Protection of Heart Under Hypothermia with Acetylcholine Arrest.* (22381)

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(Introduced by Lester R. Dragstedt.)

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Hypothermia will protect specific areas of the body or the total body during periods of circulatory arrest(1,2), and most investigations have emphasized cerebral protection during this period of anoxia. The heart has been protected by the depressed metabolism of the cooled state, but formidable complications continue, and ventricular fibrillation has been considered a major deterrent to the use of hypothermia(3,4). Considering the profound environmental changes associated with hypothermia the heart is remarkably non-sensitive. This is especially true when a relatively normal acid-base relationship is maintained(5,6). However, with circulatory arrest and continuation of cardiac contractions the heart becomes progressively more cyanotic and weaker; there is electrocardiographic evidence of deterioration; and resuscitation becomes progressively more difficult.

This study was based on the thesis that arrest or inhibition of cardiac activity would afford increased protection of the heart. It has been found that a near total arrest can be obtained with the use of intracoronary acetylcholine and this effect of the acetylcholine can be reversed by atropine given shortly before release of occlusion.

Method. Fifteen adult mongrel dogs were used in this study (3 had had prior implantation of yttrium^{90} oxide pellets in the myocardium and were sacrificed for study). Preoperative medication was 45 mg of morphine sulphate only. Four received barbiturates for induction, and all animals had ether-oxygen closed circuit anesthesia with a carbon dioxide absorber in the system. Three dogs were studied at normal body temperature and 12 were cooled to 24-27°C for the experimental period. Cooling and rewarming procedures were done with the use of a Thermo-Rite circulating fluid blanket. Body temperature was observed continuously with the use of a rectal thermocouple and gauge. Lead II of the electrocardiogram was used as the monitor throughout the procedure. Standard and augmented limb lead electrocardiograms were obtained at various stages of the procedure. Total circulatory arrest was obtained by ligating the azygos vein, placing bulldog clamps on the superior and inferior vena cavae and cross clamping the aorta and pulmonary artery with a large Satinsky clamp. Respiration was halted during the periods of occlusion. Except for a period when the chest was open and a short time thereafter, the dogs were allowed to breathe normally. When respiration was assisted at the low temperature, the respiratory rate was maintained at 3 per minute. In 9 of the experiments a constant recording CO_2 analyzer was attached to the endotracheal tube at the level of the mouth and records of inspiratory and expiratory CO_2 were obtained. This indicated a level of expiratory CO_2 to be maintained by the hypoventilation during the time the chest was open. Direct blood pressure readings (via a femoral catheter and a Statham transducer) were recorded on a Grass direct-writer electromanometer. Complete inflow and outflow occlusion was accomplished and maintained for 1 minute and the "occlusion" rate obtained. After stabilization requiring 2 to 4 minutes the heart was again completely occluded from the circulation, respiration stopped, and 100 mg of acetylcholine chloride in 6 ml 154 mM saline was injected into the aorta proximal to the aortic clamp so that the solution went into the coronary system. (The first 4 dogs received only 50 mg of acetylcholine and some of the dogs received an additional 100 mg at 5 minutes.) Circulatory occlusion was maintained for 1 to 3 minutes in the normothermic animals and

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TABLE I. Effect of Temperature, Occlusion and Acetylcholine on Cardiac Rate in Dogs.

A. Hypothermia

Temp., °C	Cardiac rate/min. Normothermic	Hypothermic	Occlusion	Occlusion & acetylcholine	Return	Acetylcholine Total time, min.	Acetylcholine No. total contractions	Result
25	142	80	90	5	75	10	51	Sacrificed
24.8	180	70	73	9	75	9	91	"
24.1	170	80	60	6	70	10	58	"
25	220	74	80	3.6	80	9	33	*
24.2	170	65	55	2.5	70	10	25	Living
25	150	70	70	2.3	106	10	23	*
24.5	180	55	90	1	52	10	12	*
26	192	80	88	5	49	10	46	Died post-op.
26.3	175	60	65	13	90	10	132	*
26.8	155	74	80	8	123	9	70	Died post-op.
24.8	90	60	61	15	94	10	147	" "
24.8	140	85	85	14	85	10	158	Living
Avg	164	71	75	7	81			

B. Normothermia

Temp., °C	Cardiac rate/min. Initial	Occlusion (1 min.)	Acetylcholine & occlusion 1st min.	2nd min.	3rd min.
38	180	155	0	46	88
38.7	150	200	0	9	24
38.5	115	136	7	38	79

* Died of postoperative pneumothorax.

for 9 to 12 minutes in the hypothermic ones. Atropine sulfate (0.6 mg in 5 ml 154 mM saline) was given intracoronary 9 to 10 minutes after the acetylcholine (except in Dog 594). This was forced into the coronary system by manual compression of the heart, and by maintaining occlusion for one minute. Initially only the superior vena cava and aortic clamps were removed, the inferior cava being opened shortly thereafter as filling of the heart was decreasing. Cardiac rate during the acetylcholine to atropine time is recorded, and not the total occlusion period rate for the "acetylcholine" rate. Shortly after a normal sinus rhythm was obtained the "return" cardiac rate was determined.

Results. Table IA summarizes the data obtained on the animals undergoing hypothermia. Hypothermia *per se* produced a considerable decrease in the pulse rate. It is most significant that occlusion under these controlled conditions produced little change in the cardiac rate, 7 increased, 2 decreased and 3 remained unchanged.

Acetylcholine effected a profound and instantaneous reduction in cardiac rate. The contractions during the period of acetylcholine effect were of ventricular origin. The auricle showed no contractions in most preparations but in a few there was auricular flutter. Following injection of atropine and reinstitution of circulation, sinus rhythm and preocclusion rates were rapidly obtained.

The usual pattern for cardiac recovery was: 1. auricular flutter with a variable ventricular rhythm, 2. various lessening degrees of partial heart block and 3. normal sinus rhythm. This was usually accomplished within 2 to 3 minutes, occasionally within 30 seconds. The ventricular contractions from the beginning were of good quality and produced adequate blood pressure (with the exception of dog 124). Throughout the procedure the heart remained pink and appeared far more normal than a similarly occluded, but unprotected heart. Withholding the atropine (for 15 minutes post occlusion in Dog #594) showed a prolonged period of heart block with sinus rhythm returning 2 minutes after the atropine was given.

The usual pattern of the electrocardiogram through the various phases of temperature

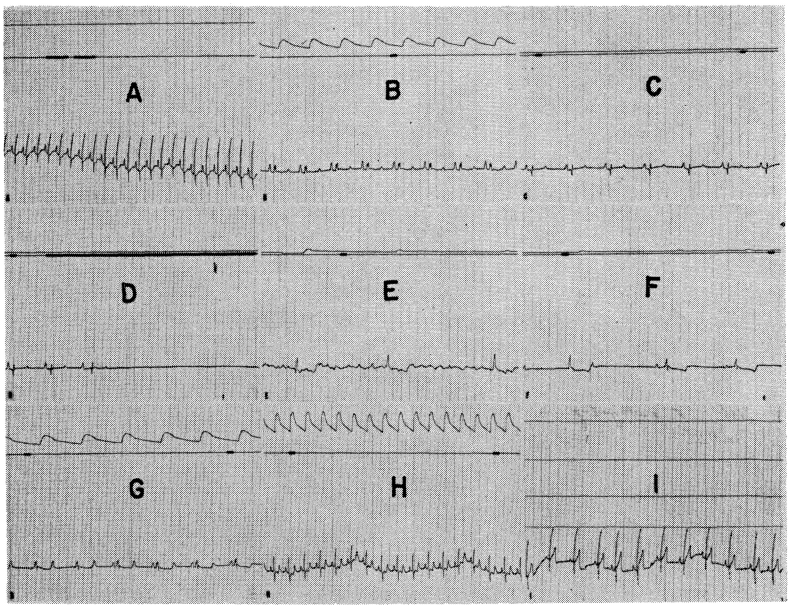

FIG. 1. Lead II electrocardiogram and blood pressure recording of Dog #466. (A) Preoperative, (B) hypothermic (25°C), (C) occlusion, (D) occlusion and acetylcholine (100 mg), (E) release of aortic and superior vena cava occlusion following atropine (0.6 mg), (F) reversion to normal sinus rhythm from heart block within 45 sec., (G) normal sinus rhythm with normal blood pressure 2 min. 12 sec. following atropine, (H) rewarming (37°C), and (I) three wk post-operatively.

change, occlusion only, occlusion with acetylcholine, atropine effect and return is shown in Fig. 1.

Two dogs with relatively high cardiac rates during the acetylcholine occlusion period showed a ventricular rhythm with some periodicity and this was not affected by a second injection of intracoronary acetylcholine.

A major complication has been an unusually high incidence of postoperative and post rewarming pneumothorax, and this has been the cause of a number of deaths. Since no atropine or similar drug has been used (because it would block the acetylcholine effect), there have been more tracheobronchial secretions than usual. This permits persistence of any air leaks. With the use of periodic tracheal suction, avoidance of high pressures when inflating and expanding the lungs, and temporary catheter chest drainage, this complication has been largely surmounted.

Three animals were studied under similar circumstances at normal temperatures (Table IB.). Again it was noted that circulatory occlusion alone had no consistent effect on the cardiac rate. Following injection of acetylcholine the heart was stopped in 2 animals and markedly slowed in the third. This effect was short-lived. The rates increased dramatically in the second and third minutes of occlusion and rapidly returned to normal sinus rhythm without the use of atropine.

Discussion. This study is the fruit of a search(6) for a method to protect the occluded heart by slowing or stopping it in a safe and reversible manner. This method has made it far easier to work within the various cardiac chambers and surprisingly simple to work directly with the coronary arteries.

A perusal of the methods of "desensitizing" the hypothermic heart shows that they have one common effect, namely, slowing the cardiac rate. It is probable that the anti-fibrillatory effect of these methods is merely the result of having protected the heart by slowing it during the period of occlusion. Furthermore, the only real success to date with extreme low temperatures in non-hibernating animals has been that of Niazi and Lewis(5) which was associated with an induced arrest at 13-16°C.

Bjork(7) used acetylcholine unsuccessfully

in attempting to stop the locally cooled heart. This failure is probably related to the use of scopolamine prior to surgery.

Conclusions. 1. Total circulatory occlusion alone does not slow the rate of the normothermic or hypothermic heart. 2. Intracoronary acetylcholine will profoundly decrease the cardiac rate in the occluded heart. The duration of this effect is short at normal body temperatures but quite prolonged during hypothermia (24-27°C). 3. Intracoronary atropine readily reverses the acetylcholine effect on the heart. 4. Cardiac slowing or arrest affords an added protection to the hypothermic heart during total circulatory occlusion.

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Rectal Administration of Warfarin (Coumadin) Sodium. Sodium [3(2-acetonyl-benzyl)-4 hydroxycoumarin]. (22382)

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Considerable experience has accrued with the use of warfarin sodium, the salt of 3-substituted - 4 - hydroxycoumarin, administered orally and intravenously in anticoagulant therapy(1-6). The drug is effective when given by either route and produces a significant prolongation of the prothrombin time in 12 to 16 hours, usually reaching therapeutic levels in 20 to 24 hours. A single dose usually reaches and maintains therapeutic levels in anywhere from 1 to 7 days and achieves a peak effect in 2 days. However, there are occasions when it may be desirable to use another route of administration if feasible. Both methods have their limitations, and rectal administration of the drug would be advantageous under certain circumstances. Experience with the rectal administration of bishydroxycoumarin (Dicumarol) has been limited to that of Meyer and Spooner(7). They reported an occasional significant decrease in the coagulability of the blood which was irregular, however; hence the route proved impractical.

Experience with the use of warfarin (Coumadin) sodium suppositories in 23 patients is the basis for this report. The suppositories contained 100 mg in a polyethylene glycol base.*

Methods. Preliminary studies were performed on 3 groups of patients to determine the latent period and the hours required to achieve the therapeutic level of 25 to 17 seconds (20 to 40% of normal). All prothrombin determinations were made by the one-stage method of Quick with the use of Difco thromboplastin (rabbit brain). Prothrombin times were determined for group A patients 12 and 18 hours after receiving suppositories. Group B patients had prothrombin determinations at 24 and 30 hours, and groups C and D patients at 18 and 24 hours. In each group daily prothrombin times were subsequently measured until they returned to normal or the patient was discharged from the hospital. It soon became apparent that the latent period was more than 12 hours and less than 18 hours, and, consequently, most of the patients had initial prothrombin determinations at 18 and 24 hours. The 19 patients comprising ex-

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