MVH Miami Valley Hospital One Wyoming Street 513/223-6192
Dayton, Ohio 45409

May 20, 1985

Applicant May 31 ...
Check No. 306030
Amount Fee Category 1C
Type of Fee Annual
Date Check Rec'd 5/31/85
Received By ...

U.S. Nuclear Regulatory Commission
Region III
799 Roosevelt Road
Glen Ellyn, Il. 60137

Reference NRC License # 34-00341-6

Dear sirs;

We would like to amend our license to include performance of isotopic studies in animals. In specific we would like to perform studies utilizing 99mTc-Macroaggregated Albumin in dogs.

In support of this request a scale drawing of our research area is included. The room where dogs are housed has large fenced enclosures, with concrete floors, each with a drain. The two enclosures farthest from the door will be used for Technetium studies and will be marked by a "Caution Radioactive Materials" sign when used. The enclosures will not be cleaned for 48 hours after the animal has last used it. They will then be cleaned by regular means and after they dry they will be surveyed with a survey meter sensitive to .1 mR/hr. For the proposed study (copy enclosed) the animals will be killed approximately 6 hours after injection of tracer, then returned to the cage after the heart has been removed. They will remain there for another 18 hours (24 hrs. after tracer injection) and then will be disposed of by incineration. At present this room is locked during off hours and this policy will be continued. A research assistant, Mr. Dan Nolan at present, is in the area at all times during working hours and controls access to the entire area. If use of isotopes other than Technetium is neccessary a separate amendment will be requested.

The animal caretaker is Mr. Dan Nolan at present and he is also the research assistant. Because of radiation exposure during fluoroscopy his exposure is monitored with a film badge. The film badge is read monthly and the results reviewed by our radiation safety officer Dr. Ruegsegger. A copy of the instructions provided to the caretaker for handling the animals, animal waste and carcasses is enclosed.

The injection of the 99mTc-MAA into the left ventricle or root of the aorta will be performed in the room labeled surgical area in the drawing. The dose will be 5 millicuries. The anesthetized dog will rest on absorbent pads to prevent contamination of work surfaces. The investigators will wear gloves at all times while handling the animals. The injection will be given under the

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supervision of Dr. Quinones. After the study is completed for the day the work area will be surveyed with a survey meter. Monthly wipes around the work surfaces and the floor will be obtained while the study is in progress. Results will be recorded and kept in the Nuclear Medicine Department.

Doses of the radiopharmaceutical will be obtained from Syncor, the commercial radiopharmacy, and will be delivered with the regular shipments to the Nuclear Medicine Department. On arrival the package will be surveyed and inspected according to our license.

Thank you very much for you attention.

Sincerely yours,

Jose D. Quinones,M.D.
Director, Nuclear Medicine

Enclosures: 3

Amendment fee attached

CONTROL NO. 7 9028

NUCLEAR MEDICINE DEPARTMENT

Instructions for handling dogs injected with radioactive materials

GENERAL PROCEDURES:

1. Radioactive materials are to be handled only by persons aware of the potential hazards of the material.
2. When handling radioactive material or animals which have received radioactive material all personnel shall wear gloveS and work on a surface covered with absorbent material.
3. Keep the work area free of material and equipment not required for the immediate procedure.
4. A survey meter will be available each time a study is performed. Monitor the hands whenever contamination is suspected and decontaminate immediately. Wash arms and hands thoroughly and recheck hands. If you have any difficulty contact Dr. Quinones EXt. 3070 or Dr. Ruegsegger Ext.3636.
5. Wear the film badge at all times while handling the animals or the material.
6. There will be no eating, drinking or smoking in the animal room or surgical area at any time during the study or while radioactive materials are in use.

SPECIFIC INSTRUCTIONS:

1. In the animal room the two enclosures farthest from the entry door only will be used for animals injected with radioactive materials.
2. When the cages are in use a sign "CAUTION RADIOACTIVE MATERIALS" will be placed in front indicating who to call for information.
3. Only one animal will be studied in one day. At the completion of the study the animal is returned to the cage and will remain there up to 24 hours after injection of the tracer. It can then be disposed of by incineration.
4. The cage should remain unused for another 24 hours then cleaned by usual procedure.
5. After the cage is cleaned please notify Nuclear Medicine to survey the cage.
6. The surgical work area should be extensively covered with absorbent material so any animal waste can be easily contained. At the end of the experiment all the absorbent material should be placed in a plastic bag, labelled and placed in front of the animal cage. After the animal is removed it may be placed inside the cage. At the time the cage is surveyed 48 hours after the experiment the bag will also be surveyed and disposed of if levels are background (< .1 mr/hr.). If not it will be stored for another 24 hours and then disposed of in regular trash.

RESEARCH PROPOSAL
SUBMITTED TO
WRIGHT STATE UNIVERSITY SCHOOL OF MEDICINE

Title: An Evaluation of DMVA on Myocardial Infarct Size in a Closed-Chest Occlusion-Reperfusion Model

Principal Investigator: Joseph P. Malone, M.D.
Mark P. Anstadt, B.S.

Department: Cardiology

Other Investigators: George R. Brown, M.D.; Jose D. Quinones, M.D.; Dan L. Meininger, M.D.; Daniel J. Nolan, B.S.

Rank of Principal Investigator: Assistant Professor

Abstract (do not exceed space provided):

Timely reperfusion of an occluded coronary artery has been shown to reduce infarct size.[8,9,10] Such evidence has stimulated interest in thrombolytic therapy as a form of treatment for myocardial infarctions,[11,12] as well as other methods including intermittent coronary sinus occlusion[3] and coronary sinus retroperfusion[4,5] which reduce infarct size by protecting reversibly injured myocardium through enhancing reperfusion.

A technically simple device for circulatory support termed Direct Mechanical Ventricular Assistance (DMVA) has provided effective cardiac actuation, hemodynamics, metabolic stabilization and long-term survival after 6-72 hours of cardiac arrest.[13,14,15] Several other studies have documented increased (generally doubled) survival rates in open chest myocardial infarct models following use of DMVA in dogs and pigs.[18,19,20,21] Increased survival in animal resuscitation models following cardiac arrest was also found when using DMVA.[16,17] Recent studies have shown DMVA to be more effective than conventional closed and open chest cardiac massage.[6,7]

There have been no studies to evaluate DMVA's effect on infarct size. It would seem, from previously cited studies, that DMVA would enhance coronary reperfusion to reversibly injured myocardium. Therefore, DMVA might further decrease infarct size in an occlusion-reperfusion model. The purpose of this study is to evaluate DMVA's effect on infarct size using an occlusion-reperfusion model in dogs.

WILL PROJECT INVOLVE:

Human subjects? No X Yes ___
If so, approval date from Human Subjects Committee _____

Lab animals? No ___ Yes X
If so, approval date from Director, LAR _____

Radiation? No ___ Yes X
If so, approval date from Radiation Safety Committee _____

SIGNATURE:

_____
Principal Investigator

Please type, single space on 8 1/2 x 11 continuation pages. Submit ten copies to: John O. Lindower, M.D., Ph.D., Associate Dean for Academic Affairs, Rm.110A Medical Sciences Bldg.

1. Seed Grant Purpose and Specific Aim:

This seed grant request is for the support of an Interdisciplinary group of Clinical Investigators and a Medical Student to study the possible effect DMVA has on infarct size in an occlusion-reperfusion model.

2. Proposed Materials, Methods, and Protocol

Twenty-six large mongrel dogs will be anesthetized with sodium pentobarbital. Swan-Ganz catheters will be positioned through the external jugular to monitor cardiac status. A #4 F intracoronary double-lumen balloon catheter will be placed just distal to the first diagonal branch of the LAD coronary artery and a #7 F Pigtail catheter will be placed in the left ventricle, both under fluoroscopic control via the left carotid artery. The balloon will be inflated for acute coronary artery occlusion. After 1 hour of occlusion, all dogs will receive ^{99m}Tc-Labeled human albumin microspheres of 20-40 m average diameter through the previously placed Pigtail catheter. These microspheres will delineate the area of low coronary flow (area at risk for infarct).[2,3]

After 90 minutes of occlusion, the balloon will be deflated and dogs will be randomized into two groups. One group (control group), will receive basic medical management including Lidocaine and attempts to defibrillate if fibrillation occurs. The second group will receive thoracotomy and application of DMVA (Fig. 1). Both groups will be treated as described for 5 hours.

After 6 hours, dogs will be sacrificed. Their hearts will be removed, washed with cold saline, and cut transversely at 0.5 cm intervals. These slices will be treated with triphenyl tetrazolium test for macroscopic mapping of the infarct size.[1,2,3] The slices will then be placed on X-ray film overnight to determine the area of risk not perfused by microspheres in the beginning of the experiment.[2,3] (Page 4)

Area of risk and true infarct will be measured by planimetry and compared. Results will be compared to previously cited studies to determine if a greater difference exists. Statistical comparisons will be made by using either Students T-test or analysis of variance with mean separation by Student Newman-Keuls Test.

Design of this experiment is based on previously described models and evaluations of myocardial infarctions found in cited references.

3. Potential Significance

As previously stated, Direct Mechanical Ventricular Assistance has been documented as a more effective method of resuscitation than conventional methods in infarct and cardiac arrest models. DMVA offers several advantages as a temporary or interim method for partial or complete circulatory support. These include ease and rapidity of application which is necessary for emergency resuscitation, simplicity of concept and control, and absence of blood to foreign surface interfaces. If it is found that this method also aids in reperfusion and thereby decreases infarct size, its application to allow initiation of thrombolytic therapy early during cardiac arrest might be warranted in selected cases.

In addition, it would also be appropriate to perform more extensive studies evaluating DMVA's application at different intervals in occlusion-perfusion models.

The ultimate goal would be to further justify the application of DMVA in the clinical arena as an adjunct to other methods of resuscitation and circulatory support.

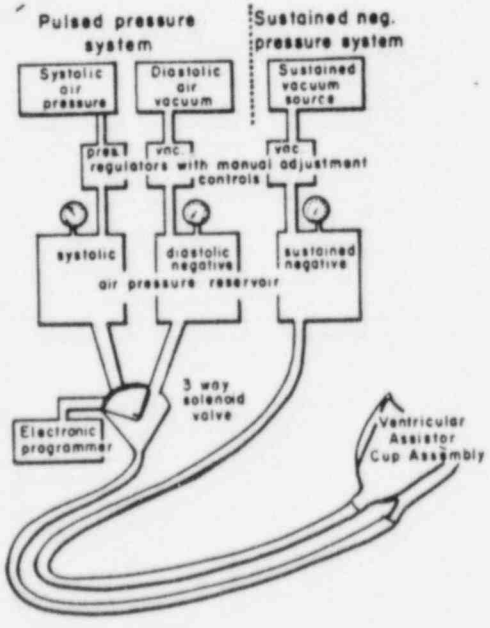


Figure 1 Schematic diagram of mechanical ventricular assistor showing components and air circuits.

EXPERIMENTAL DESIGN

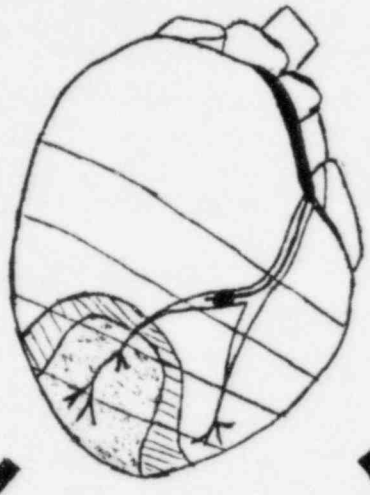


Diagram of heart, inflated balloon shown in LAD producing depicted area of ischemia and infarction.

Dots represent microspheres, defining area of perfusion during balloon occlusion.

Each myocardial slice examined by 2 techniques.

Dashed line represents zone of infarction.

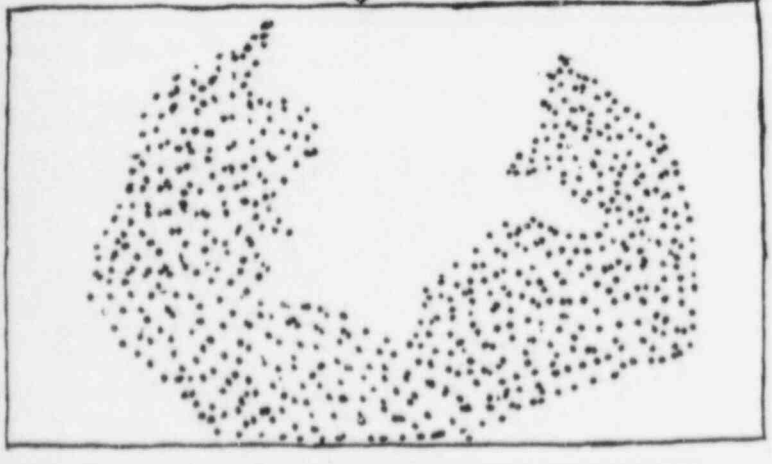
Slice placed on X-ray film.

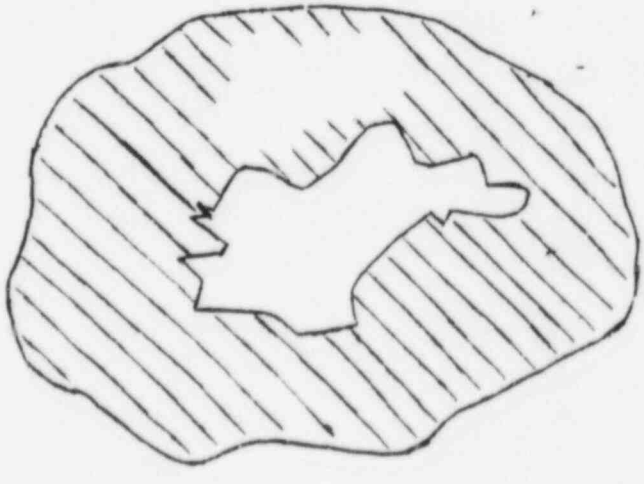
Triphenyl Tetrazolium Stain.

Myocardial Slice

X-ray film

Sit for 12 hours.





Exposed X-ray film now depicts zone of perfusion, thus defining "area at risk of infarction."

Dehydrogenase specific stain identifies viable myocardial tissue, defining size of infarction.

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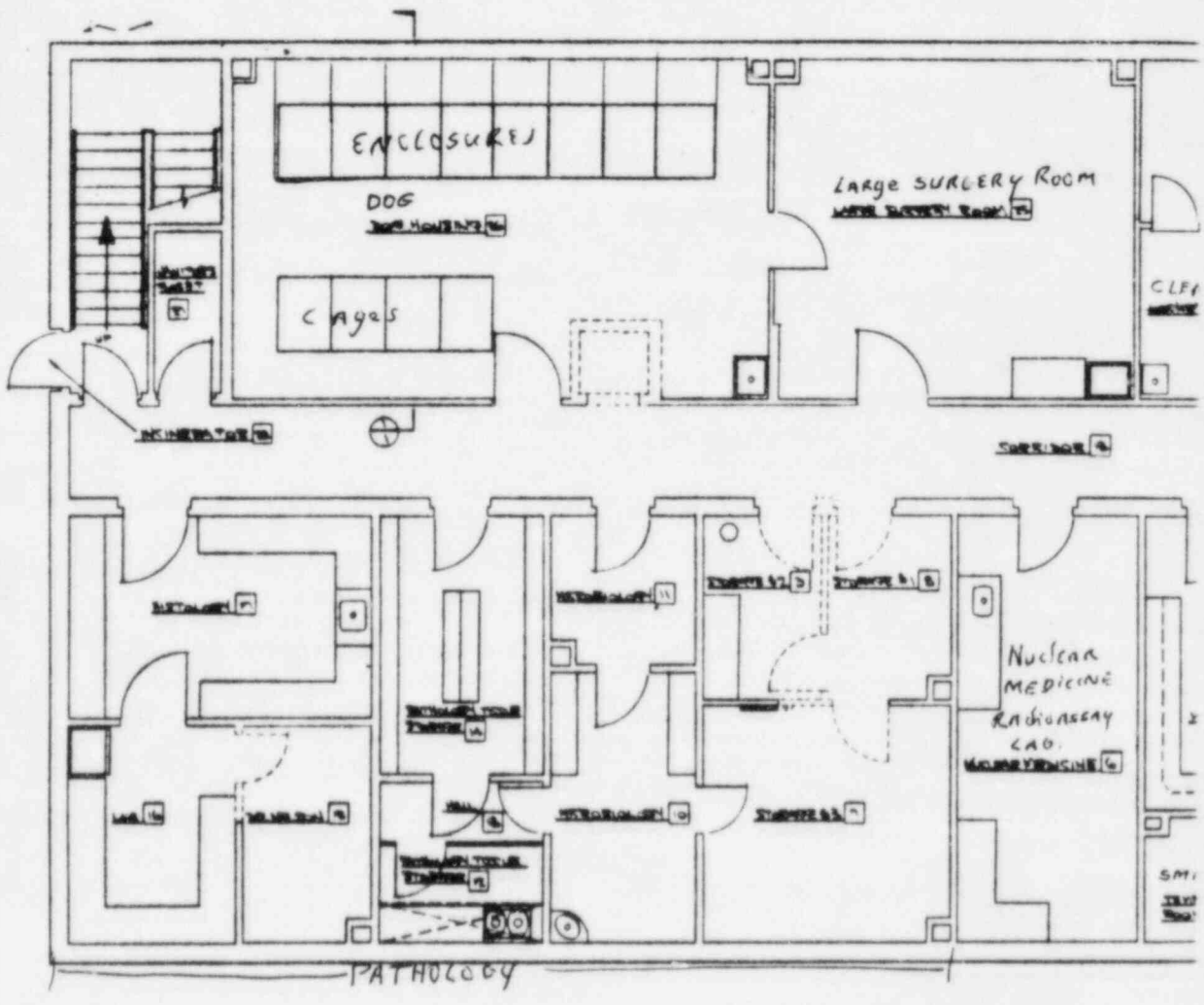

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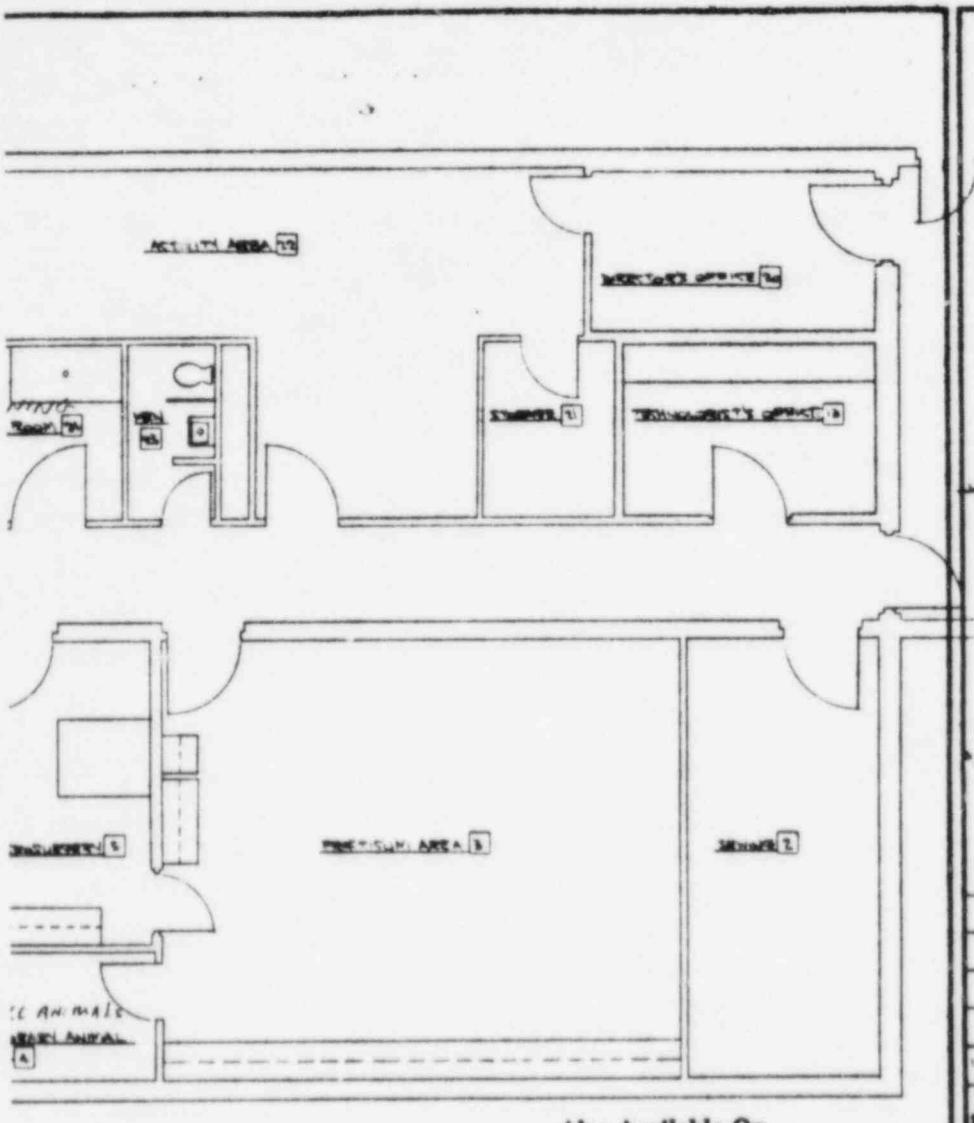

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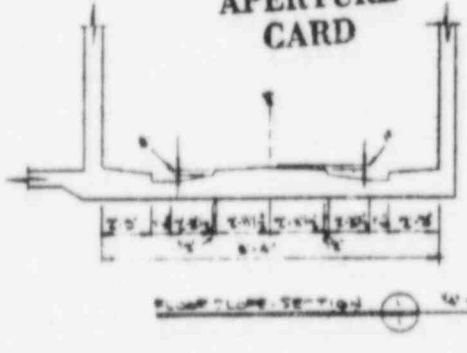

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