Surgical History

Historical Evolution of Hypothermic Liver Surgery

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Abstract. The clinical application of hypothermia dates back to the surgical treatment of blue babies (1949) and the early days of open heart surgery (1952), when generalized cooling was employed. The induction of hepatic hypothermia began with whole-body cooling in experimental models in 1953 and clinically in 1961. It was designed to minimize the ischemia-reperfusion injury associated with hepatic inflow occlusion. Body surface cooling and cooling via an extracorporeal circuit, however, were not widely accepted for hepatic surgery because of the adverse effects on the extrahepatic organs. Consequently, with the introduction of improved venoxygen bypass techniques, in situ cold hepatic perfusion has been used in selected patients since 1971. In situ hypothermic hepatic perfusion, introduced in 1995, prevents an ischemic insult to the contralateral hepatic lobe. Topical cooling using ice slush under total or hemihepatic inflow occlusion was reported in 1993. This technique does not require cumbersome hypothermic perfusion equipment. In attempts to minimize intraoperative bleeding by vascular occlusion, the liver surgeon must consider the benefits and technical demands of hepatic hypothermia.

Historical Perspective on Hypothermic Technique

At the end of the eighteenth century body cooling by immersion in chilled water was applied for the treatment of fever [9], followed by the application of local cooling for relief of pain [9]. Local and generalized cooling were first employed as an aid in the preservation of organ viability in humans on limbs with tourniquet ischemia in 1938 [10], in blue babies in 1949 [11], and for repair of intraatrial septal defects in 1952 [12].

In the field of hepatic surgery, the use of body cooling dates back to the experiments of Raffucci et al. in 1953 [13], who initially found that the hepatic inflow could be temporarily cross-clamped for up to 20 minutes without damage. Subsequently, they noted that the hypothermic dog tolerated total afferent hepatic vascular occlusion for 1 hour, whereas the mortality was 100% in normothermic animals. This observation was confirmed by Bernhard et al. [14], who concluded that lowering the body temperature to 30°C could safely extend the ischemia time to 30 minutes. Since then, hypothermia has been vigorously investigated as a adjunct to increase the tolerance of the liver to prolonged ischemia during hepatic surgery. Hypothermia was first induced during human hepatectomy for liver neoplasms by external body cooling, which was reported by Longmire et al. in 1961 [15]. Subsequently, Fortner et al. [16] reported in situ hypothermic hepatic perfusion with chilled Ringer’s solution for major liver resection in 1971. Then during the 1980s several authors reported major hepatic resections using profound hypothermia and circulatory arrest in highly selected patients with large liver tumors [17, 18].

More recently, hypothermic techniques have been refined, with liver resections being performed for HCC associated with chronic liver disease under in situ hemihepatic perfusion with or without hepatoprotective agents or with topical cooling [19–21].

Effect of Hypothermia on Liver Metabolism

The main benefit derived from hepatic hypothermia is a reduction in the oxygen requirement of the liver, which allows a longer period of total inflow occlusion. Many studies have demonstrated that total body cooling provokes profound metabolic, functional, and morphologic alterations systemically and in each vital organ [22, 23].

Regarding the systemic metabolic affects, hypothermia causes a...
significant reduction in oxygen consumption, which is directly related to the magnitude of the decrease in body temperature. Early investigators indicated that the fall in oxygen consumption was linearly related to the decrease in temperature [24]. On the other hand, studies have demonstrated that the relation between oxygen consumption and hypothermia was exponential [25], and found that oxygen consumption decreases by approximately 50% at 28°C and 78% at 18°C. Mito et al. [26] have demonstrated that in a differential hypothermia model using an extracorporeal circuit for cooling oxygen consumption of the liver at a hepatic temperature of 26°C was decreased to 36% of that at 37°C. In addition, the reduction in oxygen consumption is not the same in each organ [27]. Hypothermia at a rectal temperature of 22.5° to 23.5°C, maintained by body cooling for as long as 12 hours, produces no irreversible changes in biliary secretion, oxygen consumption, or hepatic blood flow [28]. Hypothermic perfusion via the portal vein in dogs has been shown to maintain the energy metabolism of the liver for 2 hours using University of Wisconsin solution [29]. This is in contrast to the 1 hour preservation with Ringer’s solution or longer than 1 hour with Euro-Collins’ solution [29]. Recovery of the hepatic energy charge has been demonstrated in the rat even after 60 minutes of ischemia under hypothermic conditions but not in normothermic animals [30]. Thus hypothermia unequivocally prolongs the safe ischemic period.

Methods of Hypothermia for Liver Surgery

The methods of cooling for liver surgery may be classified under four headings: (1) total body cooling, (2) hypothermic perfusion cooling, (3) extracorporeal cooling, and (4) topical (surface) cooling.

Total Body Cooling

Body cooling was achieved initially by applying ice to the body surface or immersion in a cold bath. Although this method was used for hepatic resection to prolong hepatic inflow occlusion time [15], it has not been accepted as a useful adjunct because of the adverse effects on systemic hemodynamics and metabolism, including hypotension, cardiac arrhythmias, and metabolic acidosis [9]. Other disadvantages are complexity of management and time required to obtain adequate cooling. Therefore cooling only the target organ is preferable because it has fewer adverse effects on systemic hemodynamics and metabolism.

Hypothermic Perfusion

Fortner et al. [16] perfused the liver with Ringer’s solution chilled to 4°C under total hepatic vascular exclusion. With this in situ hypothermic perfusion technique the liver was completely mobilized, keeping the major vascular attachments and the extrahepatic bile ducts intact. Then cold perfusion via both the arterial and portal systems was initiated. This method was used during 33 hepatic lobectomies for advanced liver tumors with only two operative deaths. One death was the result of a technical error, and the other was from a massive pulmonary embolus. In addition to enabling parenchymal dissection in a controlled, bloodless field, this technique also facilitates extraction or resection of the tumor from the involved vena cava, hepatic vein, or portal vein [31].

Some authors have pointed out that such techniques are unnecessary for most liver resections to remove solid hepatic tumors, and their use may actually increase the risk of operative and postoperative complications. One can only admire the courage and talent of those trying to extend the limits of liver resection using techniques developed by cardiac and transplant surgeons; but the reported results, in terms of patient survival, do not yet warrant widespread acceptance or utilization of such complex procedures. Fortner et al. warned, after further evaluation, that the technique is probably not indicated for far-advanced tumors because of the risks of coagulopathy and death after reperfusion [32, 33].

Hannoun and et al. [34] have reported a series of patients requiring liver resection. Using hepatic vascular exclusion and hypothermic perfusion with chilled University of Wisconsin solution, major hepatic resections were performed in 12 patients with a mean duration of hepatic ischemia of 121 minutes (range 65–250 minutes) and less blood loss. The postoperative complication rate (pneumonia, hepatic insufficiency, subphrenic abscess) was high. In fact, one patient died of portal vein thrombosis. They reported that the application of these new techniques should be restricted to situations in which an extensive, complex hepatic resection requiring vascular exclusion for longer than 1 hour is foreseen.

In 1990 Pichlmayr et al. [35] employed ex situ surgery in a liver subjected to in situ hypothermic perfusion with chilled HTK-Bretschneider solution. This method has been confined to use in patients otherwise deemed untreatable or in situations where the resection could not have been sufficiently radical without using the technique. Clearly, this approach is complex and occasionally requires a rescue liver transplantation.

The clinical use of hemihepatic hypothermic perfusion with hepatoprotective agents during right-sided hepatic resection for a deeply situated HCC in patients with coexisting liver disease was first described by our group in 1993 [19, 20]. This technique does not require a venovenous bypass because the left-sided hepatic blood flow and vena caval blood flow are preserved. Following occlusion of the right hepatic vein and the right portal pedicle, in situ cold perfusion is initiated using chilled Ringer’s lactate solution through a cannula placed in the right main portal branch under ultrasound guidance. The liver is cooled to 22° to 26°C for 40 to 80 minutes without any significant changes in systemic hemodynamics, body temperature, or postoperative liver function.

The hemihepatic hypothermic perfusion method is also rather cumbersome, requiring isolation of the right hepatic vein and precise placement of the tip of the perfusion catheter in the first branch of the portal vein via the mesenteric vein. Some branches of the hepatic vein on the dissected surface must be left open so the perfusate can drain. Because of these technical problems we devised a topical cooling technique that affords similar benefits but with less invasiveness and better technical feasibility.

Extracorporeal Cooling

The method of allowing blood to pass through an extracorporeal circuit immersed in a cooling medium and returning it to a vein was first used during the 1950s by Boerema et al. [36]. Cardiopulmonary bypass with profound hypothermia and circulatory arrest using this principle was clinically employed in pediatric patients with giant hepatic tumors during the 1980s [17, 37]. The technique has been applied primarily to the removal of Wilms’ tumors extending into the right atrium [38]. It is particular suitable when