DISCUSSION

The present investigation showed that hypothermia promotes spontaneous ventricular fibrillation (VF). There was 40 % incidence of hypothermia-induced VF in control rats, as shown in Table 1 and Figure 2. Previous experiments demonstrated that VF may spontaneously develop during hypothermia. In dogs, in the experiment of Buckley, et al. (1971), 5 of the 12 (42 %) control dogs developed VF when cooled to 22°C of core body temperature, although a study by Kathleen, et al. (1986), 6 of the 11 (52 %) control dogs fibrillated. In man, VF may occur when the heart is cooled excessively, usually to less than 30°C of core body temperature and it is often proved to be a fatal consequence of accidental hypothermia (Reuler, 1978). Most cases of hypothermia-induced VF reported in the literature have occurred in patients with body temperatures less than 30°C (Keeffe, 1977 ; White, 1982). The present study found that VF also occurred spontaneously when the rat body temperature decreased below 30°C, as shown in Table 3 and Figure 4.

The electrophysiological mechanism underlying development of VF in hypothermia is poorly understood. Unfortunately, in spite of much work, there is still no general agreement about the exact mechanism(s) of VF under normothermic conditions. However, the simplest working concept of the mechanism of VF may be briefly outlined as follows. An ectopic focus or foci in the ventricles starts discharging repetitively at a high and accelerating frequency (the high freguency is relative rather than absolute, being related to refractory period of the muscle). If one of these impulses is discharged very soon after another it may be blocked

on one side, provided it falls in the relative refractory period of the preceding impulse. However, the impulse travelling in other directions may proceed over the ventricular syncytium if the muscle has just recovered its excitability or is in hyperexcitable state. Conditions then would be favorable for re-entry and spread of excitation to occur in a very irregular and haphazard fashion depending upon the availability of excitable tissue. As a consequence, the ventricular contractions are fasciculated, producing the characteristic fibrillatory movements (Douglas, 1975). During hypothermia the physiology of every systems in the body of the nonhibernating homeotherm is profoundly altered and the role of these changes favor the onset of VF. Type of anesthesia is one of the factors that affects VF in hypothermia. Covino, et al. (1954) found that VF occurs more frequently in profound hypothermic dogs under pentobarbital than under thiopental or ether. Similarly, Riley and associates (1956) reported the same tendency. Pentobarbital anesthesia during hypothermia may be one of the factors of the VF development in this present study. Therefore, though the mechanism was unexplained, ether and thiopental appear to be safer agents in hypothermia.

Hypothermic VF is associated with changes of the myocardial temperature that in many respects differ from changes registered in other conditions of VF (Angelakos, et al., 1957). Hypothermia itself would expectably induce significant temperature variations in the ventricular myocardium and that such temperature gradients may be responsible for ectopic activity in the ventricles and may precipitate VF during hypothermia as in the present study. Pinkston and associates (1954) demonstrated the existence of such temperature gradients by thermo-

couples placed on various parts of the heart. These 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. Experimental evidence indicates that at temperature below 25° C, there is a tendency for the development of ectopic foci in the ventricles (Angelakos, et al., 1957).

It is well known that clamping, or cutting the heart, as well as the presence of intraventricular catheters may act as mechanical stimuli for induction of VF even under normothermic conditions. Though in normothermia such stimuli rarely induce VF, in the cold state, on the contrary, such stimuli are potent factors precipitating VF (Hegnauer, et al., 1951 ; Reissmann and Kapoor, 1956). In this present study, all animals were stimulated by mechanical stimuli such as tracheal intubation, femoral vein catheterization, and such stimuli may probably precipitate VF especially in the hypothermic state. Simply placing a cuff around the chest to record respiratory movements, or removal of a rectal thermometer in the hypothermic dog, has been reported to induce VF (Towne, et al., 1972). Intraventricular catheters have been shown to raise the mean lethal temperature for VF in hypothermic dogs (DaVee and Reineberg, 1980). Also clinical experience in human beings has demonstrated hypothermia-induced VF following endotracheal intubation (Wickstrom, et al., 1976), electrical pacing (Truscott, et al., 1973), and nasogastric tube or esophageal probe placement (Coniam, 1979).

In hypothermia there is a reduction in coronary flow (Berne, 1954 ; Edwards, et al., 1954 ; Sabiston, et al., 1955). Smith (1956)

claimed that the reduction in coronary flow leads to hypoxia of the heart and is a factor in inducing VF. In cardiac surgery with inflow occlusion under moderate hypothermia, the ventricle is usually subjected to a diffuse ischemia and the question arises whether or not such ischemic hypoxia contributes to the onset of VF which usually develops sometimes after occlusion. Perfusion of the coronaries with oxygenated blood during the period of occlusion in hypothermic cardiac surgery markedly reduces the incidence of VF (Edwards, et al., 1954 ; Shumway, et al., 1955). These findings suggest that diffuse hypoxia of the myocardium may be a factor leading to VF in this present study.

Alterations in autonomic nervous system activity, probably to the heart, may be one factor responsible for the production of hypothermic VF. Previous studies showed that increased sympathetic activity and decreased vagal tone to the heart tended to favor the onset of VF in hypothermia. Acetylcholine, prolonged stimulation of the distal end of the cat vagus, suppression of the sympathetics with stellate ganglion blockade, have been observed to protect against fibrillation during hypothermia (Montgomery, et al., 1954). Electrical stimulation of the undivided right vagus nerve below the level of the caudate ganglion reduces the incidence of VF in hypothermia, though bilateral sympathetic denervation of the heart, or the use of a sympathetic ganglionic blocking agent, prevents fibrillation in hypothermic animals subjected to coronary occlusion and right ventriculotomy (Shumacker, et al., 1956). Also the studies of Riberi, et al. (1956) and Radigan, et al. (1956) used adrenergic blockade infiltration into the junction of the right atrium and the superior

vena cava and reported protection from VF during hypothermia and right ventriculotomy.

VF is a major concern in patients undergoing open heart operations and commonly develope after the release of the aortic cross-clamp during cardiopulmonary bypass with systemic hypothermia (Curling, et al., 1981 ; Fall, et al., 1987 ; Fiore, et al., 1990 ; Tchervenkov, et al., 1983). Such VF may adversely affect coronary blood flow, increase myocardial oxygen consumptions, and increase ventricular wall tension, causing a further depletion of myocardial energy reserves in an already energy-depleted myocardium (Buckberg and Hottenrott, 1975 ; Hottenrott and Buckberg, 1974 ; Hottenrott, et al., 1974). To minimize these effects, electrical cardioversion or defibrillation with direct current (DC) countershock is oftened performed. This in itself may contribute to myocardial injury (Dahl, et al., 1974), therefore, the concept of preventing VF during cardiac surgery with chemicals arises. According to this, Olson et al., (1984) recently reported the effects of Lidocaine and Bretylium on VF incidence in CPR cases. However, in cases of hypothermia-induced VF, there has been no reports comparing the effects of these two drugs yet. The present investigation showed that Lidocaine and Bretylium afford an efficient protection against hypothermia-induced VF. The effects of both drugs in lowering VF incidence in this study were about the same degree. That is, with Lidocaine, VF incidence significantly decreased to 10 %, while with Bretylium it decreased to 6.6 %, as shown in Table 1 and Figure 2. However, it seems that both chemical-treated groups showed no significant lowering of the body temperature level at which VF occurred as well as the VF duration as shown in Tables 2 and 3, and Figures 3 and 4.

From the results in this present study, Lidocaine may be used to prevent hypothermia-induced VF. Also many previous studies have investigated the use of Lidocaine to prevent VF during cardiac surgery. In two studies, Lidocaine was given as a single dose (into a pump) prior to removal of the aortic cross clamp (Fall, et al., 1987 ; Praeger, et al, 1988) ; two other studies added Lidocaine to cold crystalloid cardioplegia (Baraga, et al., 1993 ; Fiore, et al., 1990). All four studies demonstrated statistically significant decreases in the incidence of VF during the period of hypothermia in Lidocaine-treated patients. In addition, Wallace and Baker (1994) recently found that the incidence of spontaneous defibrillation in patients who developed VF undergoing coronary artery bypass surgery was higher in the Lidocaine-treated group with 33 % in contrast to the control group where only 11 % defibrillated spontaneously, though this failed to be statistically significant. The average number of direct current (DC) shocks needed to terminate VF was lower in the Lidocaine-treated patients (Lake, et al., 1986), suggesting that prophylactic administration of Lidocaine during myocardial intra-operation would permit defibrillation with few DC shocks of lower energy. The mechanism that Lidocaine decreases the incidence of VF as well as decreases the energy and the number of DC countershocks required to defibrillate the heart may be that it blocks the fast sodium channels in the cell membrane. It also decreases the slope of phase 4 of abnormal spontaneous membrane depolarization by increasing outward potassium current in ventricular tissue and increases the electrical current threshold in Purkinji fiber (Carmeliet and Saikawa, 1982 ; Weld and Bigga, 1976). The threshold to ventricular stimulation is increased, thus increasing the current required to induce arrhythmias and VF.

The present investigation revealed that Bretylium, as well as Lidocaine, affords an efficient protection against spontaneous VF during hypothermia. In cats, Bretylium increases the fibrillation threshold and produces a significant decrease in the mean body temperature at which VF occurs (Buckley, et al., 1971). Bretylium has been shown clinically to cause a spontaneous defibrillation. Pretreatment with Bretylium completely protected neurosurgical patients from VF under condition of hypothermia, spontaneous defibrillation occurred in severely hypothermic patients treated with Bretylium (Danzl, et al., 1982). Based on all of the evidence above, it seems reasonable to assume that Bretylium also might be beneficial in managing hypothermia-induced VF. The mechanism that Bretylium could decrease the incidence of VF in hypothermia may be that this agent markedly increases repolarization, thereby homogeneously prolonging both action potential duration and effective refractory period (Cardinal and Sasyniuk, 1978 ; Heissenbuttel and Bigga, 1979). Bretylium also causes an inhibition of release of norepinephrine from adrenergic nerve terminals but the exact manner in which norepinephrine release is aborted is not well understood (Koch, 1979). There is evidence that Bretylium may depress excitability of adrenergic nerve terminals or may stabilize the norepinephrine storage granules in the nerve ending (Buckley, et al., 1971 ; Day and Bacaner, 1971). It seems reasonable to believe that Bretylium is effective in controlling hypothermic VF through its suppression of sympathetic activity.

Hypokalemia has received much attention as a modifiable risk factor that can promote ventricular arrhythmias. Several reports have shown an association between a low serum potassium ion concentration and an increased incidence of ventricular arrhythmias (Dyckner, et al., 1975 ;

Nordrehaug, et al., 1983 ; Nordrehaug, et al., 1985). It is possible that the movement of potassium ion within the body, and in particular within the myocardium, may be of significance in explaining the cardiac abnormalities that are encountered during hypothermia. In this present study, hypokalemia was induced by hypothermia in all groups of animals as shown in Tables 4 and 5. Hypothermia-induced hypokalemia has been frequently reported in various studies (Koht, et al., 1983 ; Sprung, et al., 1991 ; Sprung, et al., 1992 ; Todd, et al., 1977), and it is postulated that it may result from extracellular shifts of potassium ion but the exact site and mechanism of the compartmental shift of potassium ion during induction of hypothermia are presently uncleared. Hypokalemia induced by hypothermia is transient, and can be normalized during rewarming (Koht, et al., 1983). Increased sympathetic tone associated with mild hypothermia (Johnson, et al., 1977 ; Ludue, 1961) may facilitate intracellular potassium uptake (Rosa, et al., 1980 ; Vick, et al., 1972). The effects of adrenergic activation on the distribution of body potassium are complex and inadequately understood. There is evidence that beta-adrenergic receptor stimulation decreases serum potassium level and this is thought to be due mainly to increased potassium uptake by the liver and skeletal muscle (Adrogue and Madias, 1981). Intracellular potassium content in the hepatocytes increases, especially in deep hypothermia, indicating this organ's potential role in potassium homeostasis (Machida, et al., 1977). Another probable mechanism of hypokalemia in hypothermia is hyperventilation leading to respiratory alkalosis that might promote intracellular potassium distribution (Adrogue and Media, 1981). It was observed that hyperventilation (up to 300 %) decreased serum potassium level some 70 % in the euthermic dog (Osborn, 1953). Hyperventilation

with hypothermia apparently causes a potassium shift into the intracellular phase (Swan, et al., 1953). This factor might be the mechanism that explains the decline of serum potassium concentration during hypothermia in the present study.

The level of serum potassium is related to the function of insulin hormone and carbohydrate metabolism. To ascertain this relationship, serum glucose concentrations were examined in this study and it was observed that serum glucose concentrations were not significantly different among the normorthermia, at 25°C, and at 10°C or at VF-onset as shown in Table 6 and Figure 22. Disturbances in blood glucose homeostasis during hypothermia have been reported. Hypothermia increased hepatic glucose production so that glucose in extracellular cells might be greater (Kuntschen, et al., 1986). Increase in plasma insulin concentration has been shown previously during hypothermia (Yokata, et al., 1977). Insulin increases the accumulation of potassium by muscle cells and, hence, reduces the serum potassium level by stimulating the active potassium uptake by cells via sodium-potassium adenosine triphosphatase (Clausen and Hansen, 1977 ; Knochel, 1977). Increased plasma insulin in response to hypothermia might induce the greater potassium and glucose uptake. While hypothermia itself may induce hypokalemia and hypoglycemia at the same time. The parallel increases of both hepatic glucose production and insulin secretion might possibly be responsible for the facilitated glucose uptake and thus blood glucose concentrations were apparently unchanged in contrast to the potassium levels which were significantly affected in this study. However, whether insulin-induced potassium uptake is the mechanism that regulates the serum potassium concentration in hypothermia is not known and needs to be investigated.

In summary, this study demonstrated that Lidocaine and Bretylium decreased significantly the incidence of hypothermia-induced VF in anesthetized rats. However, the efficacies of both chemicals were not significantly different. There was also evidents that hypothermia induced hypokalemia with no changes of serum glucose concentration. The mechanism that produce hypokalemia was probably though respiratory alkalosis accompanying hypothermia.