Drug Responses of the Transplanted Heart*

THEODORE COOPER, M.D., F.C.C.P., VALLEE L. WILLMAN, M.D. AND C. ROLLINS HANLON, M.D.

St. Louis, Missouri

AUTOTRANSPLANTATION OF THE HEART results in total extrinsic denervation. Such denervation has been shown to alter the response of an organ to chemical agents.1 We have studied the response of the dog's heart to various drugs after removal and replacement in its original site. These studies provide information on basic mechanisms of drug action, which may assume practical importance in management of transplanted hearts in the laboratory and ultimately in patients.

METHODS

Studies were carried out on five normal dogs and on eight dogs surviving excision and orthotopic reimplantation of the heart. The operative techniques employed in this autotransplantation procedure have been described.2 In essence, the two vena cave, ascending aorta and main pulmonary artery are divided and reanastomosed. Temporary separation of the heart from the mediastinum with total extrinsic denervation is completed by cutting the left atrium away from its posterior attachment and resuturing it in its original location. The animals were studied from eight to 300 days after operation.

Chronotrophic responses to drugs were measured in unanesthetized dogs trained to lie on an observation table while intravenous infusions were given and the electrocardiogram was recorded. A stopcock was interposed in the infusion line to permit injection of selected drugs without further manipulation of the animal.

Inotropic response was evaluated with a strain gauge arch sewn to the myocardium.3 For these studies, the animals were anesthetized with thiopental sodium. The trachea was intubated, positive pressure respiration was initiated and thoracotomy was carried out. The gauge was then fixed to the ventricular myocardium. The carotid artery was cannulated for measurement of arterial blood pressure and an appropriate vein was cannulated for the administration of drugs and fluid. Arterial pressure, electrocardiogram and contractile force tracings were recorded on a direct writing oscillograph.

The following drugs were studied: epinephrine and norepinephrine (in the levorotary form), isopropyl norepinephrine, tyramine, mephentermine, ephedrine, metaraminol, ouabain, calcium chloride and cryptenamine alkaloids. All were given intravenously in doses as indicated below.

Responses of the eight cardiac autotransplants were compared to the responses obtained from five normal dogs.

RESULTS

Intravenous administration of norepinephrine to normal dogs in doses of 0.01 to 0.25 µg./kg., results in little change in heart rate, whether unanesthetized or anesthetized. There may be slight bradycardia following the pressure response produced by the 0.25 µg./kg. dose. A positive inotropic response is also usually recorded at doses above 0.1 µg./kg.

In the cardiac autotransplant, we always observed significant acceleration in rate at 0.25 µg./kg., often at 0.1 µg./kg. and occasionally at 0.01 µg./kg., norepinephrine intravenously. The duration of the responses was prolonged. This altered reactivity is illustrated in Fig. 1.
Similar enhancement in chronotropic response was observed with epinephrine and isopropyl norepinephrine. In Fig. 2, the response curves for contractile force in the normal dog and in the cardiac autotransplant.

Tyramine was administered in doses of 60 µg./kg. Normal dogs exhibit the usual positive inotropic and chronotropic responses. However, the cardiac autotransplant shows neither cardiac augmentation or acceleration. A modest pressor response remains. There was also attenuation of response to that group of sympathomimetic amines which are said to exhibit significant "indirect" cardiac action. These include metaraminol (30 µg./kg.), ephedrine (0.3 mg./kg.), and epinephrine (0.5 mg./kg.).
mg./kg.) and mephentermine (1.0 mg./kg.).

Ouabain (0.05 mg./kg.) given intravenously has a positive inotropic action in the normal canine heart. The cardiac autotransplant responds to ouabain in an apparently normal manner as seen in Fig. 4. The positive inotropic action of calcium chloride is apparently unaffected, at least qualitatively, in the cardiac autotransplant.

Cryptenamine alkaloids, which contain components of veratrum viride, cause bradycardia in normal unanesthetized dogs following an intravenous dose of 7.7 µg./kg. In the cardiac autotransplant, these alkaloids in this dosage cause no bradycardia.

**DISCUSSION**

This survey of drug responses in dogs surviving cardiac excision and reimplantation indicates that one will not regularly obtain the expected pharmacologic response to certain cardiovascular drugs in the transplanted heart. Such alterations in action might also be anticipated after "pharmacologic" denervation with agents such as reserpine.

We have previously shown that cardiac autotransplants frequently manifest a clinical status in the early postoperative period which is indistinguishable from congestive heart failure. It is of interest therefore, that the cardiac autotransplant appears to respond to cardiac glycosides in a normal manner. Digitalization of edematous dogs after transplantation has resulted in diuresis and weight loss.

Depletion of myocardial catecholamines follows excision and reimplantation of the heart. These changes have been attributed to interruption of the sympathetic nerve supply. Such interruption eliminates the capacity of the heart to react to stress or disease, a situation which may predispose to cardiac decompensation.

The catecholamine depletion may explain the lack of response to tyramine and the attenuation of response to metaraminol, ephedrine and mephentermine. These agents are said to depend on local stores of norepinephrine for some of their normal actions. Because metaraminol is frequently used in treatment, one should be aware of the altered response which regularly follows sympathetic denervation.

The enhancement of reaction to epinephrine, norepinephrine and isopropyl norepinephrine seems to indicate that the heart follows Cannon's "Law of Denervation." The mechanism of this enhancement is not clear. Evidence for a true supersensitivity could be provided by the demonstration of an alteration in threshold response. This may require a more precise testing system.

The bradycardia which occurs following the administration of veratrum alkaloids is mediated by the Jarisch-Bezold reflex. It is not surprising, therefore, to find that the reflex is eliminated in the cardiac autotransplants, since the extrinsic innervation is totally interrupted.

These alterations in response appear to revert toward normal in animals in which reestablishment of innervation takes place. Further studies on this phenomenon are in progress.

**SUMMARY**

The autotransplanted canine heart differs significantly from the normal heart in its response to various drugs. There is enhanced response to direct acting catecholamines such as epinephrine, norepinephrine and isopropyl norepinephrine. In contrast, the reactions to many other sympathomimetic drugs are eliminated or strikingly attenuated. The response of the autotransplanted canine heart to digitalis seems to be unaltered.

**Resumen**

El pulmón autotrasplantado en el perro difiere considerablemente en su respuesta a las drogas, del corazón normal. Hay una respuesta aumentada a las catecolaminas de acción directa como la adrenalina, la norepinefrina y la isopropil norepinefrina. En contraste, las reacciones a muchas otras drogas simpaticomiméticas es eliminada o notablemente atenuada. La respuesta del corazón canino autotrasplantado a la digital parece no alterada.
RESUMÉ

Le coeur du chien autotransplanté diffère nettement du cœur normal dans ses réponses à des médicaments variés. Il y a une réponse augmentée aux catécholamines agissant directement, telles que l'adrénaline, la noradrénaline, et l'isopropyl noradrénaline. En contraste, les réponses à beaucoup d'autres médications sympathomimétiques sont supprimées ou nettement atténuées. La réponse à la digitalis du cœur de chien autotransplanté, ne semble pas être altérée.

ZUSAMMENFASSUNG

Das autotransplantierte Hundeherz weicht beträchtlich vom normalen Herzen ab hinsichtlich seiner Reaktion auf verschiedene Medikamente. Es findet sich eine verstärkte Reaktion auf direkt wirkende Catecholamine, sowie Epinephrin, Nor-epinephrin und Iso-propyl Norepinephrin. Im Gegenatz dazu werden die Reaktionen gegen viele andere sympathikomimetische Stoffe aufgehoben oder auffallend verzögert. Die Reaktion des autotransplantierten Hundeherzens auf Digitalis scheint unbeinflußt zu sein.

REFERENCES


DIFFERENTIAL DIAGNOSIS: IMPORTANCE OF EOSINOPENIA IN MYOCARDIAL INFARCTION AND STENOCARDIA

The author studied the eosinophils according to Dunger in 40 patients suffering from acute myocardial infarction, and in 40 from stenocardia. In all patients with acute myocardial infarction, eosinopenia was observed from the first day of the disease; on the fourth or fifth day, the number of eosinophils gradually reverted to normal values. In stenocardia, no essential morphologic changes of the blood were revealed. Eosinopenia is one of the sensitive indices indicating the presence of a necrotic process in the heart. It merits attention as an early diagnostic sign.


PULMONARY LESIONS DURING LUPUS ERYTHEMATOSUS

Three cases of various lesions in the respiratory system occurring in the course of lupus erythematosus are reported, viz., bilateral pleural effusion, reticulo-micro-nodular lesions with a considerable reaction in the lung hilus, reticulo-micro-nodular lesions localized mostly in the subpleural parts of the lungs with probably pleural reaction. In the first two cases, the lesions described were the initial infestations of LE. The patients were treated with prednisone combined with anti-malarial drugs. In all cases, clinical symptoms disappeared and several months' remission was obtained.