LITERATURE REVIEW

Hypothermia in General Consideration

Hypothermia is defined as a core (rectal, esophageal, tympanic) temperature less than 35°C. Most clinically significant episodes of hypothermia result from an injury in a cold environment, submersion in cold water, or a prolonged exposure to low temperatures without adequate protective clothing. For practical reasons, it is useful to classify hypothermia according to core temperature achieved. The classification which has been generally accepted is that of Okamura (1969) and is presented as Table A.

Table A

Hypothermia	Core temperature down to
Mild	30°C
Moderate	30 - 25°C
Deep	25 - 20°C
Profound	20 - 10°C
Severe	below 10°C

The therapeutic application of cold to humans dates back many years. Hippocrates applied cold to provide analgesia for various injuries and believed that cold minimized hemorrhage. Observations on

accidental hypothermia and experimentally induced hypothermia in animals appeared in the late nineteenth and early twentieth centuries. However, it was probably the description of the tolerance of dogs to circulatory arrest for 15 minutes when cooled to 20°C that initiated further interest in the use of induced hypothermia, particularly for the problems of cardiac surgery (Bigelow, et al., 1956). In 1953, the first successful open repair of an atrial septal defect using surface cooling was reported by Lewis and Taufic. Thereafter, there have seen much experimental and clinical investigations into the methods of induced hypothermia and their physiological sequelae. The technique has now been extended to permit periods of complete circulatory arrest during complex neurosurgical, aortic and cardiac surgery (Cooley, et al., 1981). A fall in temperature causes a reduction in tissue oxygen requirement. Induced hypothermia is employed to provide a margin of safety during the ischemic insult associated with a wide variety of complex surgical procedures, particularly in the field of cardiac surgery. With more than 110,000 open heart operations being performed each year in the USA alone, this is the most common application of the technique (Kolata, 1981). Moderate systemic hypothermia, combined with topical cooling of the heart, is used to provide myocardial protection during obligatory periods of reduced or absent coronary blood flow. Complete circulatory arrest without organ injury for varying time periods may be accomplished under hypothermia.

Complication of Induced Hypothermia

Induced hypothermia permits the performance of surgical procedures that otherwise would be extremely hazardous. Cooling the patient's body

temperature to approximately 30°C allows the correction of certain cardiac anomalies, such as secundum-type atrial septal defects, and also permits a range of vascular operations, such as treatment of carotid artery stenosis or aneurysm resection, when a period of diminished circulation is necessary. A moderate or deep level of hypothermia is sometimes combined with cardiopulmonary bypass to reduce the pump perfusion rates ordinarily needed or to provide safer conditions to correct more complex defects. Hypothermia and circulatory arrest provide a bloodless field and an optimal surgical environment for repairing of certain lesions of the heart, ascending aorta and aortic arch. The most serious complication seen with induced hypothermia is the development of ventricular fibrillation (VF) or asystole. With cooling below 30°C, VF frequently occurs (Keefe, 1977 ; White, 1982). Thus, cooling below 30°C is unsafe in cardiac surgery if reliance is to be placed on a spontaneously beating heart. VF is a major concern in patients undergoing open heart operation, despite the improvement in myocardial protection strategies. VF is reported to occur from 74 % to 96 % of patients (Fall, et al., 1987 ; Fiore, et al., 1990). VF may result in increased myocardial wall tension, increased myocardial oxygen consumption and impaired subendocardial blood flow (Buckberg, et al., 1975 ; Hottenrott, et al., 1974). Furthermore, defibrillation with direct current (DC) countershock will result in myocardial injury (Dahl, et al, 1974). Thus, it is advantageous to prevent the occurrence of VF during hypothermia, especially in cardiac surgery.

Electrophysiological Mechanisms Involved in Ventricular Fibrillation

Ventricular fibrillation (VF), first produced with Faradic stimulation by Hoffa and Ludwig in 1850, may be defined as chaotic,

random, asynchronous electrical activity of the ventricles due to repetitive re-entrant excitation and/or rapid focal discharge. Each mechanism has its proponents and has been supported by experimental data. Which of these mechanisms account for VF in man cannot be unequivocally established ; very likely, both re-entry and automaticity play a role, depending on the specific situation. No single mechanism or factor can be proposed to explain all types of spontaneous or experimentally produced VF. The factors that increase vulnerability to VF include increased automaticity, currents resulting from differences in the membrane potential during activity or at rest, imbalance between conduction velocity and refractoriness and nonhomogeneous refractoriness. In brief, the pathogenesis of all VF may be divided into two general catagories : disorders of impulse formation (automaticity), disorder of impulse conduction (re-entry) or combination of both (Cranefield, et al., 1971 ; Sasyniuk and Mendez, 1971).

Hypothermia - Induced Spontaneous Ventricular Fibrillation

There appears to be no general agreement on the factors that influence the onset of VF. Whereas during hypothermia the brain cells become less sensitive to ischemia and anoxia but the myocardium becomes more sensitive to anoxia. During hypothermia, excitability of the myocardium is modified by cold itself and the general reduction in metabolism. That is, a lowering of the threshold of the heart for VF occurs (Rose, 1957).

Though the electrophysiological mechanisms underlying development of VF in hypothermia are poorly understood, there are some factors in the production of hypothermia-induced VF and are summarized in the following :

Influence of Anesthetics

Covino, et al. (1954) noted that cardiac arrhythmias and VF occur less frequently in profoundly hypothermic dogs under thiopental and ether than under pentobarbital anesthesia. Riley and associates (1956) similarly reported that there is a lower incidence of VF with thiopental anesthesia compared with pentobarbital during hypothermic condition.

Role of Cardiac Nerves

The influence of extrinsic cardiac nerves on the VF of hypothermia is yet an unanswered question. Shumacker and colleagues (1956) showed that bilateral sympathetic denervation of the heart, or the use of a sympathetic ganglionic blocking agent, prevented VF in hypothermic animals subjected to inflow occlusion and right ventriculotomy. Riberi (1956), and Radigan and co-workers (1956) have used procaine infiltration of the junction of the right atrium with the superior vena cava and reported protection from VF during hypothermia and right ventriculotomy. Contrary to these observations, Covino and co-workers (1954) found that adrenergic blockade with Dibenamine offered no protection against hypothermic VF in the absence of cardiac surgery. Shumacker, et al. (1956) also noted that bilateral cervical vagotomy offered no protection to the incidence of

VF in hypothermic animals. Again, on the contrary, electrical stimulation of the undivided right vagus nerve below the level of the caudate ganglion reduced the incidence of VF in hypothermic animals (Montgomery, et al., 1954). From these studies, one might conclude that increased sympathetic activity and perhaps decreased vagal tone on the heart tend to favor the onset of VF in the hypothermic state. Whether or not such a change in the activity of cardiac nerves prevails during hypothermia is uncertain, although some investigators postulated that it does (Montgomery, et al., 1954). Furthermore, the actions of the neurohumoral agents, epinephrine and acetylcholine, released by the postganglionic autonomic nerve endings are increased in cold. Garb and Penna (1956) showed that in isolated cat auricles, epinephrine produces a proportionately greater increase in rate and amplitude at 29°C than at 37°C. Vagal inhibition of heart lasts much longer in dogs at 30°C than at 37°C, probably because enzymatic hydrolysis of acetylcholine is delayed by cold (acetylcholinesterase is less active at low temperature) (Cookson and Palma, 1955). In contrast to the above results, the work of Reissmann and Kapoor (1956) suggests that the extrinsic cardiac nerves play little if any role in precipitating VF in profoundly hypothermic dogs. They noted that the terminal hypothermic temperature at which VF occurs is about the same in the denervated heart-lung preparation as in the intact dogs.

Role of Blood Hormones and pH Changes

Berne (1954) has shown that the administration of epinephrine to the hypothermic heart precipitates VF. This is in accordance with the

observation of Shumacker and co-workers (1956) that cardiac sympathectomy partially protects the heart from VF. Brown and Cotten (1956) have noted that in hypothermic dogs there is an increase in the levels of circulating epinephrine and norepinephrine and they play a role in precipitating VF. It has been shown that hypothermia induces a respiratory as well as a metabolic acidosis in anesthetized animals breathing spontaneously. Swan and colleagues (1953) presented the data which suggested that VF in hypothermic dogs may be initiated by a sudden rise in blood pH from abnormally low levels. This was avoided to a certain extent by vigorous hyperventilation with oxygen to a state of alkalosis during the period of cooling and has been widely used by cardiac surgeons. Studies in the heart-lung preparation suggest that alkalemia does not play a role in precipitating or preventing VF in profound hypothermia. On the other hand, Moulder and coworkers (1956) noted that a state of alkalosis is associated with considerable VF before surgery is done in hypothermic animals. Covino and Hegnauer (1955) had emphasized the importance of acidosis in hypothermic VF and in their preliminary studies, had suggested that acidosis favors VF by increasing the excitability of ventricular myocardium.

Direct Effect of Lowered Temperature on Heart Muscle

Hegnauer (1959) pointed out that during hypothermia one would expect significant temperature variations in the ventricular myocardium and that such gradients may be responsible for ectopic activity in the ventricles. Berne (1954) demonstrated the existence of such gradients by thermocouples placed on various parts of the heart. These temperature gradients could readily produce differences in the relative refractory

period in different parts of the ventricular myocardium and thus play an important role in precipitating VF by blocking an ectopic impulse in some areas and allowing it to travel in others.

Mechanical Stimuli

It is well known that manipulating, clamping, or cutting the heart, as well as the presence of intraventricular catheters, act as mechanical stimuli even under normothermic conditions. In normothermia such stimuli rarely induce VF. In the cold state, on the contrary, such stimuli are potent factors precipitating VF (Reissmann and Kapoor, 1956). The difference probably lies in the slowed conduction and variations in the refractory period of different parts of the hypothermic myocardium.

Coronary Blood Flow

It is generally accepted that in hypothermia there is a reduction in coronary flow (Berne, 1954 ; Badeer, 1955). Smith (1956) claimed that the decline in coronary flow leads to hypoxia of the heart and is a factor in the onset of VF during hypothermic state. Edwards (1954), Shumway (1956) and their associates showed that perfusion of the coronaries with oxygenated blood during the period of occlusion markedly reduces the incidence of VF. These reports suggest that diffuse hypoxia of the myocardium may be a factor leading to VF, at least in the hypothermic heart.

Electrolyte Changes Associated with Hypothermia

Much interest is centered on the possible role of alterations in the concentrations of plasma electrolytes on the onset of VF in hypothermia. Most investigators find no significant change in plasma sodium, chloride, phosphorus, and magnesium during hypothermia. The cation of the greatest interest is potassium because of its well known effects on cardiac activity. Hypokalemia has received much attention as a modifiable risk factor that can promote VF during acute myocardial infarction. Several reports have shown an association between a low serum potassium ion concentration and an increased incidence of VF in acute myocardial infarction (Dycker, et al., 1975 ; Nordrehaug and Lippe, 1983 ; Nordrehaug, et al., 1985). In a previous study by Hohnloser, et al., (1986), an acute decrease in serum potassium concentration by hemodialysis lowered the VF threshold during myocardial ischemia. There were no experimental data showing a direct relationship between hypokalemia and the incidence of VF during hypothermia, although Swan (1953) identified a high incidence of VF with lowered serum potassium levels during cooling and hyperventilation. Hypothermia-induced hypokalemia was frequently reported in the previous studies, (Koht, et al.,1983 ; Sprung, et al., 1991 ; Sprung, et al., 1992 ; Todd, et al., 1977). Acute hypothermia induces hypokalemia which is redistributional in nature and reversible on rewarming (Sprung, et al., 1991), but the mechanism of hypothermic hypokalemia and the sites of potassium redistribution are presently uncleared. Hypothermia depletes intracellular myocardial potassium content, which tends to lower ventricular threshold to

fibrillation (Mavor, et al., 1956). During the induction of hypothermia, potassium does not redistribute into the red blood cells, kidneys, or skeletal muscles. Intracellular potassium content in the hepatocytes increases, especially in deep hypothermia, indicating this organ's potential role in potassium homeostasis. Increase in portal vein insulin concentrations in response to a potassium load is five times greater as compared with the concentrations in the systemic circulation (Blackard and Nelson, 1970). Insulin increases the accumulation of potassium by muscle cells and reduces the serum potassium by stimulating the active potassium uptake by cells via sodium-potassium adenosine triphosphatase (Clausen and Hansen, 1977 ; Knochel, 1977). Whether insulin-induced potassium uptake into the liver cells is the mechanism that regulates the serum potassium concentration in hypothermia is not known and needs to be investigated.

Antifibrillatory Drugs : Historical Perspectives of Lidocaine and Bretylium

Lidocaine or Xylocard® is 2-Diethylaminoaceto-2', 6'-xylidide hydrochloride. The Australian approved name is Lignocaine hydrochloride. Lidocaine is classified as a membrane stabilizing agent, local anesthetic and class IB antiarrhythmic agent, sodium channel blocker at the membrane (Jen, et al., 1986). In cardiac tissue, Lidocaine depresses slow spontaneous depolarization (phase 4), that is the automaticity of isolated non-depolarised Purkinje fibers. Lidocaine shortens both the action potential period and the effective refractory period of Purkinje and ventricular cells. A one-time dose of 1-5 mg/kg body weight of Lidocaine

should guarantee therapeutic level for a prophylactic agent against arrhythmias (Olson, et al., 1984). A number of previous studies have investigated the use of Lidocaine to prevent VF during cardiac surgery. Some workers gave Lidocaine as a bolus dose into a pump prior to removal of the aortic cross-clamp (Fall, et al., 1987 ; Praeger, et al., 1988), while some other workers gave Lidocaine continuously with the cardioplegia (Baraka, et al., 1993 ; Fiore, et al., 1990). All studies demonstrated statistically significant decreases in the incidence of VF at the time of aortic declamping in Lidocaine-treated patients. It has been observed that Lidocaine promotes spontaneous defibrillation during the reperfusion phase of coronary artery bypass grafting (Curling, et al., 1981 ; Fall, et al., 1985). Lidocaine is also shown to decrease defibrillation threshold in humans (Schnittger, et al., 1978), fewer shocks were required, as noted by other investigators (Fall, et al, 1985) because VF did not recur after successful shocks. The lower myocardial resistance noted in Lidocaine-treated patients may also affect the intramyocardial spread of current and facilitates defibrillation. Prophylactic administration of Lidocaine during myocardial reperfusion would permit defibrillation with DC shock of lower energy (Lake, et al., 1986).

Bretylium tosylate, or Bretylol^{R}, is a bromobenzyl quaternary ammonium compound. Bretylium tosylate was marketed in the United States for the tratement of life-threatening ventricular arrhythmias. The effects of Bretylium on cardiac electrophysiology have been studied in a variety of isolated myocardial tissues and with in situ heart arrhythmia models (Cardinal and Sasyniuk, 1978 ; Koch, 1979). The possible mechanism of the antiarrhythmic action of Bretylium can be divided into those related to its effects on adrenergic function and those due to its direct

myocardial action. Bretylium is class III antiarrhythmic agent (Jen, et al., 1986) and differs from other antiarrhythmic agents in that it does not directly affect automaticity or conduction velocity. It is only direct membrane effect is to markedly delay repolarization, thereby prolonging both action potential duration and effective refractory period (Heissenbuttel and Bigger, 1979). Bretylium also causes a subsequent inhibition of release of norepinephrine from adrenergic nerve terminals. In many models and in several animal species, Bretylium has been proven to be a potent antifibrillatory drug. The initial dosage of Bretylium in therapeutic level for prophylactic agent againt VF is 5 to 10 mg/kg body weight, and it can be given to maximum doses of 20 mg/kg body weight (Olson, et al., 1984). The ability to prevent VF has been demonstrated in several studies. According to Bacaner (1966), treatment with Bretylium prolonged the electrical stimulus duration required to produce fibrillation in the dog. Marked elevation of VF threshold from control values was also found following Brethylium administration in the normal, ischemic and infarcted canine heart (Anderson, et al., 1980 ; Bacaner and Schienemachers, 1968 ; Bacaner and Visscher, 1969). Holland and associates (1983) developed a canine model simulating the electrical instability and re-entrant ventricular arrhythmias that may precede sudden cardiac death. After temporary occlusion of the left anterior descending coronary artery, a current was applied to the intimal surface of the left circumflex artery. Ninety percent of saline-treated animals fibrillated, compared with 20% of Bretylium -treated animals. Mortality was significantly higher in the saline-treated group (Holland, et al., 1983).

Bretylium has also been shown to be protective effect against VF in hypothermia. In cats, Bretylium produces a significant decrease in

the mean temperature at which VF occurs (Nielson and Owman, 1968). Similarly the incidence of VF is significantly reduced in dogs subjected to the combined stress of hypothermia and rapid phlebotomy (Buckley, et al., 1971). Danzl and associates (1982) reported a case in which spontaneous defibrillation occurred in a severely hypothermic patient treated with Bretylium.