

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[a]A bicuspid aortic valve increases the risk of dissection and rupture of an ascending thoracic aortic aneurysm, but not a descending aneurysm (18).

Regardless of the size, though, all symptomatic aneurysms should be resected; the main symptom is pain consistent with the aneurysm location and unexplained by other causes. Rarely compression of adjacent organs (especially trachea, esophagus, or left main stem bronchus) may be the presenting symptom. Ascending aneurysm patients may experience congestive symptoms due to aortic insufficiency caused by distraction of the aortic valve leaflets as the aorta expands (19). Aneurysmal growth rate of ≥ 1 cm/year (rare with proper measurement techniques (20)) or substantial growth with the aneurysm rapidly approaching the size criteria listed in Table 2 are also valid indicators for which we would recommend surgical intervention (19).

DHCA

History Behind DHCA as a Cerebral Protection Strategy. The concept of using hypothermia for organ preservation was not applied to cardiac surgery until the mid-20th century when a few innovative and courageous surgeons discovered the usefulness of deep hypothermia in surgery. The DHCA era began in 1952, when what is probably the world's first successful open-heart surgery was performed by American cardiac surgeon John Lewis, who used systemic hypothermia with no cardiopulmonary bypass in his closure of a secundum-type atrial septal defect (21).

Across the Atlantic Ocean in England, another cardiac surgeon was also paving the way for the use of hypothermia in cardiac surgery. In 1957, Charles Drew began experimenting with the use of hypothermia in dogs. He found that it was possible to cool a dog down to 15°C, turn off cardiopulmonary bypass, keep the dog under circulatory arrest for 30 minutes, and then rewarm it with a subsequently normal heart rhythm. Based on these pioneering animal experiments, Dr. Drew applied the technique in humans. Called at that time the "Drew technique," hypothermia was applied by Dr. Drew in operations on both infants and adults until his retirement in 1981 (22).

Going further East, a cardiac surgeon was exploring the use hypothermia in cardiac surgery in the mid-20th century. Professor Eugene N. Meshalkin worked in central Siberia, where snow and ice were more than abundant. In the 1960s. He began using the snow and ice as topical hypothermic agents to cool patients down to 28 to 29°C. Using this technique, he operated on ventricular septal defects, atrioventricular canals, and other congenital pathologies. It has been reported that he even operated on tetralogy of Fallot cases and replaced mitral and aortic valves with hypothermia without cardiopulmonary bypass (23, 24).

While the 1950s saw the start of the use of hypothermia in cardiac surgery, it would still be another decade until hypothermia found its way into aortic surgery. In 1963, Barnard and Schrire introduced the use of hypothermia in thoracic aortic surgery, describing three cases involving the aortic arch where profound hypothermia was used during surgery (25). In these pioneering efforts, two patients died on the table or post-operatively, but one was discharged from the hospital in good condition. In the mid-1970s, Randall Griepp validated the use of hypothermia for cerebral protection, publishing additional successful operations in which hypothermia was used for cerebral protection against ischemic injury during aortic arch replacement surgery (26). Based on

Griepp's exceptional clinical and scientific studies, hypothermia for aortic surgery became a widely used and accepted method for cerebral protection during aortic arch operations. More recently, other cerebral protection strategies have also been developed and promoted, namely antegrade cerebral perfusion (ACP) and retrograde cerebral perfusion (RCP). Many centers have adopted these new techniques in lieu of hypothermia. However, which method—deep hypothermia, ACP, or RCP—is actually the most effective and safest has been, and still is, under hot debate.

Science Behind DHCA. The brain is particularly susceptible to ischemic injury due to its high metabolic rate of oxygen and glucose consumption, which is several times faster than other organs (27). Though the brain only accounts for approximately 2% of total body weight, it accounts for 20% of the resting total body oxygen consumption and receives 15-20% of the cardiac output (28). Unlike other tissues, the brain does not have stored glucose reserves, so that any interruption of blood flow has an immediate impact on neuronal function (27).

DHCA is able to protect the brain from ischemic injury in a number of ways, one of which is by lowering the brain's high metabolic rate. It is well established that hypothermia significantly decreases global cerebral metabolic rate for glucose and oxygen. It has been shown that for every 1°C drop in body temperature, cellular metabolism decreases by an average of 5 to 7% (29, 30). Therefore, at 18°C, cellular metabolic rate is only 12 to 25% of the metabolic rate at normal body temperature (Figure 5) (31).

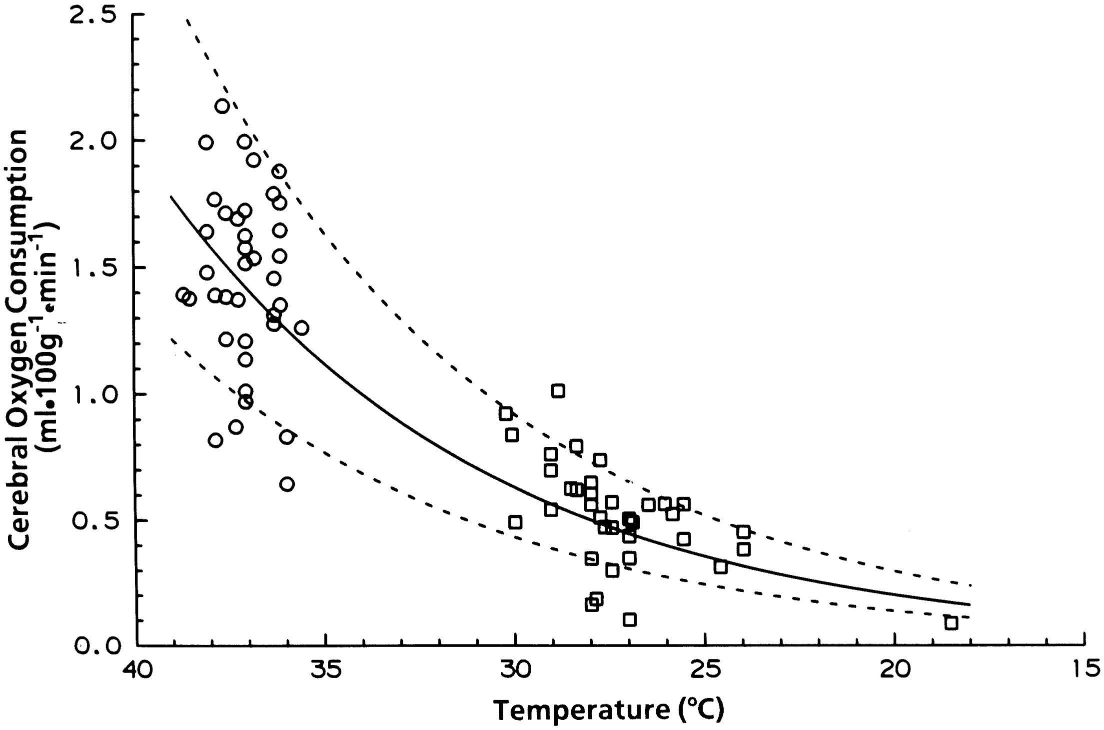


Figure 5. Decrease in cerebral metabolic rate with decreasing body temperatures. Reprinted with permission from Kirklin JW et al. (31).

Another useful rule of thumb is that metabolism of any cell, tissue, organ, or organism decreases exponentially as temperature falls—by 50% for every 6^{o} C drop in temperature (32). Hypothermia decreases anaerobic metabolism, and decreases lactic acid generation. These effects minimize neuronal damage and necrosis that would otherwise have been caused by the acidosis created by the excess lactic acid production (29).

Hypothermia also significantly reduces temperature-dependent release and extracellular levels of excitatory neurotransmitters such as glutamate, a *N*-methyl-D-aspartate (NMDA) receptor agonist. NMDA receptor activation leads to the unfavorable release of calcium ions, which then enter cells and accumulate. This leads to activation of intracellular proteases and mitochondrial dysfunction, resulting ultimately in neuronal cell death. Hypothermia reduces NMDA receptor activation, thus significantly decreasing calcium ion release and preventing irreversible neuronal injury (33).

Hypothermia provides cerebral protection also by reducing neuronal apoptosis, decreasing the release of pro-apoptotic proteins such as caspases and bcl-2, and by interfering in pro-apoptotic pathways such as the mitogen-activated protein kinase pathway. Hypothermia also significantly reduces free radical release after neuronal damage and decreases the production of inflammatory cytokines. Yet another way that hypothermia protects the brain from ischemic injury is by reducing post-ischemic cerebral edema by decreasing disruption of the blood-brain barrier and damage of endothelial vasculature after ischemia (33).

Overall, the protection of tissues by hypothermia reflects a panoply of powerful and wide-ranging beneficial effects. Simply put, there is no better protection against ischemic injury than hypothermia.

Comparison with Antegrade and Retrograde Cerebral Perfusion. Since DHCA was first used as a cerebral protection method in aortic arch surgery in the 1960s by Drs. Barnard and Schrire (25), other strategies for cerebral protection have been developed, including ACP and RCP. Besides DHCA, these are two of the most commonly used cerebral protection techniques during interventions on the aortic arch. There is considerable debate about which of these three strategies offers superior cerebral protection (34-36). We present here a summary of currently published data from large studies that either describe their experience with one technique or compare outcomes with different techniques (specifically, stroke and mortality rates) (Table 3).

***Table 3**. Review of pertinent literature on post-operative outcomes of straight deep hypothermic circulatory arrest, antegrade cerebral perfusion, and retrograde cerebral perfusion.*

First author	Patients (n)	Mortality (%)	Stroke (%)	Comments
Retrograde Cerebral Perfusion				
Safi, 1993 (37)	11	0	9.1	
Ueda, 1994 (38)	33	12.1	6.1	
Deeb, 1995 (39)	35	8.6	2.9	
Lytle, 1995 (40)	43	9.3	9.3	
Ueda, 1999 (41)	249	10	4	Retrospective
Ogino, 2001 (42)	28	0	3.6	Type A dissections
Bavaria, 2002 (43)	163	9.8	3.0	
Appoo, 2006 (44)	79	7.6	3.8	Confined to elective cases
Antegrade Cerebral Perfusion				
Matsuda, 1989 (45)	34	9.0	2.9	
Bachet, 1991 (46)	54	13.0	1.8	
Ando, 1994 (47)	42	7.1	7.0	Type A dissections (acute and chronic)
Kazui, 1994 (48)	80	16.3	1.3	
Tabayashi, 1994 (49)	77	19.4	5.0	
Kazui, 2000 (50)	220	12.7	3.3	
Di Eusanio, 2002 (51)	403	9.4	3.7	

First author	Patients (n)	Mortality (%)	Stroke (%)	Comments
Bachet, 2002 (52)	206	17	4.5	Rate of non-fatal strokes 6%
Kazui, 2007 (53)	472	9.3	3.2	Probably includes patients from studies in 1994 (50), 2000 (38)
Khaladj, 2008 (54)	501	11.6	9.6	9.6% PND, 13.4% TND. Multivariate analysis relates PND to renal insufficiency
Ogino, 2008 (55)	531	4.0	2.9	Retrospective
Toyama, 2009 (56)	26	3.8	7.7	
Krahenbuhl, 2010 (57)	280	4.0	7.5	Mortality and stroke rates in patients with mean circulatory arrest time >40 min 6.8% and 13.7% respectively
Leshnower, 2010 (58)	412	7.0	3.6	Retrospective
Minakawa, 2010 (59)	122	8.2	4.1	
Zierer, 2011 (60)	245	8.0	6.0	Retrospective, ACP combined with mild HCA
Numata, 2012 (61)	164	6.1	7.9	Retrospective

Deep Hypothermic Circulatory Arrest

First author	Patients (n)	Mortality (%)	Stroke (%)	Comments
Svensson, 1993 (62)	656	12.0	7.0	DHCA > 45 min correlated with stroke DHCA > 65 min correlated with death
Gega, 2007 (*author's group*) (63)	394	2.2 for asc/arch	3.1 for asc/arch	DHCA > 40 min correlated with (embolic) stroke
Comparison studies				
Deep Hypothermic Circulatory Arrest and Antegrade Cerebral Perfusion				
Alamanni, 1995 (64)	DHCA = 19 ACP = 16	DHCA = 26.3 ACP = 18.7	DHCA = 15.7 ACP = 12.5	Compared straight DHCA to ACP
Immer, 2004 (65)	DHCA = 322 ACP = 41	Overall mortality= 8.6	DHCA = 6.5 ACP = 1.0	No comparisons of DHCA vs ACP were statistically significant

First author	Patients (n)	Mortality (%)	Stroke (%)	Comments
Halkos, 2009 (66)	DHCA = 66 ACP = 205	DHCA = 22.7 ACP = 8.8	Overall = 4.3	Retrospective; method of randomization to groups is unclear; 61% of DHCA group patients had emergent operations compared to 32% of the ACP group; DHCA stroke rate for elective cases was 0
Kruger, 2011 (67)	DHCA = 355 ACP = 1081	DHCA = 19.4 ACP = 14.8	DHCA = 14.9 ACP = 13.3	Retrospective. Results from 44 different centers. All patients with Type A dissections

Deep Hypothermic Circulatory Arrest and Retrograde Cerebral Perfusion

Safi, 1997 (68)	DHCA = 41 RCP = 20	Overall mortality = 6	DHCA = 9 RCP = 3	Retrospective study with large size discrepancy between groups;
Wong, 1999 (69)	DHCA = 34 RCP = 96	Overall mortality=17	Overall = 6.9	Nonrandomized; RCP was not protective against for mortality or stroke.

First author	Patients (n)	Mortality (%)	Stroke (%)	Comments
Moon, 2002 (70)	DHCA = 36 RCP = 36	DHCA = 8.0 RCP = 11.0	DHCA = 11.0 RCA = 6.0	Retrospective case control; no statistically significant difference in mortality or stroke between groups.
Dong, 2002 (71)	DHCA = 15 RCP = 50	DHCA = 20.0 RCP = 2.0	DHCA = 25 RCP = 2.0	Retrospective; large size discrepancy between patient groups
Harrington, 2003 (72)	DHCA = 18 RCP = 20	DHCA = 5.5 RCP = 5.0	Overall = 2.6	Prospective randomized trial to evaluate effect of procedure neuropsychometric outcomes; no difference found between groups
Safi, 2011 (73)	DHCA = 191 RCP = 1002	DHCA = 13.1 RCP = 8.6	DHCA = 4.2 RCP = 2.8	Retrospective, a trend towards reduced mortality and stroke in the RCP group found

Antegrade Cerebral Perfusion and Retrograde Cerebral Perfusion

First author	Patients (n)	Mortality (%)	Stroke (%)	Comments
Okita, 2001 (74)	RCP = 30 ACP = 30	RCP = 6.6 ACP = 6.6	RCP = 3.3 ACP = 6.6	No straight DHCA patients; only difference found was higher incidence of transient brain dysfunction in RCP patients.
Apostolakis, 2008 (75)	RCP = 25 ACP = 23	RCP = 16.6 ACP = 13.0	RCP = 4.0 ACP = 4.3	All patients with type A acute dissections. No significant difference in mortality or stroke.
Milewski, 2010 (76)	RCP = 682 ACP = 94	RCP = 2.8 ACP = 3.2	RCP = 2.8 ACP = 3.2	RCP and ACP conducted in two different institutions. Arch reconstruction period no longer that 45 minutes in all cases.
[a]Estrera, 2010 (77)	RCP = 34 ACP = 30	RCP = 9 ACP = 20	RCP = 2 ACP = 13	A select group of patients requiring extended hypothermic circulatory arrest (>40 min)
Usui, 2012 (78)	RCP = 583 ACP = 2209	RCP = 4.1 ACP = 5.3	RCP = 3.1 ACP = 6.8	Retrospective. No significant difference between mortality or stroke rates.

First author	Patients (n)	Mortality (%)	Stroke (%)	Comments
Deep Hypothermic Circulatory Arrest and Antegrade Cerebral Perfusion and Retrograde Cerebral Perfusion				
Svensson, 2001 (79)	DHCA = 10 RCP = 10 ACP = 10	DHCA = 0 RCP = 0 ACP = 0	DHCA = 0 RCP = 0 ACP = 0	Prospective randomized controlled study. Neurocognitive results demonstrate superiority of DHCA in long-term outcome.
Matalanis, 2003 (80)	DHCA = 14 RCP = 23 ACP = 25	DHCA = 7.1 RCP = 0 ACP = 16.0	DHCA = 0 RCP = 4.3 ACP = 12.0	Retrospective; no significant differences in mortality or stroke rate among groups
Sundt, 2008 (81)	DHCA = 220 RCP = 53 ACP = 74	DHCA = 7 RCP = 17 ACP = 8	DHCA = 9 RCP = 9 ACP = 5	Study showed superiority of ACP for total arch replacements only; overall results show no superiority.

First author	Patients (n)	Mortality (%)	Stroke (%)	Comments
Apaydin, 2009 (82)	DHCA = 48 RCP = 94 ACP = 19	Overall mortality= 15.5	DHCA = 4.1 RCP = 1 ACP = 10	Retrospective. No significant difference in mortality or stroke between the perfusion groups.
Forteza, 2009 (83)	DHCA = 32 RCP = 26 ACP = 23	DHCA = 12.5 RCP = 23 ACP = 8.6	DHCA = 6.2 RCP = 11.5 ACP = 8.6	Retrospective. All patients with type A acute dissections. No significant difference in mortality or stroke between groups.
Shihata, 2011 (84)	Non-ACP =78 ACP = 46	Non-ACP =10 ACP = 4	Non-ACP =13 ACP = 2.2	Retrospective, 38% of the non-ACP group had RCP as an adjunct to DHCA. Mortality rates not significantly different.
Misfeld, 2012 (85)	DHCA = 220 RCP = 51 ACP = 365	Overall mortality = 11	Non-ACP =15 ACP = 9	No statistical difference in mortality rates between groups.

[a]In this study patients with ACP received brief RCP before terminating DHCA

ACP = antegrade cerebral perfusion; DHCA = deep hypothermic circulatory arrest; PND = permanent neurologic deficit; RCP = retrograde cerebral perfusion; TND = temporary neurologic deficit. Reprinted with permission from Ziganshin BA, et al (86).

The data from these studies show very similar stroke and mortality rates when using DHCA, ACP, or RCP. The small and inconsistent differences in outcomes are not surprising and likely related to patient selection, disease complexity, and institutional variations (such as extent of surgical experience with a technique). This shows that all three techniques are relatively safe and effective cerebral protection methods, and the choice of which technique to use depends on institutional preference.

While DHCA, ACP, and RCP have similar stroke and mortality rates, there are still important differences in the pros and especially the cons between the three techniques. Of the three, RCP is becoming the least popular due to increasing evidence that very little oxygen actually reaches the brain via venous perfusion because of venous valves, whose purpose is to prevent exactly what RCP is trying to achieve. Also much of the retrograde perfusion is diverted via collaterals and never reaches the brain, but rather is wasted on the soft tissues of the head and upper chest wall (87, 88). The positive outcomes attributed to RCP (36, 41, 42, 73, 78) may therefore arise from non-oxygen carrying properties. One major advantage of RCP is that it flushes embolic debris out of the arterial circulation system and reduces the incidence of air emboli (37). However, our clinical experience and studies have shown that patients with aortic root aneurysms are protected against arteriosclerosis (89, 90), and so debris is not frequently a problem. Also, DHCA allows for a bloodless and uncluttered field with wide-open exposure of the aorta, which permits the surgical team to visualize and capture any debris liberated during aortic debridement and preparation of aortic cuffs for anastomoses (91). DHCA is therefore intrinsically conducive towards avoiding embolization.

Unlike RCP, which has decreased in popularity, ACP has markedly increased in popularity in recent years. ACP makes good sense, as it delivers oxygen-rich blood to the brain, and is the most similar to physiological brain perfusion of the three cerebral protection techniques. There are, however, several important issues with using ACP, one of which regards how many vessels should be perfused during ACP, on which there is no consensus. This is a crucial issue, as adequate and balanced perfusion of all brain structures is the cornerstone of effective cerebral protection. Some institutions prefer to perfuse all three of the head vessels (59, 61), including the left subclavian artery, while others prefer to perfuse just the right axillary and left common carotid artery (50, 60). Still other institutions believe that unilateral perfusion (innominate artery only) is sufficient (58, 66, 92).

The other extremely important issue with ACP is that there is no standardization of appropriate flow rates. Many centers use 8-10 cc/kg/min, which may well be excessive. High flow rates have been demonstrated to cause cerebral edema (93) and low flow rates result in cerebral hypoperfusion, defeating the purpose of ACP. ACP can therefore cause significant cerebral damage, as the balance between hypo- and hyperperfusion has yet to be optimized. Other issues with the use of ACP include the potential to cause catheter-induced trauma to head vessels, which are often fragile or themselves affected by dissection. Embolization, both air and particulate, is another danger with using ACP. Particulate embolism is of particular concern, as debris may be liberated during catheter introduction. All these issues raise concerns about the use of ACP, especially during emergency cases, such as acute aortic dissections, where there is little time to spare on establishing a sophisticated perfusion system of the brain.

DHCA, on the other hand, avoids all the previously mentioned concerns with both RCP and ACP, as well as provides a bloodless and uncluttered field with no intrusive clamps or perfusion cannulae (31). And, unlike ACP, DHCA is especially appropriate in emergency situations where time is of the essence and the simplicity of DHCA allows for immediate life-saving procedures while providing good cerebral protection. DHCA does, however, raise the issue of how much time under DHCA is safe, on which there is no consensus as of yet. Some studies have found 20 to 25 minutes to be the safe upper limit of time under DHCA (65, 94-96), while in our previous studies, we have found that upper limit to be 40 minutes or more (63).

All in all, DHCA, ACP, and RCP have comparable results in terms of stroke and mortality rates, with each technique entailing its own set of pros and cons. The choice of technique is ultimately based on each surgeon's preference and comfort level. We invited all members of the Editorial Board of the new journal AORTA (members are listed on the journal website http://aorta.scienceinternational.org) to fill out an online survey in which they were asked: which method of cerebral protection do you favor during aortic arch surgery? The choices they were given were: (1) DHCA; (2) selective ACP; (3) RCP; (4) DHCA, *or* cerebral perfusion depending on case complexity. 29 board members responded with the results shown in Figure 6.

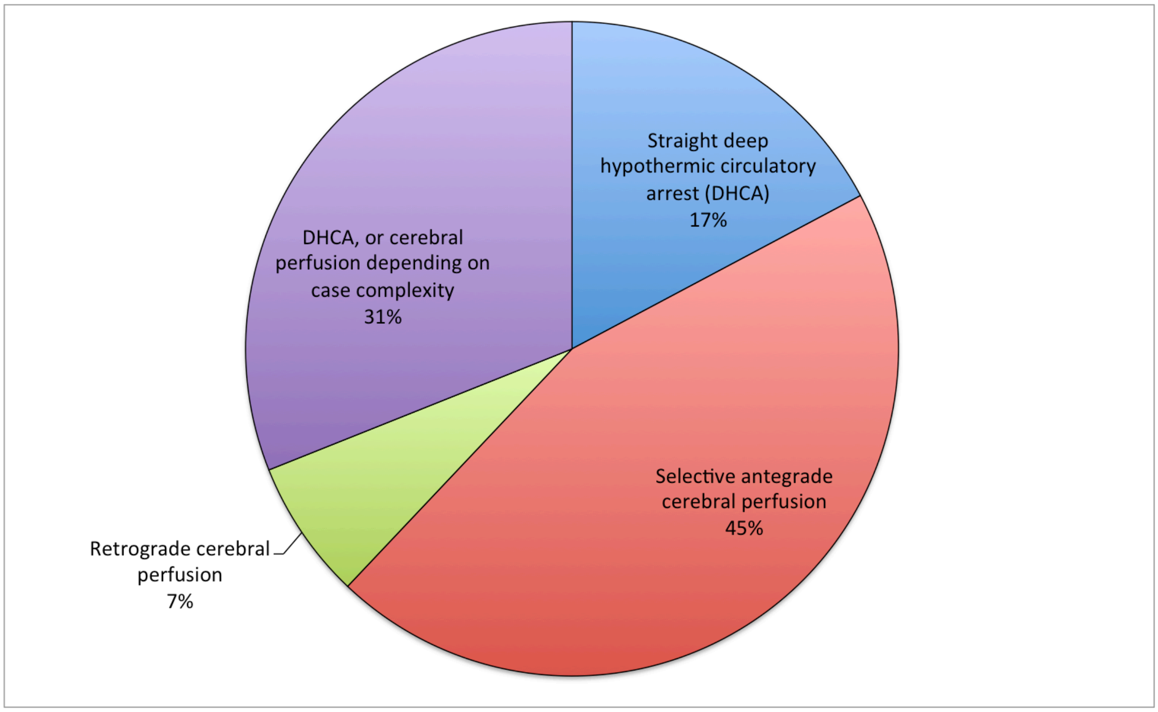


Figure 6. Pie chart of AORTA Editorial Board members' preferences in terms of cerebral protection during aortic arch surgery. Note that almost half of the cardiac surgeons (more than those with a preference of ACP) responded with a preference of using DHCA (either alone or with a cerebral perfusion technique depending on the case complexity). Reprinted with permission from Ziganshin BA (1).

The responses reflect current trends in cerebral protection strategy, with ACP being the most popular among the surgeons polled (45%) and RCP being the least (7%). It is interesting, however, to note that almost half of the surgeons (48%), more than those stating a preference for ACP, preferred using either DHCA or choosing between DHCA and a cerebral perfusion technique depending on case complexity (1).

Neurocognitive Effects. While the advantages of DHCA are largely undisputed, there are many conflicting studies on DHCA-related detrimental effects, especially neurocognitive. Of the three most commonly used cerebral protection methods, antegrade cerebral perfusion (ACP), retrograde cerebral perfusion (RCP), and DHCA, Svensson et al found all 3 to be equivalent in terms of brain injury (by looking at levels of brain injury markers), but found DHCA to be the superior method in preserving neurocognitive function (79). We previously published a retrospective clinical study looking at mortality and post-operative neurological complications that showed using DHCA as the sole means of cerebral protection is both effective and neurologically safe (63). In another retrospective study, we showed that in patients with high cognitive needs for their professions, DHCA had no adverse effect on their reported cognition or work performance (97). A number of other studies, however, have found DHCA to have a negative impact on neurologic function (65, 72, 94, 98, 99). Some studies also report a cutoff time of 20 to 25 minutes under DHCA, above which neurologic deficits may appear (65, 94-96).

Also, while it is well established in the literature that memory is commonly negatively affected after cardiac surgery (100, 101), any long-term effects that DHCA may have on neurocognition, and memory in particular, are relatively unknown. There have been multiple studies on the temporal nature of neurocognitive deficits incurred post-operatively in coronary artery bypass graft (CABG) patients. There is some controversy about the persistence of deficits incurred post-operatively, with some studies showing the deficits incurred shortly after surgery to persist (102-104), with other studies showing that deficits resolve in the long term (105, 106). However, when it comes to the temporal nature of memory deficits incurred after thoracic aortic aneurysm surgery and also DHCA, there is a dearth of literature, with only one study to the author's knowledge following patients beyond the first follow-up visit at 4 to 6 weeks (72).

Most studies on the neurocognitive effects of DHCA in adults have been retrospective with either only gross assessment of neurologic function, only qualitative assessment, or quantitative tests administered only post-operatively. There have been very few studies that quantitatively measured changes in neurocognitive function based on scores of tests administered both pre and post-operatively, and even fewer studies that have followed patients longitudinally past the first post-operative follow-up visit at 4 to 6 weeks. That is precisely the type of study we present here.

We studied patients undergoing only ascending aortic replacement (without approach to the aortic arch), who did not require DHCA, as a control group. We compared their function to patients undergoing ascending and arch surgery, our DHCA group. Thus, both groups were exposed to cardiac surgery and aortic surgery and their general effects. In fact, this comparison is likely to bias against DHCA, as the DHCA operations were more extensive and complicated.

A battery of neuropsychometric tests was administered to 62 patients—33 undergoing surgery without DHCA, and 29 undergoing surgery with straight DHCA (DHCA as the only method used for cerebral protection)—once pre-operatively and then post-operatively at the first post-operative follow-up visit and again months to a few years after the after surgery (4.5 months to almost 3 years) with the tests administered focusing on the areas of memory and processing speed, as those are the two cognitive domains that have most commonly been shown to be vulnerable for patients undergoing DHCA (72, 79, 94, 98). We also take a more in depth look at memory, examining multiple aspects, instead of accepting a general effect as other studies have done. In addition, we included in our assessment battery the Clock Drawing Test (CDT), which is very sensitive for detecting deficits in global cognitive function, executive functions, as well as the integration of many advanced cortical functions (107).

Aims

We hope to determine if there are any differences in neuropsychometric test scores between the pre-operative testing and the post-operative testing, both within the DHCA and non-DHCA groups and between them. We hope also to determine the temporal nature of any negative effects that DHCA may have on neurocognitive function.

Methods

This study was approved by the Yale University School of Medicine Human Investigative Committee (number 1210010969).

Patient Population

Patients who were scheduled for surgical repair of an ascending aortic or aortic arch aneurysm between July 2010 and February 2013 were asked to participate in this study. Of the 62 total patients enrolled in this study, 29 underwent straight DHCA and 33 did not require DHCA.

In the DHCA group, there were 23 males and 6 females. Mean age was 64.5 years with a range of 43 to 79 years. 1 patient had Marfan syndrome, and 1 had Loeys-Dietz syndrome. 2 patients underwent surgical repair for chronic Type A aortic dissections. 11 underwent root-sparing procedures (7 with aortic valve replacement, 4 without aortic valve replacement), and 18 underwent root replacement procedures. For the distal anastomoses, 24 patients had hemiarch replacements and 5 had total arch replacements. Mean duration under DHCA was 28.2 minutes with a range of 20 to 54 minutes.

In the control group of 33 patients who did not undergo DHCA, there were 27 males and 6 females. Mean age was 58.6 years with a range of 36 to 75 years. There were no Marfan or Loeys-Dietz syndrome patients. There were no Type A aortic dissection repairs. 6 patients underwent root-sparing procedures (4 with aortic valve replacement, 2 without aortic valve replacement), and 27 underwent root replacement procedures. There were no arch resections in this group.

All 62 patients who entered into this study survived surgery with no post-operative strokes or seizures.

In the follow-up study looking at the temporal nature of effects that DHCA had on neurocognition, the patients consisted of those from the first study who tested positive for memory deficits based on their neurocognitive testing scores, 11 of whom were in the DHCA group and 13 of whom were in the non-DHCA group. 5 of these patients, 3 in the DHCA group and 2 in the non-DHCA group, declined further testing and were therefore excluded from this follow-up study.

Among the patients completing the follow-up study, in the DHCA group, there were 6 males and 2 females. Mean age was 65.9 years with a range of 52 to 78 years. There were no patients with Marfan syndrome or Loeys-Dietz syndrome. 1 patient underwent surgical repair for chronic Type A aortic dissections. 3 underwent root-sparing procedures (2 with aortic valve replacement, 1 without aortic valve replacement), and 1 underwent a root replacement procedure. For the distal anastomoses, 4 patients had hemiarch replacements and 4 had total arch replacements. Mean duration under DHCA was 33.8 minutes with a range of 20 to 54 minutes.

Among the patients completing the follow-up study, in the control group of 11 patients who did not undergo DHCA, there were 8 males and 3 females. Mean age was 60.6 years with a range of 44 to 75 years. There were no Marfan or Loeys-Dietz syndrome patients. There were no Type A aortic dissection repairs. 1 patient underwent a root-sparing procedure without aortic valve replacement, and 1 underwent a root replacement procedure. There were no arch resections in this group.

Deep Hypothermic Circulatory Arrest Management

The surgical techniques for induction of deep hypothermia and use of circulatory arrest were constant for all patients. Total systemic perfusion is usually established by cannulating the femoral artery, unless the patient is shown to have arteriosclerotic disease of the descending aorta on intraoperative transesophageal echo or pre-operative computed tomography. If that is the case, the axillary artery is used for cannulation, or the aneurysm or distal aorta are cannulated directly. Venous return occurs via the right atrial appendage with a two-stage cannula (in very rare cases via the femoral vein), and carbon dioxide instillation into the surgical field is used in all cases. The extent of aortic resection is determined by the extent of the disease. The patient is put on cardiopulmonary bypass (CPB) and core cooling occurs. The head is packed in ice for topical cooling. No barbiturate coma is used during the operation. No electroencephalogram, sensory evoked potential, or jugular venous bulb oxygen saturation monitoring are used. No special glucose management techniques are applied. Deep hypothermic circulatory arrest management is by the Alpha-stat method. The mean core temperature (bladder) during

DHCA is 18.7°C with a range from 18 to 20°C. Rewarming, which usually takes about 60 minutes, is taken to a temperature of 34 to 36°C. The non-DHCA patients are cooled to a mean temperature of 24.9°C. The maximum temperature gradient between perfusate and body temperature during rewarming is kept less than 10°C in order to prevent protein denaturation (63, 91).

For aortic arch reconstructions, the technique that we have used most commonly involves a two-vessel island with just the innominate and left common carotid arteries, instead of the traditional technique of creating a three-vessel Carrel patch (Figure 7).

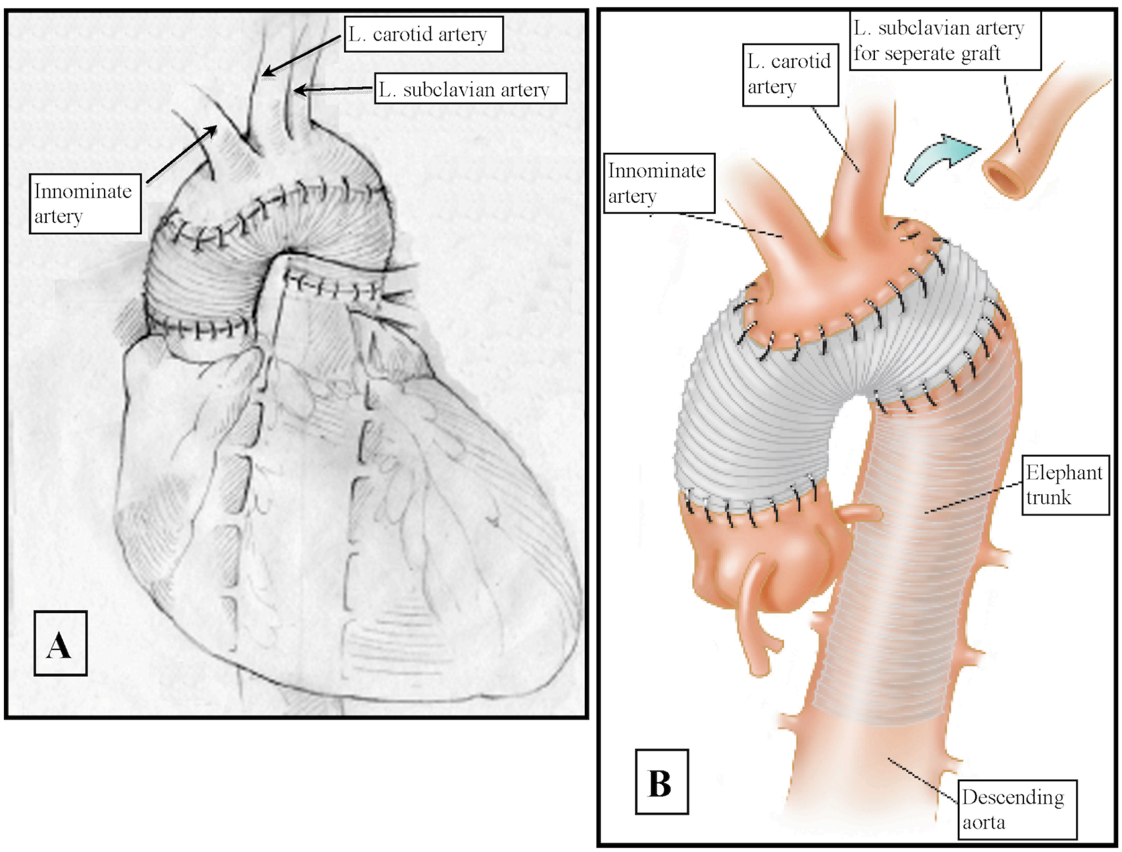


Figure 7. Aortic arch resconstruction methods. Traditional technique creating a three-vessel Carrel patch (left) versus our preferred alternative technique creating a two-vessel Carrel patch. Reprinted with permission from Gega et al (63).

The left subclavian artery is re-attached using a small diameter graft either during rewarming or after termination of CPB. There are several advantages to using this technique, including an initially smaller Carrel patch suture line, allowing for less time to be spent under DHCA, and also excellent suture-line access for inspection and additional placement of hemostatic sutures if needed (63, 91, 108).

Deep hypothermic circulatory arrest was used as the sole means of cerebral protection. Carbon dioxide flooding of the field was used in all cases. Extent of aortic resection was determined by the extent of disease, with the goal of excising all severely dilated aortic segments.

Neurocognitive Tests

A battery of neurocognitive tests was administered by a trained medical student, pre-operatively at either the office consultation visit or at the time of pre-admission testing, and post-operatively at the first follow-up visit. The mean time between pre and post-operative testing among the patients who underwent DHCA was 46.3 days with a range of 30 to 75 days, and among the patients who did not undergo DHCA the mean was 45.2 days with a range of 31 to 77 days. The battery consisted of three tests that were chosen, and the results interpreted, with the help of a neuropsychometric specialist: Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test (TMT)-A and B, and Clock Drawing Test (CDT). RAVLT tests multiple aspects of memory, including acquisition (sum of trials A1 through 5), learning rate (difference between trials A5 and A1), retention (trial A6), delayed recall (trial A7), and recognition (word list). TMT A and B test attention and processing speed. CDT tests advanced cortical executive functions and their integration, as well as global cognitive function (107). "Neurocognitive deficit" was defined as greater than 20% decline in 2 or more tests (72). (We counted each aspect of memory that we tested as a separate test.)

In the follow-up study, the RAVLT was administered again to patients months to years after surgery in order to reassess memory function. In the follow-up study, the mean time between pre and post-operative testing among the patients who underwent DHCA was 39.4 days with a range of 30 to 46 days, and among the patients who did not undergo DHCA the mean was 48.0 days with a range of 27 to 77 days. The mean time between post-operative and further follow-up testing among patients who underwent DHCA was 422.4 days with a range of 169 to 1033 days. Among the patients who did not undergo DHCA, the mean was 653.5 days with a range of 138 to 1089 days.

Patients' neurological function and status were assessed and tracked both pre and post-operatively by the intensive care unit and surgical teams.

Statistical Analysis

Very few studies have examined neuropsychometric test score changes after undergoing DHCA, and so there is no standardized sampling distribution for such score changes. Therefore, neither a reliable study power nor sample size could be calculated at the time of study design. However, our sample size of 62 is greater than the mean and median of the sample sizes of previous such studies, 55.8 and 57, respectively (72, 79, 94, 96, 98). We also retrospectively calculated the sample size necessary to have a power of 0.8 with a Cohen's *d* effect size of 0.8 and the *p*-values that we found using an on-line statistical sample size calculator (109). The samples sizes that were calculated were all smaller than the sample sizes used in each of our statistical tests.

Analyses of dichotomous variables were done using Fisher's exact test. Analyses involving continuous variables were done using the Mann-Whitney *U* test for data not normally distributed and student's *t* test for normally distributed data. Normal distribution was assessed using Kolmogorov-Smirnov test. A repeated measures analysis of variance test was done to assess statistical significances of differences of test scores administered pre-operatively, post-operatively, and at further follow-up between groups and within each group. *p*-values less than 0.05 were considered significant. Statistical analyses were done using IBM SPSS Statistics software and were reviewed by Yale Center for Analytical Sciences.

The medical student was the primary person participating in all aspects of this project from study design to writing the IRB to enrolling patients and data collection to the statistical analyses of the data to the writing of the manuscripts for this study.

Results

Follow-up at 4-6 weeks post-operatively

The demographic data and surgical characteristics for the non-DHCA and DHCA groups are presented in Tables 4 and 5, respectively, with no statistically significant differences between the two groups. Table 6 shows the means and standard deviations of pre and post-operative neuropsychometric test scores, and the means and standard deviations of the differences in scores (post minus pre-operative) for the non-DHCA group and the DHCA group. The means and standard deviations of the differences between post and pre-operative scores for each group are also depicted in Figure 8.

Table 4. *Patient Demographics*

Variable	Non-DHCA	DHCA	*p*-value
Total	33	29	
Sex			1.00
Male	27	23	
Female	6	6	
Mean Age (range), y	58.6 (36-75)	64.5 (43-79)	0.08
Mean Education (range), y	13.3 (8-18)	13.7 (8-18)	0.65
Marfan syndrome	0	1	0.47
Loeys-Dietz syndrome	0	1	0.47
Stroke, pre-op	0	2	0.50
Post-op neurologic events	0	0	1.00
Pre to post-op test time (range), d	45.2 (27-77)	46.3 (30-75)	0.66

DHCA = deep hypothermic circulatory arrest; post-op = post-operative; pre-op = pre-operative.

Table 5. *Surgical Characteristics*

Variable	Non-DHCA	DHCA	*p*-value

Duration DHCA (min), average	0	28.2	n/a
Cooled temperature (°C), average	24.9	18.7	n/a
Proximal anastomosis			
Root-sparing	6	11	
With valve	4	7	0.32
No valve	2	4	0.41
Root replacement	27	18	0.10
Valve-sparing	12	13	1.00
Distal anastomosis			n/a
Hemiarch	0	24	
Total arch	0	5	
Type A dissection repair	0	2	0.22
Concurrent CABG	7	3	0.31
Duration CPB (min), average	144.1	150.8	0.38
Duration cross-clamp (min), average	104.3	96.6	0.18
Post-operative hospital stay (days), average	5.88	5.97	0.91

p-values were listed as n/a for characteristics that were specific to the DHCA group. CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass; DHCA = deep hypothermic circulatory arrest.

Table 6. *Comparison of Mean Pre and Post-Operative Neuropsychometric Test Scores*

Test	Pre-Op (SD)	Post-Op (SD)	Difference (SD)	*p*-value
Memory				
RAVLT				
Acquisition[a]				
Non-DHCA	40.82 (10.32)	38.18 (12.29)	-2.64 (7.21)	0.04
DHCA	37.52 (9.35)	34.52 (10.21)	-3.00 (4.46)	0.001
Non-DHCA vs DHCA				0.19
Learning Rate[b]				
Non-DHCA	4.61 (2.66)	3.94 (9.61)	-0.67 (2.88)	0.19
DHCA	3.69 (1.97)	2.21 (4.40)	-1.48 (3.97)	0.054
Non-DHCA vs DHCA				0.07
Retention[b]				
Non-DHCA	8.18 (3.02)	7.09 (2.99)	-1.09 (1.72)	0.001
DHCA	7.31 (2.92)	6.28 (2.97)	-1.03 (0.94)	0.00
Non-DHCA vs DHCA				0.26
Delayed Recall[b]				
Non-DHCA	8.27 (3.14)	7.30 (3.06)	-0.97 (1.61)	0.002
DHCA	7.48 (3.11)	6.45 (3.48)	-1.03 (1.18)	0.00
Non-DHCA vs DHCA				0.30
Recognition[b]				
Non-DHCA	4.61 (2.66)	3.94 (3.78)	-0.67 (2.12)	0.08

DHCA	3.69 (1.97)	2.21 (4.40)	-0.97 (1.30)	0.00
Non-DHCA vs DHCA				0.63
Processing Speed				
Trail Making Test-A (seconds)				
Non-DHCA	41.88 (9.61)	40.91 (9.61)	0.97 (6.67)	0.41
DHCA	47.38 (16.66)	48.35 (17.07)	-0.97 (2.69)	0.06
Non-DHCA vs DHCA				0.07
Trail Making Test-B (seconds)				
Non-DHCA	91.30 (35.02)	91.91 (34.36)	-0.61 (9.86)	0.73
DHCA	101.79 (36.38)	102.41 (36.85)	-0.62 (4.18)	0.43
Non-DHCA vs DHCA				0.25
Executive Function				
Clock Drawing Test[c]				
Non-DHCA	9.70 (0.59)	9.70 (0.59)	0.00 (0.00)	n/a
DHCA	9.62 (0.62)	9.62 (0.62)	0.00 (0.00)	n/a
Non-DHCA vs DHCA				0.70

[a]Maximum possible score of 65. [b]Maximum possible score of 15. [c]Scored on a scale of 1 through 10 using the system adapted from Sunderland et al (1989) and Libon et al (1993) (107). *p*-values of n/a were for comparisons of equal mean scores. For normative data, see Appendix. DHCA = deep hypothermic circulatory arrest; post-op = post-operative;

pre-op = pre-operative; RAVLT = Rey Auditory Verbal Learning Test; SD = standard deviation; vs = versus.

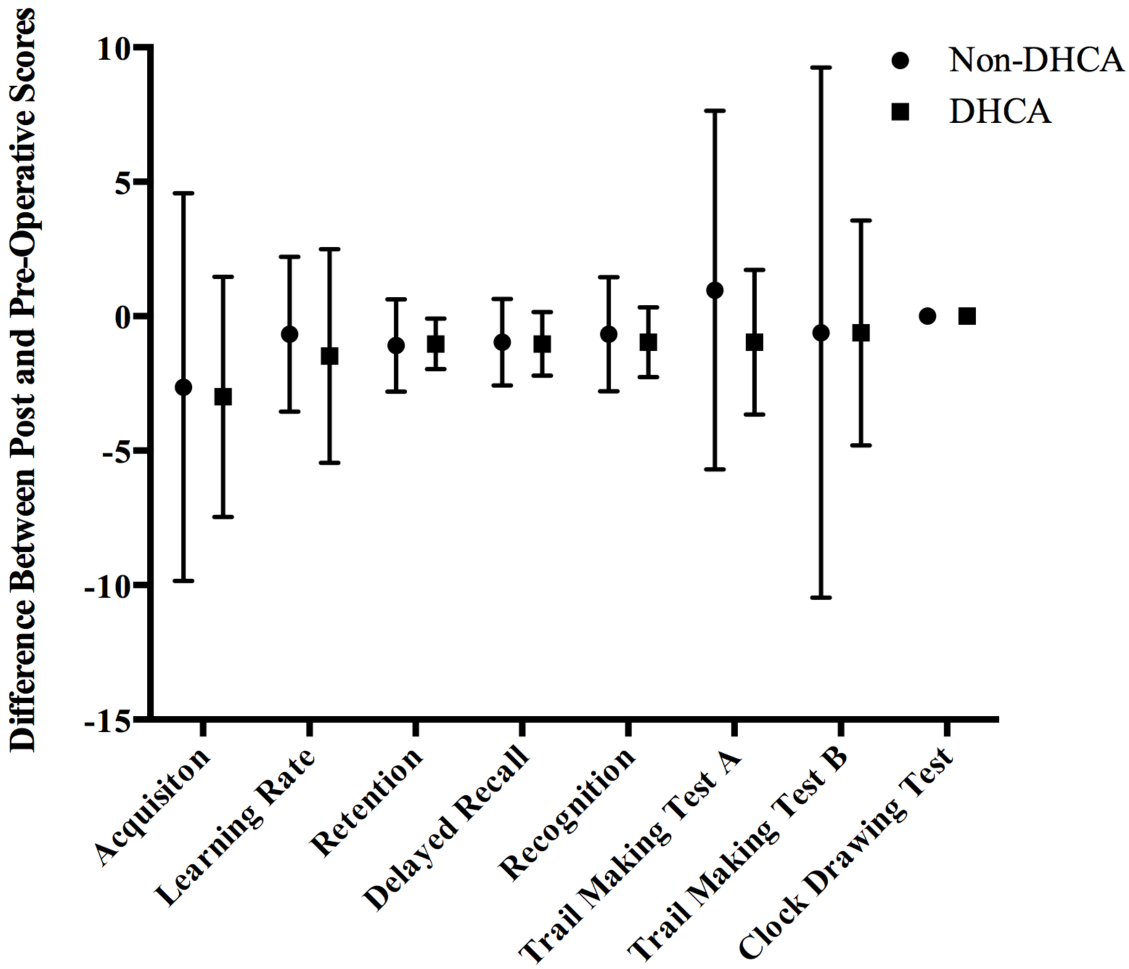


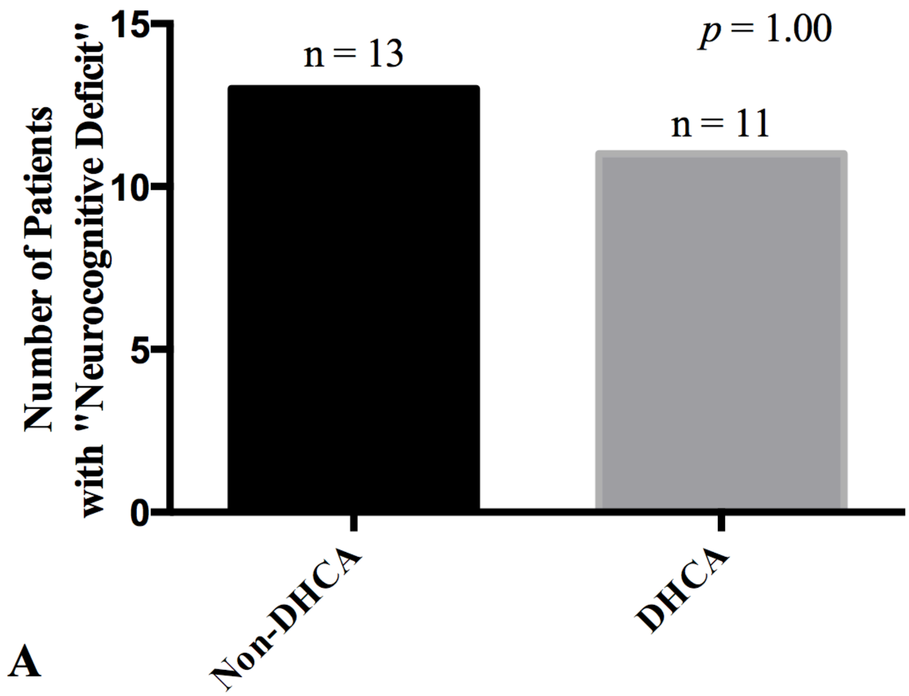
Figure 8. Difference between post and pre-operative scores. Mean and standard deviation of the difference between post and pre-operative scores for the non-DHCA and DHCA groups. Note how similar the 2 groups are in all tests. DHCA = deep hypothermic circulatory arrest.

Memory. In the non-DHCA group, in comparison to baseline pre-operative scores, there was a decline in post-operative scores seen in the memory areas of acquisition, retention, and delayed recall. In the DHCA group, declines were seen in the same memory areas as seen in the non-DHCA group, but with the addition of recognition. There were, however, no differences between the non-DHCA and DHCA groups in the post versus pre-operative scores in any area of memory tested.

Processing speed, executive function, global cognition. There were no declines seen in processing speed or executive function in either group. In comparing the post and pre-operative scores between the non-DHCA group and the DHCA group, there were no differences in any cognitive area tested. It is important to note that there were no changes in CDT scores post-operatively in all 62 patients, as any changes in CDT scores would have reflected a change in global cognitive function.

"Neurocognitive deficit". We also looked at the incidence of "neurocognitive deficit", defined as a greater than 20% decline in 2 or more tests, and compared incidences between the non-DHCA and DHCA groups. In the non-DHCA group, 13 patients incurred a "neurocognitive deficit", and in the DHCA group 11 patients incurred a "neurocognitive deficit". Through Fisher's exact test, we found no difference in the incidence of "neurocognitive deficits" in the non-DHCA group versus the DHCA group (p = 1.00) (Figure 9A).

In addition to assessing for differences in neurocognitive functions between patients who did or did not undergo DHCA, we also looked to see if there was any relationship between time under DHCA and incidence of "neurocognitive deficit". Figure 9B plots all the times under DHCA at which a "neurocognitive deficit" did or did not occur. Mean time under DHCA was 28.2 minutes with a range from 20 to 54 minutes. Using the Mann-Whitney *U* test, we found no difference in time under DHCA between those who had a “neurocognitive deficit” versus those who did not (U = 82.50, Z = -0.75, $p = 0.47$). It is interesting, however, to note that all 3 patients who underwent DHCA for longer than 40 minutes experienced a “neurocognitive deficit”.



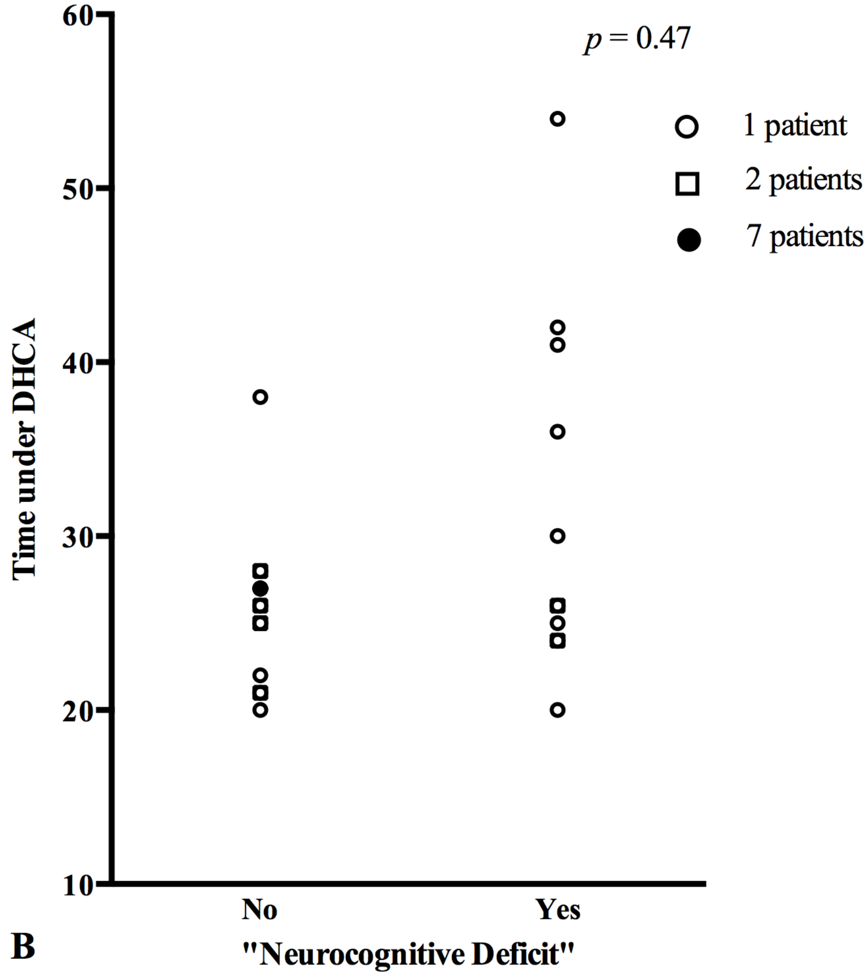


Figure 9. Incidence of “neurocognitive deficit”. (A) Number of patients in the non-DHCA group and the DHCA group who experienced a “neurocognitive deficit”. (B) Scatterplot of the times under DHCA at which a patient did or did not experience a “neurocognitive deficit”. DHCA = deep hypothermic circulatory arrest.

Follow-up months-years post-operatively

The demographic data and surgical characteristics for the non-DHCA and DHCA groups are presented in Tables 7 and 8, respectively, with the only statistically significant difference between the two groups being duration of cardiopulmonary bypass (CPB), with the DHCA group undergoing a longer duration of CPB.

Table 7. *Follow-Up Patient Demographics*

Variable	Non-DHCA	DHCA	*p*-value
Total[a]	11	8	
Sex			1.00
Male	8	6	
Female	3	2	
Mean Age (range), y	60.6 (44-75)	65.9 (52-78)	0.25
Mean Education (range), y	13.6 (9-18)	13.6 (8-18)	0.90
Marfan syndrome	0	0	1.00
Loeys-Dietz syndrome	0	0	1.00
Stroke, pre-op	1	0	1.00
Post-op neurologic events	0	0	1.00
Pre to post-op test time (range), d	48.0 (27-77)	39.4 (30-46)	0.09
Post-op to follow-up test time (range), d	653.5 (138-1089)	422.4 (169-1033)	0.19

[a]24 patients had tested positive for memory deficits in the original study, but 5 declined any follow-up testing. Of the 5, 2 were non-DHCA patients and 3 had undergone DHCA.

DHCA = deep hypothermic circulatory arrest; post-op = post-operative; pre-op = pre-operative.

Table 8. *Follow-Up Surgical Characteristics*

Variable	Non-DHCA	DHCA	*p*-value
Duration DHCA (min), average	0	33.8	n/a
Cooled temperature (°C), average	25.3	18.5	n/a
Proximal anastomosis			
Root-sparing	1	3	0.26
With valve	0	2	0.16
No valve	1	1	1.00
Root replacement	1	1	1.00
Valve-sparing	9	5	0.60
Distal anastomosis			n/a
Hemiarch	0	4	
Total arch	0	4	
Type A dissection repair	0	1	0.42
Concurrent CABG	2	2	1.00
Duration CPB (min), average	131.5	171.4	0.01
Duration cross-clamp (min), average	97.0	110.1	0.12
Post-operative hospital stay (days), average	5.18	5.25	0.30

p-values were listed as n/a for characteristics that were specific to the DHCA group. CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass; DHCA = deep hypothermic circulatory arrest.

Of the 19 patients who incurred memory deficits based on the post-operative testing and who agreed to participate in further follow-up neurocognitive testing months to years after their surgery (8 who underwent DHCA and 11 who did not), 6 continued to have memory deficits. 4 of those patients underwent DHCA and 2 did not ($p = 0.32$). While there was no statistically significant difference between patients who continued to have deficits who did or did not undergo DHCA, the patients in the non-DHCA group continued to have a greater than 20% decline in the same aspects of memory as they did at the 4 to 6 week post-operative testing, while of the 4 patients in the DHCA group, 3 had a greater than 20% decline in additional memory aspects (Table 9).

Table 9. *Deficits in Specific Aspects of Memory*

	Acquisition	Learning Rate	Retention	Delayed Recall	Recognition
Non-DHCA					
Patient 1					
4-6 weeks	X	X	X	X	
months-years	X	X	X	X	

Patient 2					
4-6 weeks		X		X	
months-years		X		X	
DHCA					
Patient 3					
4-6 weeks		X		X	
months-years		X	[X]	X	
Patient 4					
4-6 weeks					X
months-years			[X]		X
Patient 5					
4-6 weeks	X	X		X	
months-years	X	X	[X]	X	[X]
Patient 6					
4-6 weeks	X	X			
months-years	X	X			

[X] signifies additional aspects of memory since the first post-operative testing that declined by greater than 20% from pre-operative scores. DHCA = deep hypothermic circulatory arrest.

For all 3 patients, retention was an additional aspect of memory where a decline was seen at further follow-up. There was no statistically significant difference between the times under DHCA at which patients did or did not continue to have memory deficits ($p = 0.56$) (Figure 10). There was also no statistically significant difference in the days between surgery and the follow-up test in patients who did or did not have persistent memory deficits ($p = 0.97$).

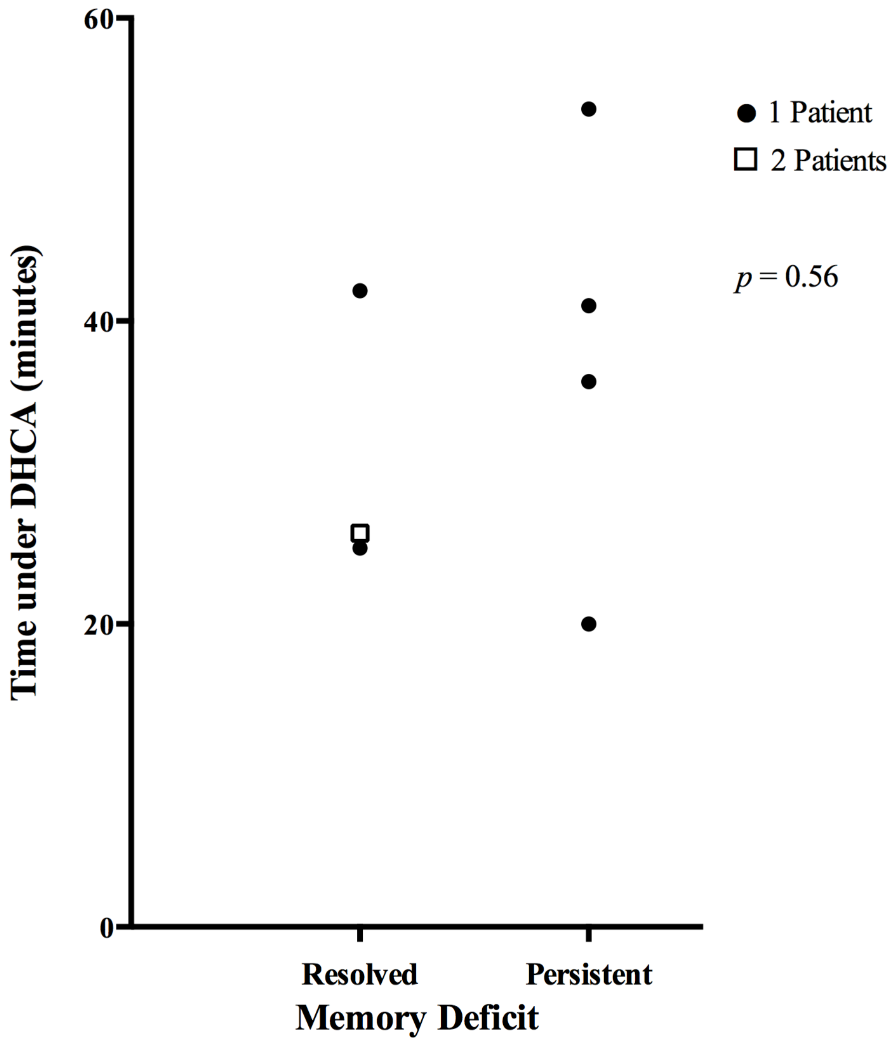


Figure 10. Time under DHCA and memory deficit resolution. Scatterplot of the times under DHCA which patients endured and whether their memory deficits resolved or persisted.

There was a statistically significant difference between patients whose memory deficits persisted or resolved, and that was age. All 6 patients who had persistent memory deficits were greater than 70 years old ($p < 0.001$) (Figure 11).

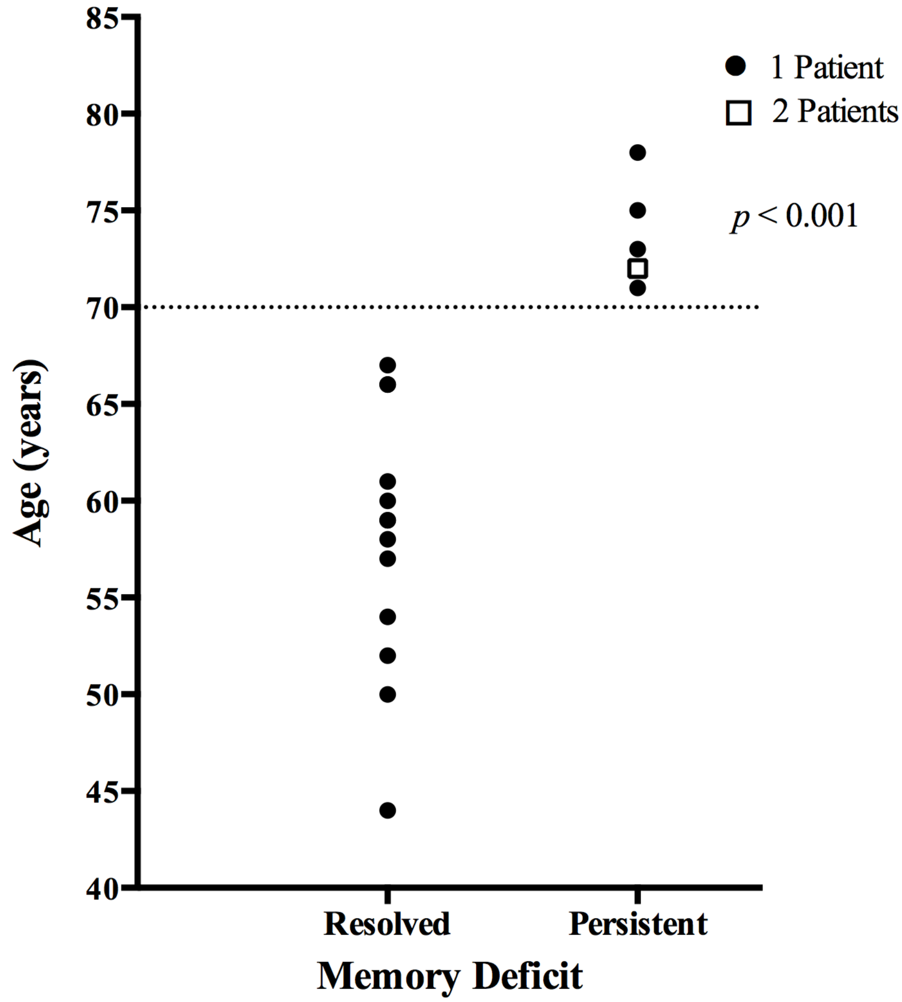


Figure 11. Age and memory deficit resolution. Scatterplot of the age of patients and whether or not their memory deficits resolved or persisted. The dotted line marks 70 years old and note that all patients who memory deficits persisted are over 70 years old.

Table 10 shows the means and standard deviations of memory test scores at the pre-operative, post-operative, and follow-up sessions for both DHCA and non-DHCA patients. When comparing test score across the 3 time points, there were statistically significant differences between patients under 70 years old and patients over 70 years old in all aspects of memory tested except in retention.

Table 10. *Comparison of Follow-Up Mean Neuropsychometric Test Scores*

Test	Pre-Op (SD)	Post-Op (SD)	Follow-Up (SD)	*p*-value
Memory				
RAVLT				
Acquisition[a]				
< 70 years old	40.31 (10.40)	34.92 (11.09)	39.85 (11.67)	
> 70 years old	33.00 (7.62)	23.17 (8.54)	22.50 (8.24)	
< 70 vs > 70				0.02
Learning Rate[b]				
< 70 years old	3.92 (1.71)	2.31 (4.17)	4.31 (1.49)	
> 70 years old	3.00 (2.19)	-2.17 (4.36)	-2.17 (4.58)	
< 70 vs > 70				0.01
Retention[b]				
< 70 years old	7.77 (3.11)	5.69 (3.07)	8.00 (3.16)	
> 70 years old	5.50 (2.35)	4.00 (1.67)	3.50 (1.64)	
< 70 vs > 70				0.053
Delayed Recall[b]				
< 70 years old	8.15 (3.08)	5.92 (3.09)	8.46 (3.28)	
> 70 years old	5.17 (2.64)	3.17 (2.14)	3.33 (2.25)	
< 70 vs > 70				0.02
Recognition[b]				

< 70 years old	11.77 (2.01)	9.54 (1.94)	11.92 (2.06)	
> 70 years old	9.50 (1.38)	7.67 (1.97)	7.17 (1.47)	
< 70 vs > 70				0.003

[a]Maximum possible score of 65. [b]Maximum possible score of 15 (107). DHCA = deep hypothermic circulatory arrest; post-op = post-operative; pre-op = pre-operative; RAVLT = Rey Auditory Verbal Learning Test; SD = standard deviation; vs = versus.

Discussion

This study adds to the evidence that using straight DHCA for cerebral protection during ascending aortic surgery is effective in the preservation of neurocognitive function both in the immediate post-operative period and also long term.

Follow-up at 4-6 weeks post-operatively

Neurocognitive testing battery. We tested two of the most common cognitive domains thought to be negatively affected after undergoing DHCA, memory and processing speed, (72, 79, 94, 98) and took the domain of memory, which is often the most common cognitive domain to be affected after DHCA (96,110), and analyzed multiple aspects rather than treating it as one general cognitive function as other studies have done. We also included the Clock Drawing Test in our battery of tests, as this is a very sensitive indicator of global cognitive dysfunction and also assesses executive function along with the integration of many cognitive areas (107). In this way, we hoped to be able to catch any cognitive dysfunction that could be occurring that would not be seen by administering only the Rey Auditory Verbal Learning Test and Trail Making Tests.

Equal neurocognitive preservation as non-DHCA aortic surgeries. By comparing post-operative scores to the patients' baseline pre-operative scores, we found no difference in any cognitive area tested between those who underwent DHCA and those who did not. We therefore show that patients who undergo aortic arch aneurysm surgeries using only DHCA for cerebral protection have the same level of neurocognitive preservation as those who undergo less extensive ascending aortic aneurysm surgeries without DHCA.

Time under DHCA. On top of analyzing the effects of DCHA on neurocognitive function, we also looked at the relationship between time under DHCA and changes in neurocognition, as time under DHCA has been shown in other studies to be an important determinant of decline in neurocognitive function, with a cutoff time point cited between 20 to 25 minutes (65, 94-96) or beyond 40 minutes (63). Defining a "neurocognitive deficit" as experiencing a greater than 20% decline from baseline in 2 or more tests based on a previous neuropsychometric study done by Harrington et al (72), we found there to be no relationship between incidence of "neurocognitive deficit" and time under DHCA (range of 20 to 54 minutes). However, we did notice that all 3 patients who were under DHCA for longer than 40 minutes experienced a "neurocognitive deficit", so a larger study might reveal a statistical correlation with DHCA time. That would support our previous study, in which we found that time under DHCA for 40 minutes or longer leads to an increased risk of neurologic impairment (63). It is important to note that although we have applied the term "neurocognitive deficit", based on the detailed neuropsychometrics and clinical observations, these patients were in excellent clinical neurologic status, with no detectable clinical issues or abnormalities, or discernible impairments in daily life, school, or work.

Memory. While we found no difference in the post versus pre-operative test scores between the non-DHCA group and the DHCA group, there was a decline in function seen in certain areas of memory post-operatively within both groups, namely acquisition, retention, and delayed recall. In the DHCA group, a decline in recognition was also seen. Processing speed and executive function were not affected. This finding that memory is negatively affected after cardiac surgery is not surprising, as this has been well established in the literature (100, 101). One possible mechanism behind this is in the metabolic nature of the hippocampus. The hippocampus plays a critical role in memory formation, but it has a high metabolic rate and so is particularly sensitive to ischemic injury (111-113). What is interesting, however, is that we found only specific aspects of memory to be affected after cardiac surgery, and also, that learning rate does not seem to be affected by cardiac surgery at all, in either the non-DHCA or the DHCA group. We were interested to know if the subtle alterations in measures of memory are durable or improve over time, as our testing was done relatively early after the surgical procedures (mean 36.4 days), and so we followed up with patients at a time-point of months to years after their surgeries.

Follow-up months-years post-operatively

DHCA Does Not Affect Recovery from Memory Deficits. In our previous study, we found that there was no difference between patients who underwent DHCA and those who did not in the occurrence of neurocognitive deficits incurred post-operatively. The question then became: Are the deficits that were incurred short-term or long-term, and does undergoing DHCA affect the temporal nature of these deficits. In this study, following up with those patients who did test early-positive for memory deficits, with follow-up months to years post-operatively, we found no difference in terms of recovery from or persistence of memory deficits in patients who did or did not undergo DHCA. Time under DHCA was also found to have no effect on the resolution or persistence of memory deficits, confirming findings by Harrington et al, which was the one study that followed patients beyond 4 to 6 weeks (72). The time between surgery and further follow-up testing did vary among patients, but it was also found that there was no difference in the time between further follow-up testing and surgery in patients who did or did not recover from their memory deficits.

Effects of Age. While DHCA was not found to affect the resolution or persistence of memory deficits incurred post-operatively, we found age to significantly affect the temporality of memory deficits. Specifically, whether a patient was over or under 70 years old was found to be a significant difference between patients who did or did not recover from their memory deficits, with all 6 patients who were over 70 years old having persistent memory deficits.

This finding is well-supported by the literature on both open heart surgeries and general surgeries, where it is well established that age is risk factor for post-operative cognitive decline, and that the elderly have a higher incidence of long-term post-operative cognitive decline, with memory being the most commonly affected cognitive area (101, 114-117). The cause of this has to do with the fact that the brain of an elderly person is different from the brain of a younger person. Important differences include size, distribution and type of neurotransmitters, metabolic function, and the capacity for plasticity (101).

Memory Deficits in DHCA Patients that Persist Tend to Worsen. Although DHCA was found to have no significant effect on whether or not patients recovered from memory deficits incurred post-operatively, we did find that in patients who did have persistent memory deficits, those who underwent DHCA seemed to have declines in additional aspects of memory than what they manifested previously, particularly retention, while those who did not undergo DHCA had declines in the same aspects of memory as they did originally. It has previously been shown in 2 studies that in patients who undergo DHCA, poor neuropsychometric outcomes at early follow-up is a predictor of persistent poor outcomes at a later follow-up, with later follow-up occurring at 6 weeks in one study and 12 to 24 weeks in the other (72, 96). Our study includes neuropsychometric follow-up 24 weeks to over 2 years post-operatively, and so we build upon previous studies by showing that if memory deficits persists past 24 weeks in patients who underwent DHCA, then in those patients, the deficits tend to worsen to affect additional aspects of memory. This leads to the question of why this occurs and further studies are needed to investigate the mechanism behind this finding. It should be emphasized that these deficits are subclinical—only elicited by detailed investigative testing, and manifested in only a very small subgroup of all patients undergoing DHCA.

Limitations

While there are no statistically significant differences in demographic data and surgical characteristics between the non-DHCA group and DHCA group, the nature of the indication for DHCA is such that those in the DHCA group were undergoing a more extensive surgery (aortic arch involved), whereas in the non-DHCA group, the arch was not involved, and so there was no indication for DHCA. However, the fact that the non-DHCA group patients underwent simpler and less extensive procedures should suggest that the non-DHCA group would experience a smaller decrease in scores post-operatively than the DHCA group. Since we found no difference in post versus pre-operative scores between the non-DHCA and DHCA groups, the less extensive surgical procedures undergone by the non-DHCA group lends strength to our findings. Also, while there was no statistically significant difference in the ages of the two groups, the average age of the non-DHCA patients (58.6 years) was younger than that of the DHCA patients (64.5 years). In essence, despite biases against the DHCA group, brain preservation was still equivalent despite DHCA.

Another limitation of our study was that we primarily focused on assessing the cognitive domains of memory and processing speed. There are other cognitive areas that could be assessed. However, we incorporated the CDT in order to compensate for other cognitive areas. CDT assesses executive function along with many other advanced cortical functions, as well as the integration of various functions. CDT is also very sensitive in detecting global cognitive dysfunction (107). We therefore believed the CDT to be an adequate test to detect cognitive areas besides memory and processing speed that may experience a deficit after DHCA.

In this study, we showed that time under DHCA does not affect neurocognition. However, as mentioned previously, this study only had 3 patients who underwent DHCA for 40 minutes or longer, with most of the patients being under DHCA for less than 30 minutes. We therefore recognize that our sample size for patients under prolonged DHCA time was not very large. However, this study shows that longer DHCA times are rarely required even in a vigorous aortic practice. Our previous clinical study found a ceiling time of 40 minutes DHCA to be safe (63), while other studies have shown a time range of 20 to 25 minutes as the upper limit of safe duration under DHCA (65, 94-96). Our mean and median DHCA times were 28.2 and 27 minutes, respectively, and only above 40 minutes was any suspicion raised by the present study. We feel we can confidently say that time under DHCA up to 25 minutes, and likely up to 40 minutes, does not negatively affect neurocognitive function. It is also important to remember that clinical, and likely sub-clinical, neurological dysfunction are multi-factorial, with air and particulate embolization playing a major role, especially in open aortic surgery (63). Those factors, of course, are technical and not directly related to DHCA duration.

In terms of the long term follow-up portion of this investigation, that part of the study is limited by its small sample size, and we recognize that the cohort of patients participating in this study may not be representative of other patient populations, and that a study with a larger sample size may produce different results. However, our study is the only study to the author's knowledge that investigates the effects of DHCA on the long-term nature of memory deficits incurred post-operatively. Our study therefore provides important novel findings that will hopefully stimulate further studies in this area.

Conclusions

In conclusion, we augment evidence that using DHCA as the sole means of cerebral protection during ascending aortic surgery is effective at preserving neurocognitive function both in the short and long-term. Time under DHCA for less than 40 minutes is found to not be an important contributor to quantitatively measured neurocognitive outcome. In addition, we show that while DHCA does not affect whether or not memory deficits incurred post-operatively persist, what does affect the temporal nature of memory deficits is age, with patients over the age of 70 having a higher incidence of persistent long-term memory deficits. This study therefore shows that when considering the long-term neurocognitive outlook for aortic arch aneurysm patients, it is not the DHCA technique that comes into question, but the age of the patient. We do show, however, that whether by comparing raw scores or by comparing incidence of "neurocognitive deficits", DHCA is an effective technique for the preservation of neurocognitive function.

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