

# PRINCIPLES OF CEREBRAL PROTECTION DURING OPERATIONS ON THE THORACIC AORTA

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A period of interruption or temporary exclusion of the cerebral circulation has proved to be an indispensable technical addition in surgery of the thoracic aorta in general, and of the aortic arch in particular. This maneuver is necessary not only during open anastomosis and reconstruction of the arch vessels but also during dissection and mobilization of these structures in preparation for the anastomosis, in order to prevent particulate embolization to the brain during such manipulation. The neurologic outcome of these operations ultimately depends on the quality of the central nervous system protection during this critical period of interruption or exclusion of the cerebral circulation. The introduction of deep hypothermic circulatory arrest (DHCA) for this purpose has revolutionized the surgical treatment of thoracic aortic pathology in the last two decades.<sup>1</sup> However, cumulative clinical experience also shows that the protection afforded by DHCA alone is not quite perfect. Therefore, the search for an ideal strategy of cerebral protection continues. This search and the application of the currently available methods of protection are contingent upon a thorough understanding of the principles of cerebral protection. This chapter is a synopsis of our current state of knowledge of the pertinent physiology of brain protection, as well as the principles, rationale, and application of the current clinical methods of cerebral protection.

## Physiology

### Energy Generation

The adult brain constitutes 2% of the body mass but uses 15% of the total energy generated by body metabolism. The brain metabolic rate at rest is seven times that of the remainder of the body. The main source of neuronal energy, adenosine triphosphate (ATP), is generated through aerobic glycolysis. Complete breakdown of one molecule of glucose to H<sub>2</sub>O and CO<sub>2</sub> in the aerobic cycle

produces 38 molecules of ATP to power the neurons. Anaerobic glycolysis produces only two molecules of ATP for each molecule of glucose. Anaerobic glycolysis in the brain, unlike in other tissues such as muscle or liver, cannot sustain required energy demands. Persistence of anaerobic glycolysis and accumulation of lactate as its by-product in the brain tissue proves to be fatal to the neurons by rapidly lowering the intracellular pH.

### Blood Flow and Autoregulation

Although glucose is its primary substrate for energy generation, the brain has no glucose or glycogen stores. To sustain active metabolism the brain, therefore, requires a constant supply of glucose, oxygen, and a regulated blood flow to maintain appropriate function; 60 mg of glucose and 3 to 4 mL of oxygen per 100 g of brain tissue is required to meet the demand every minute. This is supplied by a blood flow of about 50 mL/100 g of brain tissue per minute. Changes in metabolic demand are met by appropriate changes in blood flow. This coupling of blood flow to metabolic demand is controlled by autoregulation of the cerebral circulation.<sup>2</sup> Automatic adjustment of the cerebral vascular resistance maintains the ratio of cerebral blood flow to oxygen use at approximately 20 over a wide range (50 to 130 mm Hg) of perfusion pressures. Conditions such as advanced age, diabetes, and hypertension (common in patients with thoracic aortic pathology), in addition to other anesthesia and perfusion-related conditions associated with these operations, alter the autoregulation of cerebral blood flow. Perfusion pressures need to be adjusted according to predicted changes in autoregulation in order to avoid under- or overperfusion. As Table 31-1 illustrates, preexisting patient-related conditions or physiologic changes induced by anesthetic management alter the autoregulation of the cerebral blood flow. Perfusion pressures during cardiopulmonary bypass and cerebral perfusion have to be adjusted according to these

**TABLE 31-1. Modifiers of Autoregulation of the Cerebral Blood Flow**

● Hypertension	↑↑
● Diabetes	↑↑
● Hypothermia	↓↓
● Prolonged nonpulsatile flow	↑↑
● Hypotension due to hemorrhage	↑↑
● Anesthetics; sympatholytic drugs	↓↓
● pH-stat management	⊖

predicted changes to avoid cerebral under- or overperfusion. Maintenance of cerebral autoregulation of blood flow during cardiopulmonary bypass in general, and during application of selective cerebral perfusion methods in particular, has an important protective role. During deep hypothermia, autoregulation is maintained at perfusion pressures as low as 30 mm Hg. Impaired autoregulation leads to purely pressure-driven brain blood flow, uncoupled from metabolic demand. Autoregulation is also lost with pH-stat management of the acid base balance during anesthesia. Nonpulsatile flow increases the cerebral vascular resistance over a period of time. Higher pressures may be required for effective perfusion toward the end of a long bypass period (and immediately thereafter) to avoid underperfusion in the presence of upward “re-regulated” autoregulation. Experimental use of pulsatile assistance has been shown to ameliorate these changes in the cerebral vascular resistance.<sup>3</sup>

### Luxury Perfusion

The impairment of autoregulation creates extra blood flow exceeding the metabolic need: a state of “luxury perfusion.” Under the artificial conditions of extracorporeal circulation and low pressure (low-flow hypothermic perfusion), the relatively large proportion of the pump flow reaching the brain exposes the brain to higher macro- or microembolic loads due to overperfusion.<sup>4,5</sup> Luxury perfusion per se under these circumstances may be injurious to the brain.<sup>6</sup> This mechanism of brain injury attains special importance in older patients, who are prone to enhanced luxury cerebral perfusion due to age-related changes in the autonomic vasomotor tone during hypothermia and nonpulsatile flow. Luxury perfusion may partly explain the higher incidence of strokes seen in older patients.<sup>7</sup>

## Ischemic-Anoxic Brain Injury

There are two basic mechanisms that lead to ischemic cerebral injury during operations on the thoracic aorta that require temporary exclusion of the cerebral circulation. Global ischemia due to interrupted or inadequate flow leads to subtle brain injury that manifests itself as the clinical syndrome that we have called “temporary neuro-

logic dysfunction.” This condition, commonly believed to be self-limited and benign, has permanent functional sequelae detectable with detailed neuropsychological testing, especially of the memory function. It is a direct consequence of inadequate cerebral protection. In its extreme form, it results in anoxic brain injury. The second type of injury that has traditionally received the most attention (because of its devastating consequences) is represented by localized strokes caused by ischemic infarcts. These infarcts, detectable by conventional imaging techniques, are due to embolic events and were generally thought to be independent of the method of brain protection used. Recent studies regarding methods of cerebral perfusion have stimulated great discussion regarding the latter issue.

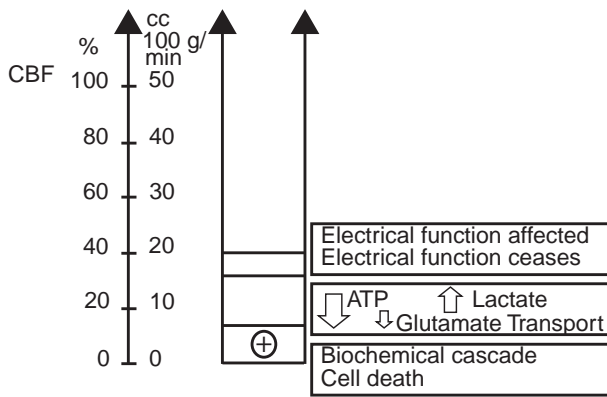
## Pathogenesis

### Neurotransmitter Toxicity

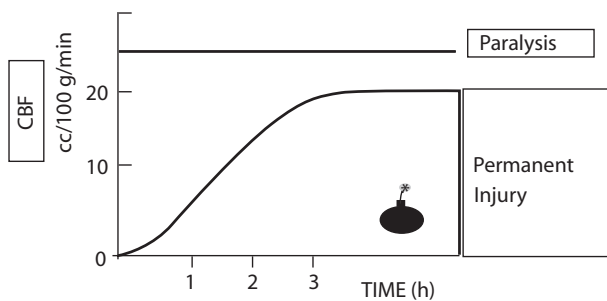
The importance of the failure of the neurotransmitter transport mechanism and the toxicity of excitatory neurotransmitters as common pathways in the pathogenesis of many neurologic disorders (including ischemic cerebral injury) has been well demonstrated.<sup>8</sup> Glutamate and aspartate are the primary messengers used by neurons for interneuronal communication. After release into the intercellular space, glutamate rapidly is converted to glutamine and then reenters the neuron ready to be used for the next message. Any cause that interrupts conversion of glutamate to glutamine will lead to accumulation of glutamate in the intercellular space, where in increasing concentrations it acts as a potent neurotoxic substance. It opens calcium channels, leading to an influx of calcium, which starts the catastrophic intracellular activation of several enzyme systems in a vicious “biochemical cascade,” ultimately leading to neuronal autodigestion and cell death. Currently, there is a substantial amount of basic and pharmacologic research being conducted toward modification of the biochemical reactions that follow the failure of the neurotransmitter transport mechanism. Some information gained from these studies has already been incorporated into current preventive and therapeutic approaches.<sup>8</sup> There is also an intense search for appropriate pharmacologic agents to enhance the current cerebral protective methods. Certainly, more insight into these reactions is needed for effective clinical intervention.

### Phases of Ischemic Cerebral Injury

The brain will tolerate an acute reduction in blood flow down to about 40 to 50% of normal during normothermia. Below that, functional and cellular biochemical changes that start with depletion of ATP stores, and progress to eventual impairment of glutamate transport, occur quite rapidly (Figures 31-1 and 31-2).<sup>9</sup> These changes ultimately lead to the unrelenting biochemical cascade that ends with the death of the neuron.<sup>8</sup>



**FIGURE 31-1.** Thresholds of cerebral ischemia. This diagram illustrates the effect of reduced cerebral blood flow (CBF). Data are from awake primate experiments and show that at normothermia, a gradual reduction of the blood flow in the middle cerebral artery leads to cessation of function and reversible paralysis at around 50% reduction in the regional blood flow. At about 20 cc/100 g/min cerebral blood flow, cell death is a function of time, with rapid onset of the biochemical changes that lead to ultimate loss of the neuron. ATP = adenosine triphosphate. Reproduced and modified with permission from Jafar JJ et al.<sup>9</sup>



**FIGURE 31-2.** Thresholds of cerebral ischemia. This diagram illustrates the time course of the effect of reduced cerebral blood flow (CBF). Data from awake primate experiments and show that at normothermia, a gradual reduction of the blood flow in the middle cerebral artery leads to cessation of function and reversible paralysis at around 50% reduction. At about 20 cc/100 g/min cerebral blood flow, cell death and permanent injury is a function of time. With further reduction in flow, neurons are lost exponentially earlier, reaching down to about 5 to 8 minutes at zero flow. Reproduced and modified with permission from Jafar JJ et al.<sup>9</sup>

The pathogenesis of ischemic cerebral injury follows a set sequence of events in three distinct phases.

#### PHASE 1: DEPOLARIZATION

Depolarization is the first phase of this process. Lack of adequate oxygen to support aerobic metabolism rapidly leads to depletion of ATP and to accumulation of adenosine monophosphate (AMP), adenosine, and nitric oxide—all potent vasodilators—in the intercellular space. At the same time, glucose that is available is shunted into the anaerobic pathway. Vasodilatation makes more glucose

available for anaerobic glycolysis. The process is accelerated in the presence of hyperglycemia, and there is ample clinical evidence to suggest that hyperglycemia compounds ischemic cerebral injury. The inability of the brain to use lactate (the metabolic byproduct of anaerobic glycolysis), and the lack of adequate blood flow to carry it away, rapidly leads to its accumulation and the eventual decrease in the intracellular pH. This decrease in pH is a potent stimulator for the release of the neurotransmitters glutamate and aspartate. These substances accumulate in the interneuronal spaces because there is insufficient ATP available for their conversion to glutamine before they can reenter the neuron. All events in this phase are reversible, and current clinical protective methods are aimed at delaying or preventing the sequence of these events, which ultimately leads to the failure of the neurotransmitter transport mechanism at the end of the depolarization phase. As Table 31-2 illustrates, all events in this phase are reversible. They are either completely preventable or can be ameliorated and delayed by currently available protective modalities. Hypothermia and continued antegrade perfusion are the most effective measures to maintain aerobic glycolysis in the presence of reduced flow. Hypothermia and retrograde cerebral perfusion (RCP) are effective in delaying the depletion of ATP in zero antegrade flow state. Circulatory arrest helps reduce anaerobic glycolysis and accompanied acidosis by eliminating continued glucose supply to fuel the pathway. The trickle flow supplied by RCP supplies substrate to maintain anaerobic glycolysis, yet at the same time may help to remove acid metabolites. Depending on how effective the RCP flow is, the net effect of RCP may be marginally superior to DHCA alone.

#### PHASE 2: BIOCHEMICAL CASCADE

The collapse of the neurotransmitter transport mechanism starts the vicious cycle that constitutes the second phase, the biochemical cascade. Accumulation of neurotransmitters in the intercellular space opens up the calcium channels, leading to massive calcium influx and activation of several intracellular enzyme systems, with catastrophic consequences. This self-sustaining biochemical reaction ultimately results in neuronal autodigestion

**TABLE 31-2. Phase 1 of Ischemic Injury: Depolarization Sequence and Preventive Measures**

Phase 1: Depolarization	Prevention
1. ↓ Aerobic glycolysis	Perfusion, hypothermia
2. ↓ ATP depletion	Hypothermia, RCP
3. ↑ Anaerobic glycolysis Hyperglycemia Trickle flow	Arrest, RCP
4. ↑ Lactate, acidosis	Hypothermia, RCP
5. ↓ Neurotransmitter transport	Hypothermia

ATP = adenosine triphosphate  
RCP = retrograde cerebral perfusion

and permanent loss of the cell. There are some promising experimental pharmacologic approaches (neurotransmitter-antagonists, neurotransmitter-receptor blockers, and calcium channel blockers) to the modification or prevention of the failure of the neurotransmitter mechanism and of the events of the biochemical cascade.<sup>8,10</sup> Currently, however, there is no practical pharmacologic remedy ready for clinical application for brain protection during aortic surgery. As Table 31-3 illustrates, these events cannot be reversed by currently available modalities. The search for effective inhibitors of neurotransmitter release and neurotransmitter receptor blockers continues. There are promising compounds in phase three clinical trials. There is experience with calcium channel blockers with mixed clinical results. Aminosteroids show promise in countering the toxic effects of free fatty acids, especially arachidonic acid. Suppression of apoptosis offers a new venue for prevention of delayed neuronal loss. It is hoped that ischemic injury can be substantially modified to preserve neuronal integrity by the discovery of the effective compounds aimed at the sequence of the biochemical cascade. The combination of these compounds may be an integral part of brain protection during surgery of the thoracic aorta in the near future.

#### PHASE 3: REPERFUSION INJURY

The last phase of ischemic brain injury occurs during reperfusion. Although the reperfusion injury, especially in the context of the present methods of cerebral protection, may be the most important phase in the pathogenesis of ischemic cerebral injury, our current understanding of its mechanism is rudimentary. Maintenance of adequate oxygen delivery during this vulnerable period is of paramount importance, especially following hypothermic circulatory arrest. In addition, leukocyte infiltration and cytokine-mediated inflammatory reactions are known to play an important role during this phase. In recent animal studies, leukocyte-depleting filtration seemed to mitigate reperfusion injury in the brain.<sup>11</sup> Currently, we employ leukocyte filtration in all of our hypothermic circulatory arrest cases. Local release of nitric oxide (NO) in response to ischemia is a protective mechanism designed to increase blood flow through vasodilatation. However,

overproduction and accumulation of NO following hypothermic arrest has been shown to be neurotoxic and is implicated in the genesis of reperfusion injury.<sup>12,13</sup> The principal elements of all current methods of cerebral protection are designed to interrupt the pathogenetic process during the initial phase, aiming at prevention of cellular anoxia and acidosis.

#### Apoptosis and Delayed Neuronal Loss

Increasing knowledge of the importance of programmed cell death in the pathogenesis of heart failure and chronic neurologic disorders recently led to exploration of the role that apoptosis plays in producing delayed neuronal loss and the associated delayed decline in cognitive function following acute ischemic cerebral injury. It has been shown that sublethal cellular injury sustained during acute ischemia can trigger apoptotic pathways that result in delayed loss of neurons.<sup>14</sup> Neurons that are not lost immediately by necrosis cover a wide spectrum of pathologic and physiologic states, from absolute viability and function to one of various stages of “suspended animation,” apoptosis, and variable function or nonfunction.<sup>15</sup> The possibility that effective pharmacologic intervention may salvage some of these cells undergoing apoptosis and ameliorate the extent of delayed neuronal loss and late sequelae of hypothermic circulatory arrest is intriguing (see Table 31-3).

#### Selective Vulnerability and Location of Injury

Different regions of the brain have a substantial variation in energy requirements. Gray matter uses more energy than white matter, the cortex more than the basal ganglia, and active neurons more than quiescent ones. Some regions of the brain, therefore, are clearly more vulnerable to ischemic or anoxic injury. The earliest manifestation of such injury occurs in the regions of the brain with higher metabolic rates and activities that persist even under profound hypothermia. In experimental models, the earliest histopathologic signs of ischemic injury can be found anatomically in the hippocampus.<sup>16</sup> It is well known that this region of the brain is the locus for acquisition of new information and is particularly sensitive to anoxic or ischemic injury because of its high metabolic rate.<sup>17</sup> As a clinical corollary of this pathologic finding, the subtlest sign of brain injury following DHCA is represented by the deficits of memory function that can be detected by neuropsychological evaluation.<sup>18</sup> It is quite likely that the impairment of memory function in adults with prolonged DHCA is related to neuronal injury in the hippocampus. Recent evidence suggests strongly that the early postoperative syndrome of “temporary neurologic dysfunction” correlates significantly with the long-term deficits seen in memory and motor function following prolonged periods of DHCA.<sup>19</sup> Identification of a reliable biochemical marker for neurologic injury has remained elusive. Most such marker evidence regarding neurologic

**TABLE 31-3. Phase 2 of Ischemic Injury: Biochemical Cascade and Modification of Injury**

Phase 2: Biochemical Cascade	Modification
1. ↑ Neurotransmitter release	Inhibitors, blockers
2. ↑ Calcium influx	Ca <sup>2+</sup> channel blocker
3. ↑ Protease and lipase	Steroids
4. ↑ Arachidonic acid	Aminosteroids
5. ↑ Free radicals	Steroids, scavengers
6. Neuronal autodigestion	
7. Apoptosis	Caspase suppressors

injury surrounds the study of astrocyte protein S-100 $\beta$ . Increased levels of S-100 $\beta$  have been measured after routine cardiopulmonary bypass and recovery of shed mediastinal blood with pump suckers. In some studies elevated levels have been shown to correlate with adverse cerebral events.<sup>20</sup> However, the utility of S-100 $\beta$  in assessing the efficacy of adjuncts for cerebral protection has not been proven.

## Cerebral Protection

Currently, there is no practical way of completely turning off the functional component of the brain's activity to reduce the energy demands to the bare minimum required to maintain cellular viability during the critical periods of interruption or exclusion of the cerebral circulation. The objective of all current clinical methods of cerebral protection is prevention of cellular anoxia and acidosis in order to preserve the integrity of the central nervous system. These methods have evolved into three principal applications or their combinations. Hypothermic circulatory arrest, and the presence of no flow, rely on drastic reductions of oxygen demand with profound hypothermia, whereas methods that depend on continuous selective antegrade cerebral perfusion (SCP) or RCP aim at preserving oxygen supply while at the same time reducing oxygen demand with the aid of varying degrees of hypothermia.

### Deep Hypothermic Circulatory Arrest

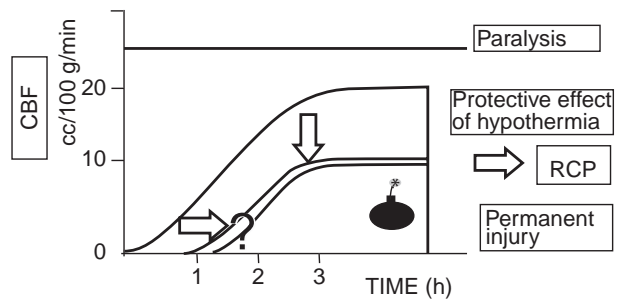
Hypothermia is the principal element of all current methods of brain protection in general and of DHCA in particular.

#### General Considerations

The protective effect of hypothermia primarily is based on the temperature-related reduction of intracellular enzymatic reactions. Proportionately, the need for oxygen delivery and, therefore, blood flow requirements, is reduced. Although the metabolic effects of drugs that are active depressants of neuronal function are comparable to hypothermia, experimentally hypothermia affords better protection against cerebral anoxia.<sup>21</sup> The cerebral protective effect of hypothermia is multifaceted in addition to temperature-related metabolic suppression. Hypothermia specifically preserves the tissue pH and ATP.<sup>22</sup> It also prevents release of excitatory neurotransmitters and delays the onset of the biochemical cascade that eventually leads to cell death due to ischemia (Figure 31-3).

#### Metabolic Suppression and "Safe Period of Arrest"

Michenfelder and colleagues have expressed the relationship between the temperature and the cerebral metabolic rate for oxygen (CMRO<sub>2</sub>) as the temperature coefficient Q<sub>10</sub> for CMRO<sub>2</sub>. Q<sub>10</sub> reflects an exponential function for



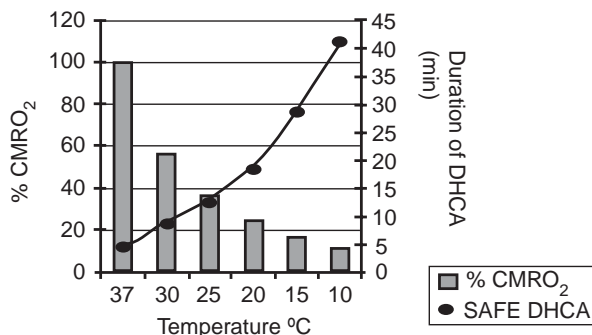
**FIGURE 31-3.** Protective effect of hypothermia. This diagram, in relation to Figure 31-2, summarizes the known effects of deep hypothermia on preservation of the brain during circulatory arrest or at low flow states. Hypothermia delays the onset of permanent cellular injury during arrest. Clinical and experimental evidence points that a safe period of arrest may extend up to 40 minutes at an esophageal temperature of 10° to 12°C. There is increasing risk of permanent ischemic injury if this limit is exceeded. Hypothermia also reduces the blood flow requirements during perfusion. A blood flow of 10 cc/100 g/min, or 20% of the resting cerebral blood flow at normothermia, is adequate to preserve cerebral integrity for prolonged periods of time in the presence of hypothermia. Whether the addition of RCP adds any further protection over that afforded by hypothermia remains largely unproven (?). CBF = cerebral blood flow. RCP = retrograde cerebral perfusion.

the rate of reduction in the metabolism over a 10°C temperature range within a clinically relevant temperature limit of 38° to 14°C. Q<sub>10</sub> is reported to be between 2.0 and 3.0.<sup>23</sup> Recent studies in puppies show that the reduction of the cerebral metabolic rate for oxygen is substantially more modest than what had been reported earlier. There is 39% of the baseline metabolic activity still present at 18°C, a temperature generally thought to be safe for prolonged periods of clinical circulatory arrest. In the same study, quantitative electrocardiography (EEG) also showed significant slow-wave activity at 18°C, whereas EEG silence was present at 13°C and 8°C.<sup>24</sup> We have recalculated Q<sub>10</sub> for the adult human brain, based on direct measurement of CMRO<sub>2</sub> during DHCA.<sup>25</sup> Based on this clinical study, the safe period of arrest is calculated to be about 30 min at 15°C and 40 min at 10°C. Beyond these time limits, anoxic cellular injury is inevitable at these temperatures (Figure 31-4).

As pointed out earlier, such injury is detected in its subtlest form in the function of the regions of the brain most vulnerable to anoxia. Clinical studies in infants undergoing correction of congenital heart defects using DHCA show subclinical seizure activity on EEG, with subtle abnormal neurologic examinations at 1 year following surgery.<sup>26</sup> These studies also confirm that prolonged durations of DHCA correlate with lower IQ scores in later childhood.

There is insufficient information of this nature regarding the adult population undergoing DHCA. In our initial review of 200 patients who underwent DHCA during

Actual  $Q_{10}$  directly calculated in 37 adult patients during DHCA



**FIGURE 31-4.** Limits of “safe” duration of circulatory arrest.  $Q_{10}$  for the adult brain is calculated from direct measurement of  $CMRO_2$  in 37 adult patients undergoing thoracic aortic operations with DHCA. The temperature-related reduction in the metabolic rate and the calculated “safe periods of arrest” are shown.  $CMRO_2$  = cerebral metabolic rate for oxygen; DHCA = deep hypothermic circulatory arrest. Data from McCullough JN et al.<sup>25</sup>

operations on the thoracic aorta the incidence of “temporary neurologic dysfunction” was 19%. This significantly correlated with the duration of the arrest time and with patient age. The significant relationship between “temporary neurologic dysfunction” and the arrest time raised a flag of caution although the progress of most patients appeared to be quite benign following recovery from what was thought to be a self-limited syndrome of altered neurologic function. As a result of this finding, even at that early time in our experience, we recommended that every effort should be made to limit arrest times, especially in older patients.<sup>7</sup> To further investigate whether DHCA in the adult is associated with long-term neuropsychological deficits, a detailed study was conducted to compare patients undergoing “routine” cardiac surgery with cardiopulmonary bypass to those having surgery of the thoracic aorta with periods of DHCA. This study showed that circulatory arrest times longer than 25 min and advanced age were significant predictors of poor performance at 6 weeks for the memory and fine motor domains.<sup>18</sup> Recent evidence strongly suggests that the early postoperative syndrome of “temporary neurologic dysfunction” correlates significantly with long-term deficits in memory and motor function following prolonged periods of DHCA, and confirms the belief that this clinical syndrome is a manifestation of subtle brain injury due to inadequate cerebral protection.<sup>19</sup> Duration of DHCA, on the other hand, has no influence on mortality or occurrence of permanent neurologic injury caused by embolic strokes.<sup>7</sup>

There is now a consensus that affirms that temperatures colder than previously thought to be safe are necessary if prolonged periods of arrest are anticipated. Similarly, the duration of the arrest even at these cold temperatures should not exceed 40 (preferably 30) min at 12° to 15°C. Durations of circulatory arrest exceeding 60 min are universally regarded as risky, but success has been reported.

## Current Clinical Application

### Monitoring

Adequate and uniform cooling, and the demonstration of suppression of brain metabolic activity by monitoring of function and metabolism, is of paramount importance before the initiation of DHCA. In many circumstances, cerebral electrical function and activity by means of EEG and auditory- and sensory-evoked potentials are monitored.<sup>27</sup> Studies show that evoked potentials are a better guide than EEG alone and usually take longer to disappear, whereas EEG silence occurs quite variably at shorter durations of cooling and at relatively higher brain temperatures.<sup>28</sup> Because oxygen extraction is the most readily monitored parameter reflecting the metabolic state of the brain, we routinely measure jugular bulb venous oxygen saturations and continue cooling until these are well above 95%. At this level we are confident that brain metabolism is suppressed adequately to allow a period of 30 to 40 min of arrest safely.<sup>25</sup> Our current clinical practice closely follows the guidelines enumerated in the published reviews.<sup>29,30</sup> The following is a summary of the pertinent, and what we believe are the clinically important, features of hypothermic circulatory arrest.

### COOLING

Surface cooling, which was routinely used early in our experience, currently is reserved for specific indications only (ie, in cases when the risk of aortic entry during sternotomy is high). In these situations, surface cooling adds a measure of increased safety by removing substantial amounts of heat from the whole body, prior to urgent institution of hypothermic circulatory arrest. This is especially valuable in the presence of aortic regurgitation, where rapid core cooling will invariably lead to ventricular fibrillation and left ventricular distension before adequate decompression of the heart or the application of the aortic cross-clamp is possible.

It is generally agreed that too short a period of cooling may result in neurologic damage due to uneven and inadequate lowering of the brain temperature, and that packing the head in ice during prolonged periods of circulatory arrest improves the outcome by maintaining cranial hypothermia.<sup>31,32</sup> Therefore, prior to the institution of prolonged periods of hypothermic circulatory arrest, we insist on cooling down to esophageal temperatures of 12° to 15°C. This is accompanied by EEG and evoked potential silence and/or jugular venous bulb oxygen saturations of higher than 95% as indicators of adequate suppression of cerebral function and metabolism. This active cooling period in an adult commonly takes at least 30 min or longer.

### WARMING

This may well be the most crucial phase of perfusion. The critical postischemic period that was clearly seen in the experimental models at 2 h following hypothermic

circulatory arrest, where impaired autoregulation and increased cerebrovascular resistance is pronounced, probably starts with reperfusion and warming in clinical practice. At this stage, CMRO<sub>2</sub> continues at reduced blood flows, and oxygen extraction is increased to meet the demand. Any further drop in oxygen delivery will be poorly tolerated. Therefore, it is important to proceed slowly with warming and never exceed a 10°C gradient between the perfusate temperature and the core temperature, as increased gradients may be associated with the formation of gas emboli. We stop warming at 36°C esophageal or 34°C bladder temperatures and do not allow perfusate temperature to exceed 37°C. Higher perfusion pressures are maintained by fine-tuning the hemodynamics throughout the initial 16 h of postarrest recovery. The patients usually leave the operating room relatively cold, which gives an additional margin of protection in this critical postischemic period. Much research regarding the effects of postischemic cerebral temperature strategies after circulatory arrest has been done. In an animal model, hyperthermia was associated with persistent deterioration of neurologic and behavioral outcome. Histologic assessment has confirmed the adverse effects of increased temperature and has been correlated with significant injury in the brain. Conversely, post-ischemic hypothermia has been shown to significantly improve outcome relative to hyperthermia, with a reproducible trend toward improved neurobehavioral and histologic outcomes.<sup>33</sup>

#### METABOLIC MANAGEMENT

The issue of how pH should be managed during cooling remains controversial. As blood is cooled, pH changes in an alkaline direction. Cerebral perfusion unequivocally is enhanced by pH-stat management (actively adding carbon dioxide), which abolishes cerebral autoregulation.<sup>34</sup> Cerebral vasodilatation due to increasing levels of CO<sub>2</sub> favors more thorough cooling, and it likely improves oxygen availability by counteracting the leftward shift of oxyhemoglobin induced by hypothermia. This is important in the early cooling phase, when the brain is warm but the blood is cold.<sup>35</sup> However, pH-stat management undoubtedly exposes the brain to an increased embolic load because of the “luxury perfusion” that accompanies cerebral vasodilatation. pH-stat management is also associated with intracellular acidosis and alterations in enzyme function during the arrest time. Alpha-stat management (allowing the pH to drift), on the other hand, preserves autoregulation even at lower temperatures and limits the flow to meet the metabolic demand diminished by hypothermia. This provides for improved intracellular enzyme function. It results in perfusion at a higher pH and eliminates “luxury perfusion” and the associated risk of an increased embolic load.<sup>36</sup> However, this reduction in cerebral blood flow may result in greater neurologic impairment, as suggested by the histologic injury seen in

animal studies.<sup>37</sup> As recently suggested, optimal management may involve initiating cooling with pH-stat management and then using alpha-stat principles to guide the perfusion prior to the arrest.<sup>36,38</sup>

There is substantial experimental and clinical evidence showing that hemodilution is important in limiting cerebral injury following hypothermic circulatory arrest by improving cerebral blood flow at low temperatures. Because the effects of affinity of hemoglobin to oxygen at these low temperatures determines that most O<sub>2</sub> delivery to the tissues is by oxygen in solution, the effective O<sub>2</sub>-carrying capacity of the blood is changed little by the reduction of the red cell mass by hemodilution. On the other hand, the improvement in the blood flow by hemodilution, with prevention of hypothermia-related hemoconcentration and sludging, is, without a doubt, an essential element.<sup>30</sup>

The hypothermia-induced release of catecholamines and administration of steroids produce a significant tendency to hyperglycemia in the pre- or post-arrest periods.<sup>39,40</sup> High blood glucose levels in these periods are known to have an adverse effect on the intracellular pH and the neurologic outcome.<sup>41</sup> The overabundance of glucose drives the anaerobic glycolysis cycle and leads to faster accumulation of lactate and intracellular acidosis during the arrest interval. Therefore, hyperglycemia should aggressively be treated prior to and following hypothermic circulatory arrest. We use intravenous insulin drips liberally.

Among the many pharmacologic adjuncts thought to be effective in modifying ischemia and reperfusion-related cerebral responses that lead to injury, we continue to use steroids and mannitol. Steroids are used in all patients as membrane stabilizers and also to reduce cerebral edema.<sup>40</sup> In all patients with anticipated arrest times greater than 30 min, 1 g of methylprednisolone is given prior to arrest. It is continued in the first 48 h post arrest (125 mg q6h for 24 h; then 125 mg q12h for the next 24 h). Mannitol, besides reducing cerebral edema and intracranial pressure, has an important effect as a free radical scavenger and is given in standard doses both during the cooling and rewarming periods.<sup>42</sup>

We have all but abandoned the routine use of barbiturates as an adjunct to our approach, because of the associated myocardial depression and uncertain efficacy in this setting. There is experimental and some clinical indication that cerebral-specific calcium channel blockers and glutamate receptor antagonists are beneficial following ischemic cerebral insult.<sup>8</sup> Cerebral ischemia causes a rapid shift of calcium from the extracellular space into the cells. Some authors have favored the use of nifedipine, which directly reduces this influx.<sup>43</sup> Others have incorporated the use of lidocaine as an adjunct in reducing cerebral metabolism. Under normothermic circumstances, lidocaine reduces cerebral metabolism by blocking sodium channels, thus abolishing synaptic

electrical activity. During hypothermia, it can further reduce brain metabolism by inhibiting ion leaks and, therefore, reducing the energy requirement for ionic homeostasis by the Na<sup>+</sup>-K<sup>+</sup> and ATPase pumps. In an animal study, the average number of ischemic neurons in multiple sections of brain tissue was significantly less in the group receiving a continuous lidocaine infusion than in the control group.<sup>44</sup> We have not yet incorporated any of these new approaches in our management. When the efficacy and safety of these agents are proven, they will be considered in the protective protocol.

#### REPERFUSION

The possibility that some of the injury associated with DHCA may occur during reperfusion or thereafter has prompted studies suggesting that a brief period of cold perfusion following DHCA may be beneficial in prevention of cerebral vasoconstriction that results from immediate resumption of rewarming with reperfusion.<sup>45</sup> The use of pharmacologic agents for this same purpose (to regulate the cerebral vasomotor tone during reperfusion and to minimize injury related to reperfusion) is also an intense area of investigation. Perhaps this period of cerebral vasoconstriction is related to the impairment of nitric oxide production after DHCA. The loss of nitric oxide (a cerebral vasodilator) may be partly responsible for the reduction in cerebral perfusion during the recovery period. In an animal model, the stimulation of nitric oxide production with L-arginine significantly improved the recovery of cerebral blood flow after the arrest period.<sup>46</sup> On the other hand, excessive production of nitric oxide has been found to be neurotoxic.<sup>13</sup>

Some authors advocate the use of modified ultrafiltration in an attempt to improve oxygen use by the brain. Possible mechanisms in animal studies include decreased cerebral edema, removal of toxic substances, alteration of leukocyte-mediated injury, and hemoconcentration.<sup>47</sup>

## Selective Cerebral Perfusion

### Rationale

Before the introduction of hypothermic circulatory arrest, selective perfusion of the arch branches was used for cerebral protection, in many forms and permutations, with less-than-ideal results.<sup>48,49</sup>

There is little question that the concept of selective antegrade cerebral perfusion has a sound physiologic basis, especially in systems that take advantage of autoregulation of the cerebral blood flow and aim at predetermined target perfusion pressures rather than fixed flow rates. Although deep hypothermia is not an essential component, the addition of hypothermia makes the method safer by reducing the flow requirements and pressures. As the clinical experience indicates, it can be applied successfully at moderate degrees of hypothermia with equally good results.<sup>50</sup>

Probably the most important advantage of this method is that it provides the luxury of time to allow for an unhurried repair of the pathology. This luxury, however, comes at a price. To perfuse the brain evenly in the face of unknown cerebral vascular anatomy in a given patient, multiple cannulae are required for at least two, and preferably for all three, arch branches. These multiple cannulations clutter the field and may increase the risk of embolization from manipulations as well as cannula-related mishaps during the procedure. When the procedure is carried out during only moderate hypothermia, continued perfusion of the lower body is essential. Absence of lower body perfusion at these relatively higher temperatures leaves the spinal cord vulnerable to ischemic injury, especially during protracted cerebral perfusion periods. In this case, provisions for control of the descending aorta to maintain a bloodless field further complicate the exposure and prolong the operation.

### Clinical Application and Results

There are some significant differences in the application of selective perfusion in larger clinical series. Potential for over- or underperfusion exists with any of these systems. The current trend is to perfuse at least the innominate and left carotid arteries with a dedicated pump in an autoregulated system with flows determined by target pressures measured at distal sites. Optimal cerebral perfusion and prevention of perfusion mismatch can be best achieved by continuous monitoring of jugular venous bulb O<sub>2</sub> saturations. This is an indispensable monitoring tool for selective cerebral perfusion methods. Alternative use of transcutaneous near-infrared spectroscopy (NIS) for hemoglobin saturation is gaining wider acceptance as a gauge of oxygen delivery to the brain. In one study, regional cerebrovascular saturation (rSO<sub>2</sub>) was measured continuously throughout surgery. Patients receiving SCP had significant rSO<sub>2</sub> recovery while those receiving RCP showed a constant and sustained decrease.<sup>51</sup> NIS monitors that can measure the redox state of the mitochondrial cytochrome 3 aa are a more reliable indicator of cellular oxygen uptake than are the competing systems that can only measure the intravascular saturation. Other areas of research have integrated the use of somatosensory-evoked potentials (SSEPs) as an indicator of adequate cerebral blood flow.

Frist and associates used preoperative studies of the circle of Willis to determine patency and perfused the innominate artery only (superselective) through a Y connection off the main arterial line from a single pump.<sup>50</sup> This system relies on autoregulation of the cerebral blood flow, and pressure in the right radial artery is used to determine the pump flow rate. The descending aorta was occluded with a balloon catheter, and the perfusion of the lower body continued at 26°C.

Matsuda and colleagues reported 34 patients with perfusion of both the innominate and the left carotid

arteries via separate pumps and with fixed predetermined flows at 16° to 20°C.<sup>52</sup> Balloon occlusion of the descending aorta from below was used. The system again depended on autoregulation of the cerebral blood flow; however, the presence of separate pumps necessitated pressure monitoring at both temporal arteries as well as the lower body. The operative mortality was 9%, with one serious neurologic complication. The impressive finding in this series, however, was the apparently well-tolerated periods of prolonged selective cerebral perfusion, the longest being 214 min, with complete neurologic recovery.

Bachet and colleagues further modified the method and introduced the intriguing term “cerebroplegia.”<sup>53</sup> He used two pumps and two heat exchangers to perfuse the brain (through the innominate and the left carotid arteries) at 6° to 10°C with low flow and the rest of the body at 28°C. The period of selective cerebral perfusion was well within the limits that would be considered safe for hypothermic circulatory arrest. The report included 54 patients with an operative mortality of 13%, and 3 serious neurologic complications, one resulting in death. In general, the reported results of selective cerebral perfusion in other hands are similar to these three original series.

Perhaps one of the most improved surgical techniques in aortic arch reconstruction and cerebral protection can be attributed to Kazui. It involves a fairly new flexible perfusion cannula (which also contains a lumen for pressure monitoring), which can be used to separately cannulate the arch vessels and allow for selective cerebral perfusion. A multilimbed branched graft is then used to reconstruct the arch. Kazui used this method in 50 consecutive patients with atherosclerotic arch aneurysms and reported a 2% operative mortality, a 4% incidence of temporary neurologic dysfunction, and a 4% permanent stroke rate. These results are without equal in the literature.<sup>54,55</sup>

Because of the enhanced risk of embolization, we are not very enthusiastic about the routine use of SCP and reserve it only for cases requiring total arch replacement. Cannulation of the right axillary artery simplifies the routine application and maintenance of SCP in these cases but requires pressure monitoring distally. In the past, in an attempt to reduce the arrest times to less than 30 to 40 min, we had developed a simplified technique for SCP and used it in patients with anticipated complex repairs requiring longer arrest times. After cooling, during a period of arrest, we isolated the island of aortic tissue containing the origins of the head vessels. A beveled (often 18 mm) Dacron graft was sewn into this island, and flow was reestablished to all three arch branches with the perfusate temperature at 10°C. The flow rate was adjusted to achieve a perfusion pressure of about 50 mm Hg monitored at the right radial artery. At the end of the reconstruction of the remainder of the aorta, this beveled graft containing the orifices of the cerebral vessels was sewn to the rest of the aortic graft. This maneuver simply accomplished selective

cerebral perfusion without the need to manipulate cerebral vessels individually. It also established prompt antegrade perfusion of the aorta at the end of the reconstruction.<sup>29</sup> Currently, for total arch replacement, we prefer a modification of the Kazui method with initial cannulation of the right axillary artery and separate sequential grafts to innominate, left carotid, and left subclavian arteries, with individual control of these vessels while maintaining antegrade cerebral perfusion through the right axillary and innominate artery and then via the other branches as they are individually anastomosed. This technique eliminates the need for individual cannulation of the brachiocephalic branches and limits the brain ischemia time to a bare minimum.

## Retrograde Cerebral Perfusion

### Rationale

The limitations of DHCA (particularly, time, pressure, and the complexity of selective cerebral perfusion methods) led to the exploration of alternative methods of cerebral protection. The concept of retrograde perfusion for cerebral protection has its roots in the description of its use in clearing massive air embolisms during cardiopulmonary bypass.<sup>56</sup> Lemole used brief periods of retrograde cerebral perfusion for cerebral-protective purposes during insertion of intraluminal grafts in the distal ascending aorta.<sup>57</sup> Ueda and colleagues described for the first time the planned use of retrograde cerebral perfusion as a simpler alternative to selective cerebral perfusion methods.<sup>58,59</sup> The main argument of the proponents of this method is that in application, it is as simple as hypothermic circulatory arrest and is safer over longer periods of arrest because the brain is being supplied by oxygenated blood, albeit in a retrograde manner.

### Laboratory and Clinical Evidence

RCP gained widespread clinical acceptance prior to any serious experimental demonstration of its effectiveness and its mode of action. This, in part, may have occurred because RCP is difficult to study in the laboratory. There are substantial differences in anatomy and physiology of the cerebral venous circulation among species commonly used in laboratory investigations. The use of different species and different methods of delivery of RCP has yielded confusing and often conflicting experimental data. The available information does not produce a clear picture of whether RCP, in fact, is effective and, if so, how it works.<sup>60,61</sup> The two most striking and clinically relevant findings emerging from the laboratory investigation of RCP are (1) very little of the retrograde perfusate actually reaches the brain tissue and (2) RCP is highly effective in maintaining cranial hypothermia during the arrest period.

It is likely that effective maintenance of cranial hypothermia is not the only mechanism that explains the effect of RCP. Venovenous shunting, experimentally

shown in primates and confirmed in humans by anatomic studies, explains why only a small fraction of the retrograde flow reaches the brain.<sup>60,62</sup> With RCP via the superior vena cava, less than 5% of the retrograde flow returns from the arch branches, and the portion actually returning from the brain may be substantially less than 5%. The effective fraction of the flow can be enhanced experimentally by using special techniques to eliminate the influence of the valves in the jugular venous system or the delivery of the flow directly into the sagittal sinus at high perfusion pressures. Clinical relevance of these experiments is dubious at best. Pressurizing the entire body venous system similarly enhances retrograde flow to the brain clinically. This, however, is associated with unacceptable fluid retention and the associated risk of cerebral edema. The amount of flow, even when enhanced, is far too little to meet the ongoing metabolic needs of the brain even in the presence of deep hypothermia.<sup>31</sup> However, some uptake of nutrients does seem to occur because the blood returning to the arch is desaturated, and the depletion of high-energy phosphates and the decline of the intracellular pH (as assessed by magnetic resonance [MR] spectroscopy) are less severe than with DHCA alone.<sup>63</sup> It is possible that the trickle flow supplied by RCP may allow the removal of some metabolites, delay the onset of acidosis in the ischemic brain, and help modestly prolong the safe period of protection afforded by DHCA alone. However, it is also clear that retrograde cerebral perfusion, especially when it is effective, gradually leads to the development of cerebral edema at a rate directly related to the perfusion pressure. Even at the minimum pressures required for effective RCP, development of cerebral edema clearly limits the safe duration of RCP to only slightly longer times than comparable safe periods with DHCA alone.<sup>64,65</sup>

There is experimental evidence indicating that the trickle RCP flow may help prevent debris and air from reaching the terminal vessels of the brain and may in fact clear them from the major arteries.<sup>66</sup> This might be the major beneficial effect of RCP, but the use of RCP has yet to make a significant clinical impact on the incidence of embolic strokes following these operations. There is evidence that it may in fact increase the incidence of temporary neurologic dysfunction.<sup>67</sup> Studies following serum S-100 $\beta$  as a marker for detection of brain injury revealed that RCP does not provide improved cerebral protection over DHCA alone.<sup>20</sup>

### Clinical Application and Results

Despite the relative lack of substantial evidence proving the efficacy of RCP, a dearth of knowledge regarding its physiologic consequences, and continuing uncertainty regarding the best method for its implementation, some surgeons have adopted the method for routine clinical use in aortic surgery.<sup>68,69</sup> There is no uniformity in the literature regarding the mode of application, method of cannulation, or choice of perfusate temperature or pressure during appli-

cation of RCP. Originally, Ueda used a shunt between the arterial and venous pump lines to perfuse a single cannula in the superior vena cava retrogradely at 15° to 18°C while the rest of the body was not perfused.<sup>58</sup>

Since then, others have employed this modality in different configurations—by using a separate heat exchanger and pump to perfuse the superior vena cava, or by simple elevation of the central venous pressure. Each of these systems incorporates deep hypothermia as an integral part of the method. Additional retrograde perfusion of the whole body has also been used in an attempt to preserve the spinal cord and distal organs during operations on the arch and the thoracic aorta.

Although the application of retrograde cerebral perfusion varies from center to center, there is sufficient experimental, clinical, and anatomic data to suggest that the most effective retrograde perfusion of the brain is achieved when the entire venous system is pressurized. This finding reflects the important role the valve-free azygos system plays as a connection between the central nervous system veins and the systemic venous plexus.<sup>62</sup> In our practice, RCP is initiated at a core temperature of 12° to 15°C by perfusion of either one or both venae cavae at a flow rate to maintain the superior vena cava pressure between 15 and 20 mm Hg and certainly not to exceed 20 mm Hg. Snaring both caval cannulae prevents cardiac distension. We do not favor using continuous RCP for prolonged periods because the occurrence of brain edema (especially at the higher end of the recommended perfusion pressures) is a distinct risk and may, in itself, be injurious to the brain.<sup>70</sup> We currently reserve the use of RCP primarily for prevention of neurologic injury in patients at high risk for embolic strokes (those with thrombus or atheroma present in the aorta). RCP is used for brief periods, particularly prior to resumption of antegrade flow and reperfusion, to wash out debris from the cerebral vessels. We do not rely on RCP for the purpose of global cerebral protection beyond the time limits allowed by DHCA alone, and certainly under no circumstances would we use it without accompanied deep hypothermia.

## Cerebral Protection

### Current Integrated Application

Table 31-4 summarizes the desired properties of the “ideal” brain protection and how the current methods measure up to these criteria. The method should allow enough time for an unhurried repair without compromising protection. It should keep the operation simple and the operative field free of clutter. It should, at best, totally avoid manipulation of the head vessels or at least minimize such manipulation in order to reduce the risk of embolization. It should be effective without the need for prolonged deep hypothermia and associated prolongation of cardiopulmonary bypass times. Currently, only selective perfusion provides flow and the luxury of time and

**TABLE 31-4. Comparative Characteristics of the Methods of Cerebral Protection**

Requirements	DHCA	SCP	RCP
● Simple and easy application	++	--	+
● Flow to support metabolism	--	++	-
● Provide luxury of time	--	++	-
● Limit pump time	--	+	--
● Limit manipulation of arch branches	++	--	++
● Reduce or eliminate "embolic load"	-	--	++

DHCA = deep hypothermic circulatory arrest; RCP = retrograde cerebral perfusion; SCP = selective cerebral perfusion.

potentially can be used with moderate hypothermia; it will, therefore, limit the pump time, but it suffers from required manipulation of the arch branches and therefore has the potential to increase the risk of embolization. On the other hand, RCP is simpler to apply and may extend the safe limit modestly, but it certainly does not provide the luxury of time that SCP does. It might, however, minimize emboli. If time limits are observed, DHCA remains the simplest form of protection. We have tried to incorporate the advantages of each method into an integrated approach to cerebral protection. This approach is guided by the following principles:

1. Initiate DHCA only after adequate metabolic (Saturation of oxygen in the jugular vein [SjvO<sub>2</sub>] > 95%) and/or functional (EEG-evoked potential silence) evidence of suppression exists, usually at 12° to 15°C core temperatures.
2. Maintain cranial hypothermia during arrest period.
3. Keep cerebral ischemia times to less than 40 min at 12°C.
4. Cannulate the right axillary artery, anastomose the brachiocephalic vessels first, and restart antegrade SCP to limit cerebral ischemia time. The rest of the body remains arrested until the reconstruction of the descending aorta is completed.
5. During SCP, regulate flow to maintain pressures at 40 to 50 mm Hg, measured at the right carotid artery (simple autoregulated flow).
6. Do not rely on RCP to prolong the "safe arrest period."
7. Use RCP in selected cases with a high risk of stroke (age > 60, "dirty aorta"), prior to resumption of antegrade flow.
8. When using RCP, occlude the inferior vena cava for maximum effect.
9. Avoid continuous RCP at high perfusion pressures (keep the central venous pressure < 20 mm Hg in order to minimize cerebral edema).
10. Avoid femoral perfusion, particularly in patients with diseased descending aortas if at all possible; if this is not avoidable, then do not manipulate the descending aorta during cooling.
11. Cannulate the right axillary artery instead. This prevents retrograde embolization from perfusion of a diseased descending aorta. It is also useful in prevent-

ing malperfusion in complex acute dissections of the aorta.

12. Always resume perfusion in an antegrade fashion during rewarming.
13. Maintain adequate oxygen delivery during reperfusion and in the immediate recovery period.
14. Avoid perioperative hyperglycemia.

### Future Prospects

Worldwide, all the centers actively treating thoracic aortic pathology are reporting improving overall results. Besides efforts to prevent embolic strokes, there is more emphasis in optimizing long-term neuropsychological outcome. Without question, this is the result of increasing expertise in dealing with these cases, rather than the superiority of one particular protection method. Realization of the absolute limits of arrest times, with or without the addition of RCP, emphasizes the importance of reducing the duration of zero-flow periods. Further simplification of the SCP methods and their wider application should lead to better outcomes. The attempts at modification of the events during the second phase of ischemic injury and reperfusion are subjects of intense research and may hold the promise of improved neurologic outlook for these patients. Table 31-3 (see above) summarizes the developing pharmacologic approach. The strokes due to embolic infarcts remain a difficult and persistent problem. The promise of RCP remains unfulfilled. It remains to be seen whether the wider application of SCP coupled with separate anastomosis of the brachiocephalic branches as reported by Kazui will have a significant impact on the incidence of stroke.<sup>55</sup>

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