EXPERIMENTAL AND CLINICAL RESULTS WITH CONTROLLED HYPOTHERMIA

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When submitted to refrigeration, the human being may react in two different ways. First, the expression of normal reactivity, he behaves like a typical homothermal animal, showing first an increase of short duration in the body temperature, then a decrease, and finally exhaustion and death. Second, the case may be epitomized by the soldier who, worn out by fatigue, falls asleep in the snow while his body gets cooler, like any inert physical body. His death is due to the loss of all nervous association, hypoxia, ventricular fibrillation, "cardiac crisis" [Bigelow et al. (1)], inadequate coronary flow [Hegnauer et al. (2)], and progressive prolongation of diastole, which ultimately becomes infinite. The pathological picture shows congestion of meninges and brain, and intestinal, pleural and subendocardial ecchymoses [Hegnauer et al. (3)].

We studied the effects of refrigeration speed and of rewarming speed (different techniques have been proposed), working on a group of 60 guinea pigs (fig. 1, A and B). Thirty animals, divided into 3 groups of 10 each, were refrigerated to a rectal temperature of 20 C., in a period of about fifteen, thirty, and forty-five minutes, respectively. They were then transferred to a surrounding temperature of 37 C. Every animal of the first group (refrigerated fifteen minutes) reached the previous rectal temperature in about five hours, while the animals of the second group (refrigerated thirty minutes) and the third group (refrigerated forty-five minutes), during the same period of five hours reached a rectal temperature of 33 C. and 30 C., respectively (fig. 1, A). One animal of the second group and 2 animals of the third group died during the rewarming phase. The remaining 30 animals, divided into 3 groups of 10 each, were refrigerated quickly (about fifteen minutes), all under the same conditions, to a rectal temperature of 20 C., and then transferred to a surrounding temperature of 15 C. (first group), 21 C. (second group), and 37 C. (third group), respectively. All animals of the first group died within 75 minutes of refrigeration; all animals of the second group died within 165 minutes of refrigeration, while all animals of the third group survived, reaching their own previous rectal temperatures in about five hours (fig. 1, B).

These results seem to support the previous observations of Hegnauer et al. (3); Killian (4); Allen (5); Wayburn (6); and others, that

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survival of low temperatures is related directly to refrigeration speed as well as to rewarming speed.

Allen (7) demonstrated that isolation of parts of the body by excision or ligation introduces 3 changes: (1) the usual defense reactions and the injuries resulting from their breakdown are abolished; (2) the resistance to reduced temperatures is thus increased greatly; (3) the usual inverse law of survival (increasing degrees of cold reduce time of survival) becomes changed to a direct ratio—that is, increasing degrees of cold prolong time of survival up to a point. It is possible to achieve such a situation with the whole organism by means of the
methonium compounds that, by inhibiting the postganglionic transmission of impulses, both adrenergic and cholinergic: (1) prevent vascular stasis by the intravascular agglutination of erythrocytes (sludged blood) along with vasospasm [Bigelow et al., (1)], and (2) open the whole capillary bed (the precapillary sphincters and the meta-arterioles), allowing a better exchange between the cells of the extravascular tissues and the mobile oxygen-carrying erythrocytes.

From the foregoing considerations it was our contention that the use of hypothermia is enhanced by the addition of ganglion-blocking agents.

**Experimental Data**

A total of 285 guinea pigs and 112 dogs was used. The animals were divided into 2 main groups, both refrigerated in an ice bath. The first was treated by refrigeration alone, [while the second was treated by refrigeration preceded (about thirty minutes) by an intravenous injection of ganglionic blocker * of 0.25 mg. per Kg. of weight (Ciocatto et al., 8)].

1. **Clinical Symptoms.** In animals of the second group (refrigeration and ganglionic blockers), shivering was rare, breathing and circulation were efficient for a longer time, and cyanosis appeared later than in the first group. However, the narcosis by cold [Allen (5)] occurred at the same thermal level (23 C. to 25 C. in guinea pigs). In both groups, lethal temperatures were unaffected.

2. **Oxygen Consumption.** These studies were carried out on guinea pigs (fig. 2). Oxygen consumption is lowered at normal rectal temperature when the ganglionic blocker is injected, while with refrigeration alone an initial rise in oxygen consumption takes place. On the other hand, with the ganglionic blocking agents plus refrigeration, oxygen consumption diminishes more rapidly than with refrigeration alone, both groups reaching similar values (about one-sixth of the precooling control level) at temperatures below 23 C.

It is important to point out that oxygen consumption varies directly with the shivering response, but, below 23 C., shivering is no longer a factor [Penrod (9)]; furthermore, tissue oxygen deficit does not develop during the period of cooling [Bigelow et al. (10)], since the shift on the oxygen dissociation curves to the left is enough to maintain a normal arterial saturation with oxygen [Dill et al. (11)].

3. **Cardiac Activity.** Most accidents in hypothermia are due to cardiac failure. Adolph (12) found that heart-beat frequencies bore diverse relations to body temperatures (the relation tends to be linear in adults and exponential in infants), while Rosenhain et al. (13) and Hegnauer et al. (14) demonstrated that circulation and cardiac oxygenation are adequate at all temperatures to the point of asystole or to a short time before final collapse.

*Pendimiod, reported to be N,N,N',N'-3-pentamethyl)-N,N'-diethyl-3-azapentylene-1,5-diammonium dibromide.*
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Through our researches on the variations of the cardiac output, blood pressure, and central venous pressure in dogs, we achieved results similar to those of Bigelow et al. (1).

After an initial rise, the cardiac output diminishes progressively (about 20 cc. per Kg. of weight at 20°C.). Likewise, the blood pressure first undergoes a sudden increase, a decrease follows, then it stabilizes; finally, it falls again to its lowest level. The central venous pressure, as well as the peripheral venous pressure, after an initial fall, rises again, thus impairing the work of the heart.

![Graph showing oxygen consumption on guinea pigs under hypothermia.](image)

**Fig. 2.** Oxygen consumption on guinea pigs under hypothermia (FOA-Capraro apparatus). Average of oxygen consumption for 15 minutes:
- - - : first group (refrigeration alone).
- - + - : second group (refrigeration and ganglionic blockers).

Many authors [Fairfield (15); Bigelow et al. (1); Meda (16); Crisman (17); Prec et al. (18); Hoff et al. (19); Lange et al. (20); Killian (4); and others] studied the effects of hypothermia on the electrocardiogram, working on different animals as well as on human beings, and achieving about identical results which can be summarized as follows:

(a) The rate of the heart beat decreases linearly with the decrease in body temperature.

(b) The relationship "length of cardiac cycle or length of systole," which at normal temperature is 2 to 1, gradually increases to above 3 to 1, the longer duration being due mostly to diastole.
(c) Both the P wave and the P-R interval increase their length.
(d) The duration of QRS complex is first unaltered; afterwards it
lengthens, but only at pre-death temperatures.
(e) The RS-T segment and the T wave also lengthen: the more con-
stant change of T is a flattening; afterwards it becomes inverted.
(f) During the initial period of refrigeration, there is a sinus
rhythm, but AV block or fibrillation appear around death temperatures.
(g) In the main, therefore, the electrocardiographic portion which
undergoes less changes than any other is the QRS (intraventricular
conduction).

The most important thing to be pointed out recording the cardiac
activity under hypothermia is the possibility of stopping blood circu-
lation and performing an intracardiac operation in an open field with
a reasonable safety [Bigelow et al. (21-23); Juvenelle et al. (24, 25);
Ciocatto et al. (8); Dogliotti et al. (26); Laborit et al., (27); Swan et
al., (28, 29); Cookson et al., (30); Boerema et al. (31); Delorme (32);
McQuiston (33); Bobbio (34); Cocchia et al. (35) and others].

Intimately connected with the intracardiac surgery under hypo-
thermia is the problem of ventricular fibrillation. According to Swan
et al. (28), there are 3 periods during the hypothermic condition when
the animals are prone to develop ventricular fibrillation: during cool-
ing below 26 C., during cardiac manipulation, and immediately fol-
lowing restoration of circulation after occlusion. Juvenelle (24) has
also pointed out a "cardiac crisis" during the rewarming phase.

Fibrillation has been ascribed to many factors: trend toward acido-
sis, fall in serum potassium, augmentation of the peripheral resistances,
and anoxia. Several treatments therefore have been proposed: cardiac
defibrillation together with use of an artificial oxygenator [Juvenelle
et al. (25)], use of an artificial pacemaker [Bigelow et al. (21)], infil-
tration with Xylocaine® of the sinus node [Huguenard (36)], infusion
of K solutions, hyperventilation to combat CO2 excess after release of
occluded circulation, calcium, and heart massage [Swan et al. (28)],
use of adrenolytic agents before the venae cavae are unclamped to
counteract the epinephrine which has accumulated during occlusion
[Cookson et al. (30)].

In connection with this problem, our experience indicates that fibril-
lation is almost solely responsible for the death of animals during the
processes of both refrigeration and rewarming, and that once fibrillation
has taken place all the means that have been suggested are often
ineffectual.

We performed cardiac operations (opening of ventricles) in 45 dogs
in which the arrest of blood circulation was attained by occlusion of
the venae cavae, pulmonary artery, or pulmonary vein. About fift
teen minutes before the operation, 15 dogs received a dose of Pendi
omid, intravenously, of 0.25 mg. per Kg. of weight, as done previously
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by Dubost et al. (37). In this group, the occlusion of circulation lasted for five to twelve minutes, but 7 animals died: 2 from hemorrhage, 2 from ventricular fibrillation, and 3 in which no cardiac activity resumed on reopening the circulation.

Fifteen dogs of a second group were quickly (about thirty minutes) refrigerated to a rectal temperature of 25 C. Surgery was begun when the rectal temperature reached 28 C. In this group, the occlusion of circulation lasted for four to nine minutes, but 8 animals died: 6 from ventricular fibrillation (4 during intracardiac manipulation and 2 during the rewarming phase when the rectal temperature was about 29 C.); 1 from hemorrhage (at a rectal temperature of 26.7 C.); and 1 from cardiac standstill during the opening of the chest wall (at a rectal temperature of 27.9 C.).

Fifteen dogs of a third group received intravenously 0.25 mg. of Pendimiod per Kg. of weight. After fifteen minutes, they were quickly (about thirty minutes) refrigerated to a rectal temperature of 25 C. Surgery was begun when the rectal temperature was about 28 C. In this group, the occlusion of circulation lasted for five to twenty-one minutes, and only 2 animals died: 1 from hemorrhage and the other when no cardiac activity resumed upon reopening the circulation. In no case did ventricular fibrillation develop.

From these experimental data it seems reasonable to point out that: (a) refrigeration plus ganglionic blockers produces better results than either of these agents alone; (b) with this technique, cardiac disturbances, so frequent otherwise, are almost absent; and (c) the mortality ratio is maintained within reasonable limits.

4. Resistance to Infections. Another important problem related to hypothermia is resistance to infections, and we (Ciocatto et al. (38)) studied the behavior in dogs, at 25 C., of: (a) complement power of serum; (b) opsonic power of serum; (c) lysozyme power of serum; and (d) microbicidal power of whole blood. On the basis of these data, we may conclude that there are no essential changes in serologic defenses and resistance to infections (5).

CLINICAL DATA

From September, 1952, to August, 1954, 91 patients from the Departments of Cardiac Surgery and Neurosurgery were submitted to surgical treatment. Six patients with a diagnosis of patent ductus arteriosus were corrected surgically by ligation and division. All except one were males ranging in age from 6 to 12 years. Hypothermia ranging from 27.3 C. to 31.3 C. was employed, and all survived. Twenty-four patients with a diagnosis of tetralogy of Fallot and ranging in age from 4 to 25 years were subjected to either Blalock's or Potts' operation. The hypothermic range was from 25.8 C. to 27.1 C. One patient following a Blalock procedure died 36 hours postopera-
tively of cerebral thrombosis. Six patients suffering from pulmonary stenosis were subjected to valvulotomy (Brock’s procedure), utilizing hypothermia. One cardiac arrest responded to cardiac massage, and all this group survived. Five patients ranging in age from 8 to 25 years underwent resection and homografting without a fatality. Two patients required mitral commissurotomy and they were treated successfully during maintenance of hypothermia. The remaining patients in our series of 91 for whom hypothermia was produced underwent neurosurgical procedures for removal of brain tumors or, in 3 instances, for aneurysm of the anterior cerebral artery. Hypothermia was utilized in a range from 25.7 C. to 30 C. Two patients died; one fourteen hours and the other thirty-six hours postoperatively following cerebral vascular accidents.

The current management consists of the following measures:

1. Two hours before surgery, the patient is given, intramuscularly, 0.50 mg. per Kg. of weight of an antihistaminic (usually: Fargan†; diethyl-amino-2-methyl-1-ethyl-X-dihenyl-paraflhiazine), thus obtaining a certain hypnosis, and preventing the histamine-like effects of refrigeration.

2. One hour before surgery, the patient is given, intravenously, 0.25 mg. per Kg. of weight of a ganglionic blocker (usually: penidionid ‡), thus inhibiting postganglionic transmission of impulses. No hypotension or mild degree of hypotension (10-15 mm. Hg) results.

3. Forty-five minutes before surgery, refrigeration starts. Generally, the temperature drops to 28 C. within half an hour. Sometimes, but rarely, there are shivers and then it is necessary to give the patient Pentothal®. However, during all the subsequent phases of the procedure, oxygen only is administered.

4. Rectal temperature of about 27 C. usually is reached in about forty-five minutes, and the refrigeration is then stopped.

5. When the main surgical steps (anastomosis, resection, and so forth) are done, rewarming is begun.

6. Adequate blood replacement during surgery is governed carefully.

7. The postoperative period runs as usual; rarely does fever appear and it may be considered as a compensatory phenomenon representing a specific reaction to hypothermia [Grosse-Brockhoff et al. (39)].

From our clinical experience we may point out that:

1. There are no age limits to this procedure, though children and adults react in different ways to refrigeration (quicker lowering of temperature in children) and, on the other hand, the general condition of the patient plays an important role since obesity is a severe obstacle to the lowering of body temperature.

2. The indications for controlled hypothermia are represented by all those surgical conditions in which the blood supply to the vital or-

† Fargan: Farmitalia, S. A., Milano, Italy.
‡ Penidionid: Ciba, I. C. Milano, Italy.
gans must be interrupted for some time, and in which the operation can be performed only under such a situation (certain intracardiac abnormalities that demand accurate visualization of structures within the heart for a period sufficient to permit corrective measures, certain aneurysms of the upper thoracic aorta, and so forth). Hypothermia can be applied satisfactorily also in those conditions in which hypoxia is severe (surgical treatment of certain congenital heart diseases, removal of certain tumors of the brain, etc.) and even may be successful as a treatment of hyperthermic conditions.

3. The hypothermic condition is endured favorably for long periods of time (more than seven hours in some neurosurgical cases).

4. The mortality with this technique is low (3 deaths out of ninety-one patients).

5. The frequency and the seriousness of accidents (fibrillation, cardiac arrest, and so forth) pertaining to cardiac surgery are diminished greatly. We noticed only 1 case of cardiac standstill in a boy, 11 years old, during the surgical correction of pulmonic stenosis. The standstill lasted for about eight minutes, but the patient recovered with cardiac massage only and the postoperative period was normal.

6. Fuhrman et al. (40), Callaghan et al. (41), Chatfield et al. (42), Himwich (43), Fazekas et al. (44), Cate et al. (45), Wayburn (6), and others studied the influence of low temperatures on brain activity.

The changes in the central nervous system include loss of consciousness, loss of memory, irrational behavior and sometimes amnesia, while the electrical activity of the brain disappears at a body temperature of 18 C. to 20 C. Furthermore, upon rewarming, full recovery takes place without evidence of cerebral damage.

7. Refrigeration as well as rewarming performed as quickly as possible adds safety to the method, and, in association with ganglion-inhibiting drugs, more rapidly reaches the hypothermic condition, avoiding also to a great extent the cardiac disturbances connected with hypothermia.

Thus is much of the experimental data confirmed.

8. We think that a rectal temperature of 27 C. to 28 C. is optimal in neurosurgical cases as well as in many surgical corrections of congenital heart diseases; however, when the blood supply to vital organs must be interrupted for a certain period of time (intracardiac surgery in open field, resection of aneurysm of the upper thoracic aorta), a rectal temperature somewhat lower (about 25 C.) is more desirable.

9. In hyperthermic conditions, satisfactory results were obtained with a lowering of the temperature to from 32 C. to 30 C.

10. The hypothermic conditions in which the lowering of temperature does not reach at least 32 C. to 33 C. seem to offer no real advantage to the usual anesthetic procedures without hypothermia; and, on the other hand, temperatures below 25 C. only impair the safety of method.
11. Besides the good results already obtained, it must be said that more precise information on the physiology of hypothermia is necessary.

**Summary**

Controlled hypothermia is helpful in some surgical conditions in which the blood supply to vital organs must be interrupted for a certain period of time; and in many others in which hypoxia is severe.

The most common accidents pertaining to the hypothermic condition are represented by cardiac disturbances, primarily ventricular fibrillation.

Safer hypothermia is achieved when low body temperatures are reached quickly and the refrigeration is associated with the use of ganglion-inhibiting agents (methonium compounds).

More precise information on the physiology of the hypothermic conditions is necessary.

**References**


36. Huguenard, P.: Personal communication to the authors.