Cardiac Resuscitation and Neurologic Tolerance to Anoxia

By Raymond C. Read, M.D., C. Walton Lillehei, M.D. and Richard L. Varco, M.D.

Complete inflow stasis of the heart was associated with less central nervous system damage, if the heart was resuscitated with massage. Ventricular fibrillation did not occur during the period of circulatory arrest, but it was seen occasionally after the heart filled. Its incidence was increased by the use of Adrenalin and by allowing the heart to recover without massage. The administration of various doses of heparin had no effect on the degree of brain damage resulting from interruption of the circulation.

Recently it has been suggested that the period of brain tolerance to circulatory arrest could be extended by the use of heparin. We set out to test this observation because of its possible clinical application to intracardiac surgery. Two years previously in our laboratory a study was made of the tolerance of the canine heart to venous inflow occlusion. This work was used as the basis for the present investigation. However, in order to evaluate the limits of brain tolerance to ischemia without circulatory after-effects due to cardiac anoxia, the heart was massaged until it had recovered from the arbitrary period of circulatory arrest. Preliminary studies with this change in experimental conditions revealed an increase in the central nervous system tolerance when compared to the previous work. An attempt was then made to define more closely in a larger series of dogs the protection conferred by immediate cardiac resuscitation. In later groups, observations were made on the effects of heparin and ventilation with oxygen in this experimental preparation.

METHODS

All studies were made on apparently healthy mongrel dogs obtained from the pound. These animals were unselected except for age; only dogs with their adult dentition being used as puppies are known to differ from the mature animal in their response to anoxia. The anesthesia consisted of a preoperative dose of both morphine sulphate 4 mg./Kg. and atropine 0.1 mg./Kg. followed by intermittent amounts of two and one-half per cent sodium pentothal given intravenously. All animals were intubated with auffed endotracheal tube and manual respiration was performed through a closed system using a standard carbon dioxide absorber. Under sterile technic the right chest was entered through the fifth interspace. The azygos vein was ligated at its juncture with the superior vena cava which with the inferior vena cava was then looped with umbilical tape. These tapes were threaded through short lengths of rubber tubing which could be slid down giving a reversible occlusion of the great veins. For five minutes before occlusion, the animal was ventilated with 100 per cent oxygen. The venae cavae were then occluded for a predetermined interval timed with a stop watch. Following the period of circulatory arrest the dogs were resired with oxygen which in the earlier studies was also administered during occlusion as carried out by Cohen and associates. The hearts were immediately massaged to avoid dilatation and to insure a prompt return of the circulation. Massage was continued until an effective beat appeared which generally coincided with the onset of reactive hyperemia in the myocardium. Fibrillation of the ventricles if it occurred was treated with massage, Adrenalin 1:10,000 solution, and shocks from the electric defibrillator (150 volts). In a few of the animals 5 ml. of 1:10,000 Adrenalin was injected into the right atrium at the end of the occlusive episode to help in cardiac resuscitation. During the postoperative period the dogs were given antibiotics. They were examined after a recovery period of 36 hours for gross residual signs of brain damage such as blindness, paralysis, ataxia or spasticity, but no attempt was made to perform complete neurologic examinations or to evaluate psychic effects. Autopsy examination was performed on all animals either when they died as a result of the occlusion or later when they were sacrificed.
Results

Ninety-six dogs were subjected to from 6 to 10 minutes of total venous occlusion, the great majority experiencing at least eight minutes of circulatory arrest. All except two, who died from technical errors, survived the procedure.

Cardiac Effects: The early cardiac effects have been described previously. Ventricular fibrillation did not occur during the period of occlusion which extended in most cases to ten minutes. However, only rarely did it seem possible that the heart would be able to survive and not fibrillate without massage when the tapes were released. This impression was reinforced by the finding that in four consecutive animals fibrillation did occur routinely following 8 minutes of venous occlusion not supplemented with cardiac massage. Fibrillation occurred during the immediate post occlusion period in 8 of the 92 dogs resuscitated with cardiac massage. It was successfully treated in all cases. Ventricular fibrillation was connected with the use of Adrenalin. This drug was injected intra-atrially into nine dogs at the end of the occlusive period to help cardiac resuscitation. Four of these dogs fibrillated. Because of this experience its use was given up. Fibrillation was not seen among the last 36 animals operated on.

Incidence of Brain Damage: We attempted to find a period of total venous inflow occlusion which would result in a consistently high incidence of brain damage in the normal dog resuscitated with prompt cardiac massage. The effect of heparin could then be tested on this preparation.

Venous Occlusion Accompanied by Ventilation With Oxygen: Four of 11 dogs subjected to 10 minutes of circulatory arrest with continuing ventilation of their lungs sustained obvious brain damage, three of them dying as a result of these changes. The remaining members of this group survived and appeared normal.

Venous Occlusion Without Respiration: In the clinical application of venous occlusion with or without hypothermia the lungs are not ventilated throughout the procedure. It seemed of interest to determine the effect of this factor which, however, because of the total venous occlusion would probably be slight. Five of 11 animals surviving 10 minutes of circulatory interruption in this group seemed normal following the procedure. The remaining six showed various degrees of brain damage. This period of occlusion appeared ideal for analyzing any protection offered by heparin.

Three out of 12 dogs living after nine minutes of venous occlusion had obvious brain damage which, however, was transitory in two. Interference with the circulation for eight minutes resulted in 1 out of 18 dogs showing persistent brain damage. Transitive spasticity of hind limbs developed in two others. One out of five dogs had a transitory visual defect after seven minutes of venous occlusion.

Effect of Heparin: Three intravenous doses of heparin were assayed in this aspect of the study, 2 mg./Kg., 5 mg./Kg. and 10 mg./Kg. Each of these anticoagulant levels was associated with excessive postoperative bleeding and subsequent death of some of the dogs in spite of the use of protamine sulphate and blood transfusions. All but two of the animals in this group were subjected to 10 minutes of circulatory arrest. Brain damage was seen with all anticoagulant levels; four out of ten at 2 mg./Kg., 2 out of 5 survivors having 5 mg./Kg., and finally 2 out of 3 survivors receiving 10 mg./Kg. Two dogs were occluded for eight minutes with 2 mg. and 10 mg./Kg. doses of heparin. Both demonstrated brain damage, the former eventually recovered but the latter died.

Discussion

The present work demonstrates that about one out of every two dogs will survive ten minutes of complete inflow venous occlusion without permanent sequelae. The number of animals affected by this procedure is decreased somewhat by ventilation of the lungs throughout the experiment. This additional factor doubtless operates by allowing full oxygenation of the blood remaining in the heart, coronary circulation and lungs at the beginning of the occlusive episode. By decreasing to eight minutes the period during which the circulation is interrupted a uniform survival is obtained with only a rare animal suffering lasting dam-
age. However, even with seven minutes of circulatory arrest transitory neurological signs are occasionally seen. The age of these adult animals was not found to be important, senile dogs on occasions doing better than the young adult.

The procedure we used in this work was identical to that previously described by Cohen and associates except for the use of cardiac resuscitation. Whereas these previous workers found that seven minutes of cardiac exclusion resulted uniformly in brain damage our experience can only mean that the limits of brain tolerance are prolonged for a significant number of animals by prompt cardiac resuscitation. It has been recognized for a long time that it is impossible to produce brain damage in the dog with generalized anoxia alone because the animal will die of heart failure before the brain is permanently affected. With the venous occlusion procedure used in our work as well as clinically the heart although beating is empty and does not perform work. The reduction in the incidence of brain damage in this experimental preparation by the use of cardiac resuscitation demonstrates that the heart even though idling during the occlusion period is still the limiting factor in the recovery from generalized anoxia. This susceptibility of the myocardium is also reflected in the high incidence of fibrillation following release of the venous occlusion without subsequent massage. It seems as if the heart is unable to take time out for a repair whereas the higher renters of the brain may recover to a variable extent over a period of 24 to 48 hours or longer. This response is made possible by the relative resistance of the lower levels of the central nervous system to anoxia. The observed tolerance of the brain to ischemia may or may not be associated with loss of substance. It is known that the central nervous system does have a large reserve capacity and that extensive areas of the brain may be excised especially in lower animals with little outward effect.

All of our dogs with or without the administration of heparin showed a similar incidence of brain damage after circulatory arrest, the attack rate being approximately the same as achieved using maximally protective doses of anticoagulant by Crowell. Preliminary examination of the brains of some of our animals showed no evidence of cerebrovascular thrombosis or embolism. (Personal communication, Tichy, F.)

In no case did fibrillation of the ventricles ensue during the period of venous occlusion although immediately following filling of the heart this arrhythmia appeared occasionally. However, the incidence of this complication could be reduced both by preventing cardiac dilatation with effective massage and by avoiding the use of Adrenalin. These findings suggest that cardiac dilatation with stretch of the myocardium under a work load is far more important than anoxia itself in the precipitation of ventricular fibrillation. We were able to defibrillate successfully all cases of ventricular fibrillation even after ten minutes of occlusion. This result is similar to the findings of Welsowski and associates who showed that it is possible to resuscitate the heart from long periods of anoxia.

**Summary**

The prime interest of this study was to confirm the reported action of heparin in protecting the C.N.S. from damage during circulatory arrest. Ninety-six dogs have been subjected to from 6 to 10 minutes of complete venous inflow stasis. Two of these died during the operative procedure because of technical errors.

In four of the remaining animals, the heart was allowed to recover unassisted from eight minutes of anoxia; ventricular fibrillation ensued in all. The rest of the dogs were resuscitated with immediate cardiac massage. Eight out of the 90 members of this group developed ventricular fibrillation which, however, was treated successfully in each instance. These cases with arrhythmia included 4 of 9 dogs given, before its discontinuance, intra-atrial adrenalin during occlusion in an attempt to help the later cardiac resuscitation. The previously described 75 per cent incidence of brain damage, following six minutes of occlusion, was not found to occur when immediate cardiac resuscitation was used to avoid the circulatory after effects of cardiac anoxia. Under these conditions about half of the dogs...
survived 10 minutes of venous inflow occlusion without permanent neurologic sequelae.

Ventilation of the lungs with oxygen during the period of inflow stasis resulted in an insignificant improvement in the number of animals without central nervous system changes.

Reduction in the length of the occlusive episode decreased the incidence of brain damage. At eight minutes, only 1 out of 17 animals experienced permanent changes while at seven minutes or under, only an occasional transitory nervous effect was seen.

The action of heparin was assayed in dogs having 10 minutes of circulatory arrest. No significant protection to the central nervous system could be found with doses of 2 mg./Kg., 5 mg./Kg. or 10 mg./Kg. The use of heparin was associated with a significant mortality due to postoperative bleeding which could not be controlled routinely with protamine sulphate. These findings have been discussed in relation to previous work and in the light of their possible clinical application.

**SUMMARY IN INTERLINGUA**

Le objectivo principal del presente studio esseva confirmar le reportate action de heparina in proteger le systema nervose central contra damno durante arrestos circulatori. Novanta-sex canes esseva subjicite a inter 6 e 10 minutas de complete stase del influxo venoso. Duo del canes moriva durante le operation in consequentia de errores technic.

In quatro del remanente animales le corde recipieva nulle assistentia in su recuperation ab octo minutas de anoxia. Fibrillation ventricular resultava in omne iste casos. Le remanente canes esseva resuscitate per immediate massage cardiace. Octo del 90 membros de iste gruppo disveloppava fibrillation ventricular, sed isto esseva tractate con successo in omne casos. Le octo justo-mentionate casos de arrhythmia includeva 4 ex un gruppo de 9 canes que recipieva adrenalin intra-atrial durante le occlusion pro promover le subsequente resuscitation cardiace. Le previemente descriti frequencia de 75 pro cento del canes superviveva a 10 minutas de occlusion del influxo venose sin permanente sequelas neurologic.

Le ventilation del pulmones con oxygeno durante le periodo del arresto influo resultava in un negligibile melioration del numero de animales sin alterationes del sistema nervose central.

Le reduction del tempore de occlusion resultava in un reduction del frequentia de damno cerebral. Con octo minutas, solmente 1 inter 17 animales experienciava alterationes permanente, durante que con septe e minus minutas solmente alicun casos de transitori effectos nervose esseva observate.

Le efecto de heparina esseva essayate in canes con 10 minutas de arresto circulatori. Nulle significative protection del sistema nervose central esseva constatabile con doses de 2, 5, o 10 mg per kg de peso corporee. Le uso de heparina esseva associate con un significative mortalitate resultante de sangination postoperativa que non esseva subjugable per medio de sulfato de protamina. Iste constatazioni es discutite in relation a previe investigaciones e in le lumine de lor possibile applicabilitate clinic.

**REFERENCES**


Cardiac Resuscitation and Neurologic Tolerance to Anoxia
RAYMOND C. READ, C. WALTON LILLEHEI and RICHARD L. VARCO

Circ Res. 1956;4:45-48
doi: 10.1161/01.RES.4.1.45
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1956 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/4/1/45

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/