Myocardial Failure in Experimental Hypothermia

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Hypothermic animals subjected to total venous inflow occlusion and open cardiotomy develop elevations in right atrial mean pressure and postmortem evidences of myocardial failure. Acetyl strophanthidin, given before inflow stasis, prevented myocardial failure and increased survival. Myocardial failure was attributed to anoxia resulting from decreased coronary blood flow and alterations in the oxygen content of the blood supplying the myocardium. Perfusion of the coronary system with small quantities of oxygenated blood obtained from donor animals permitted open cardiotomy with survival.

THE reduction in metabolism that accompanies hypothermia affords substantial protection to the central nervous system during periods of complete interruption of the circulation. The myocardium however, seems less able to tolerate interruption of its circulation, particularly when cardiotomy is performed. The present study was undertaken to investigate this aspect of experimental hypothermia.

METHODS

Seventy-three mongrel dogs weighing 8-20 Kg. were anesthetized with 2.5 per cent sodium pentothal administered intravenously and an endotracheal tube was inserted. The dogs were hyperventilated throughout the procedures with 100 per cent oxygen furnished through a demand valve respirator. Hypothermia was induced by immersion in an ice and water bath. During cooling, small supplemental doses of pentothal were given to prevent shivering.

When the rectal temperature was 30 C, the animal was removed from the ice bath. Using sterile technic, a right thoracotomy was performed through the fourth intercostal space, and the venae cavae and azygos vein isolated. By this time the rectal temperature had fallen to approximately 28 C. The venous inflow was occluded for 8 min. during which time a 4 cm. incision was made in the right ventricle. One or two sutures were placed and tied in the interventricular septum. The ventriculotomy was closed toward the end of the occlusion period. The superior cava was then released, and within 2 min. the inferior cava. The thoracotomy was closed at which time the rectal temperature was usually 25 C. The animals were warmed to 36 C. in a water bath maintained at 42 C.

Four groups of animals were used. Groups 1 and 2 consisted of 20 dogs each. In both groups, right atrial and aortic pressures were recorded before and after inflow occlusion. Base line pressure records were made with the transducers at the level of the right atrium. Mean right atrial pressure was determined by planimetric integration. Group 2 differed from group 1 only in that the animals were given .15 mg. of acetyl strophanthidin intravenously. Three .05 mg. doses of the drug were given at 5 min. intervals beginning 15 min. before inflow occlusion.

Group 3 consisted of 15 animals studied in order to estimate the changes in coronary sinus flow before and during venous inflow occlusion. In this group, ventricular fibrillation was prevented by infiltration of the superior atriocaval junction with 1 per cent procaine. After cooling, a right thoracotomy was performed and the right atrium was opened during a short period of inflow occlusion. A polyethylene catheter was inserted into the orifice of the coronary sinus and held in place with a purse-string suture. The atrial wall was closed about the catheter which was drained into a graduated centrifuge tube and normal circulation re-established. This catheterization procedure was completed within 2 min. The end of the catheter was leveled to prevent siphoning.

The flow and oxygen content of the coronary sinus blood was determined with and without circulatory occlusion. Simultaneously, 3 ml. of blood were taken every 2 min. from the ascending aorta and analyzed for oxygen content. All animals were studied utilizing the previously described standard operation, but with 10 min. of circulatory occlusion.

Group 4 contained 8 animals (weight 10-12 Kg.) cooled in the manner described and subjected to the standard operative procedure. During the period of inflow occlusion the coronary circulation was perfused with arterial blood collected from a donor animal. The blood was cooled to the temperature of the recipient, and delivered by gravity from a transfusion bottle through a polyethylene tube into the proximal aortic segment. The aortic segment was isolated by applying a Rumelt tourniquet around the tube and aorta proximal to the brachiocephalic artery.

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RESULTS

Groups 1 and 2

A comparison of the results in these animals is made in Table 1.

Mortality. Fourteen of the 20 animals in group 1 (70 per cent) and 7 of the 20 animals in group 2 (35 per cent) died within 24 hours following the operative procedure. Eight of the animals in group 1 died after rewarming and 6 died before being rewarmed. Necropsy in the former revealed distension of the venae cavae and fluid in the pleural cavities. Grossly, the lungs were congested and microscopic examination showed intense venous engorgement with alveolar edema. The hearts were dilated, especially the right ventricles and marked flabbiness of the ventricular musculature was noted. The 6 animals in group 1 that died during the rewarming period had dilated and flabby hearts without associated pulmonary congestion.

The 7 deaths in the 20 animals receiving acetyl strophanthidin (group 2) occurred after rewarming. Necropsy findings in these animals also indicated vena caval distension, dilation of the cardiac chambers and pulmonary venous engorgement.

Six animals of group 1 and 13 of group 2 were chronic survivors and exhibited no obvious neurologic or cardiovascular abnormalities.

Right Atrial Mean Pressure (RAMP). The average RAMP before inflow occlusion was 3 mm. Hg in both groups (1 and 2). The average RAMP after inflow occlusion was 7 mm. Hg in group 1 (range 3-11 mm. Hg) and 4.2 mm. Hg in group 2 (range 3-9 mm. Hg). The pressures in the group receiving acetyl strophanthidin tended to be consistently lower than those in group 1. Statistical analysis of the individual values indicated that the differences were significant ($p < .01$).

All of the animals in group 1 demonstrated an increase in RAMP after release of inflow occlusion. The average pressures in those that died was 8.2 mm. Hg and 5.5 mm. Hg in the survivors.

Only 4 animals in group 2 demonstrated an increase in RAMP after inflow occlusion. These 4 died during rewarming. The remaining 3 animals that died did not show an increase in RAMP after release of inflow occlusion. There was no correlation between survival and body weight in the animals in group 2.

Ventricular Fibrillation. Eighteen of the animals in group 1 (90 per cent) and 9 in group 2 (45 per cent) developed ventricular fibrillation. This arrhythmia occurred only during inflow occlusion and usually began when the right ventricle was incised or when a suture was placed in the interventricular septum. All the hearts were defibrillated with massage and electric shock. Five of the 6 survivors in group 1 and 5 of 14 survivors in group 2 developed ventricular fibrillation.

Group 3

Figure 1 depicts the changes in coronary sinus flow and oxygen saturation of coronary sinus and aortic blood before and during inflow occlusion.

Prior to venous inflow occlusion, the average
coronary sinus flow was 12.5 ml./min. in the 15 animals studied. Two minutes after inflow occlusion, the coronary sinus flow decreased to an average of 3.5 ml./min. and was maintained near that level throughout the remainder of the period of occlusion.

The average oxygen saturation of the coronary sinus blood before occlusion was 40 per cent. Two minutes after occlusion the saturation approached 0. The average oxygen saturation of aortic blood before venous inflow occlusion was 100 per cent. Throughout the period of occlusion there was progressive desaturation of the blood and at the end of 10 min. the average oxygen saturation had fallen to 40 per cent.

**Group 4**

The coronary arteries of the 8 animals in this group were perfused with varying amounts of arterial blood obtained from donor animals. The coronary arteries of 2 of the animals were perfused for 17 min. with 12 and 16 ml./min. of donor blood. Both showed marked cardiac dilatation and inability to maintain arterial blood pressure following restitution of normal circulation. Death occurred in both before rewarming.

The coronary circulation of the remaining 6 animals were perfused with 25 to 35 ml./min. of donor blood. The period of inflow occlusion with perfusion ranged from 16 to 20 min. All 6 survived without sequelae. Two of these demonstrated slight elevations of right atrial mean pressure after release of the circulation. Pressures returned to normal after giving .15 mg. acetyl strophanthidin to each.

**Discussion**

The high mortality (70 per cent), elevations in RAMP, and postmortem findings in the animals of group 1, indicate that hypothermia with cessation of circulation for 8 min., is associated with myocardial failure. Although the elevations of RAMP noted after release of inflow occlusion were not marked, the changes were significant. The drastic reduction of cardiac output consequent to hypothermia is probably responsible for the lack of marked increments in RAMP. Sabiston, Theilen and Gregg have noticed a progressive decline in venous pressure as cardiac output and body temperature are lowered. Vena caval distension, pleural effusion, passive congestion of the lungs and flabbiness of the ventricular musculature further support the presence of myocardial failure.

Sixty-five per cent of the animals that received acetyl strophanthidin survived and none showed an elevation of RAMP. Four of the 7 animals that died had elevations of RAMP but 3 did not, suggesting that other factors may be responsible for death. Acetyl strophanthidin exerts a digitalis-like effect within 5 to 15 min. and is dissipated within 2 hours. A longer acting digitalis preparation might therefore have been more effective. The data, however, indicate that short term digitalization enables the myocardium to withstand temporary anoxia and if a normal functional state is maintained further digitalization is not essential. It is also apparent that the digitalis preparation decreased the incidence of ventricular fibrillation. Therefore, the arrhythmia may be due in part to myocardial failure. Data supporting this idea have been contributed by Bigelow who noted restoration of sinus rhythm after withdrawing small amounts of venous blood from hypothermic dogs with ventricular fibrillation.

The observations made in the animals of group 3 indicate that the coronary arteries are perfused when the venous return to the heart is stopped. The volume flow from the coronary sinus during venous inflow occlusion was one-third the amount noted before occlusion. In addition, the oxygen saturation of coronary sinus blood decreased markedly and approached 0 within 2 min. after occlusion of the venous inflow. The latter observation indicates that the myocardium is completely able to remove oxygen from the circulation during the hypothermic state. The progressive fall in oxygen saturation of aortic blood that occurred during the period of inflow occlusion is attributed to venous admixture from channels draining into the left ventricular cavity. Pulmonary venous occlusion did not
alter the above observation in 3 additional dogs and since the right ventricle was opened and the coronary sinus cannulated, the only possible source for blood to enter the left ventricle was from channels draining directly into the left ventricular cavity. It is therefore apparent that recirculation of coronary blood occurs during the period of venous inflow occlusion.

These data are interpreted to indicate that myocardial failure occurs in the hypothermic state when the venous inflow is occluded. The development of failure is secondary to myocardial anoxia resulting from reduction in coronary blood flow and alterations in the oxygen saturation of the perfused blood. Berne noted no evidence of myocardial failure in dogs cooled to 20°C without venous inflow occlusion.

A reduction in coronary blood flow consequent to lowering of body temperature has been noted. Of considerable significance, however, is the observation that although there is an absolute reduction in coronary blood flow at low temperatures, the myocardium receives a larger fraction of the cardiac output than at normal body temperature. In addition, the fall in total body oxygen consumption is greater than the fall in myocardial oxygen consumption. It would appear, therefore, that the heart does not share the overall beneficial effects of hypothermia as do organs such as the brain and kidneys.

Since myocardial function appeared to be adequate in the hypothermic state without venous inflow occlusion, it was decided to perfuse the hearts of animals with an amount of blood estimated from the coronary sinus volume collected before inflow occlusion. It was assumed that the coronary sinus drained approximately 65 per cent of the total coronary flow. The coronary circulation of 6 dogs was perfused with arterial blood from a donor animal at the rate of 25–35 ml./min. The blood that entered the left ventricular cavity was drained from a catheter inserted at the apex and thereby prevented venous admixture of arterial blood. All 6 animals survived whereas 2 animals that received 12 and 16 ml./min. died with myocardial failure following restoration of the circulation. These studies suggest that myocardial failure was prevented by the perfusion of small quantities of blood to the heart. Although there is a significant decline in myocardial work and oxygen consumption when the body temperature is lowered, it appears that a maintenance of oxygen supply is essential even when the mechanical work decreases with venous inflow occlusion. The oxygen requirements for the chemical events leading to myocardial contraction must be fulfilled even though little mechanical work is being performed.

**Summary**

Hypothermic animals subjected to venous inflow occlusion and right ventriculotomy demonstrated elevations in right atrial mean pressure and postmortem findings indicative of myocardial failure.

A rapidly acting digitalis preparation given before inflow occlusion prevented the evidences of myocardial failure in most of the animals and thereby increased survival. In addition, the frequency of ventricular fibrillation was diminished.

Myocardial failure during hypothermia appears to be due to anoxia resulting from diminished coronary blood flow and progressive oxygen desaturation of the blood supplied to the coronary arteries.

Hypothermic animals survived cardiotomy and inflow occlusion of 16 to 20 min. when the coronary system was perfused with small volumes of oxygenated blood.

**Summario in Interlingua**

Animales hypothermic, subjicite a occlusion de influxo venose e ventriculotomia dextere, manifestava augmentos del pression dextero-atrial medie e indicationes post morte de disfallimento myocardial.

Un preparato de digitalis a action rapide, administrate ante le occlusion del influxo, preveniva le manifestaciones de disfallimento myocardial in le majoritate del animales e per consequente resultava in un plus alte supervi-
ventia. In plus, le frequenta de fibrillation ventricular esseva reducite.

Disfallimento myocardial in hypothermia es apparentemente causate per anoxia resultante del reduce fluxo de sanguine coronari e del progressive dissaturation oxygenic del sanguine fornite al arterias coronari.

Animales hypothermic superviveva a cardiotorma e occlusion de influxo pro 16 a 20 minutas, quando le sistema coronari esseva perfundite con parve quantitates de sanguine oxygenate.

REFERENCES

Reliability of Experimental Determinations of the Refractory Period

The duration of the refractory period in cardiac muscle is determined by physical, physiologic and chemical coefficients. However, it is recognized by experimental investigators that quantitative determinations of refractoriness and recovery of excitability may be altered by effects of electric stimuli on responsiveness of cardiac muscle.

Three procedures have been used to evaluate the duration of the absolute refractory period of cardiac muscle: (A) estimation of the maximal rate of stimulation to which it responds, (B) determination of the minimal interval between a driving and an effective testing stimulus, (C) measurement of the minimal interval between responses to these stimuli.

Using isolated atria of guinea pigs and rabbits, investigators at the Nuffield Institute in Oxford found that these three procedures give different values for the refractory period. The following conclusions were reached: 1. Recovery of excitability measured by procedure A is much slower than when estimated by procedure B. 2. Using procedure B, the refractory period increases with the number of test stimuli interpolated in a series of driving stimuli. It may either increase or decrease as the frequency of the driving stimulus becomes greater. 3. An increase in the strength of the driving stimulus causes an apparent reduction in refractory period by decreasing the latency of response.

Several arguments suggest that the interval between responses (procedure C) may give a better indication of the recovery of excitability than the interval between the driving and testing stimuli. These are: 1. One would hardly expect an increase in strength of a driving stimulus to accelerate recovery. But factually this reduces the refractory period as measured by procedure B and does not alter it as measured by procedure C. 2. Use of procedure C reduces the relatively refractory period at the expense of the absolute refractory period and the slope of the recovery curve becomes more rapid.

In studying the effects of drugs, procedures B and C are both useful in giving evidence, as to effects on latency and on recovery of excitability respectively.

For details see G. S. Dawes and J. R. Vane. J. Physiol. 132: 611, 1956.
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