Pattern of Failure of the Homografted Canine Heart

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A series of puppy hearts was homografted into the necks of adult dogs. The grafts were followed for viability by palpation and by electrocardiograms. Of the grafts studied none functioned longer than one week. Others removed on successive days after transplantation revealed a pattern of failure that suggests that incompatibility to the homografted canine heart is blood-borne.

This communication presents the pathologic pattern observed in a series of experiments during which the heart of a puppy was homografted into the neck of an adult dog after the method of Mann, Priestley, Markowitz and Yater. This method of homotransplantation may be termed a "viviperfusion", that is, vascular anastomoses are performed between the recipient neck vessels and the puppy heart vessels so as to perfuse the coronary circuit of the puppy heart in vivo. The only work load demanded of the transplant is the pumping of its own coronary circuit return by the right heart. Such a preparation may be convenient for the purpose of studying homograft incompatibility because viability of the graft at any time is easily determined by electrocardiographic means, thereby avoiding the necessity of repeated biopsy.

Method

The technique of transplant used is essentially that described in detail by Markowitz. Eleven adult mongrel dogs weighing 27 to 60 pounds were used as the recipients. Healthy mongrel puppies weighing from 2 to 5½ pounds served as heart donors. The distal cut end of the recipient carotid artery was anastomosed to the central end of puppy heart aorta while the puppy heart pulmonary artery was anastomosed to the proximal cut end of the recipient external jugular vein. The anastomoses were made using continuous evverting mattress sutures of 0-0 arterial silk. (See fig. 1.)

Three grafts were followed until they were no longer viable. These three grafts were completely necrotic on the seventh postoperative day. The five succeeding grafts were interrupted on consecutive days after grafting; that is, the grafts were removed in toto on the second, third, fourth, fifth and sixth days respectively after transplantation. All of these interrupted specimens were viable as evidenced by the presence of electrical activity and a visible beat at the time of removal. These specimens were preserved in 10 per cent formalin and examined histologically. In the ninth experiment the graft was enclosed in a plastic bag and interrupted on the fourth day as a viable graft to ascertain whether the exclusion of local factors was related to the degree of graft necrosis. In one experiment daily aspiration of serous fluid was necessary to decompress the graft. In one experiment incision and drainage of a neck abscess was done on the fourth postoperative day. Two other grafts were excluded from this series on the basis of thrombosis of the carotid-aortic anastomosis.

Observations

Clinical Observations

When the graft was first inserted there was initial ventricular fibrillation which spontaneously reverted within a matter of minutes to a normal sinus rhythm at a rate varying between 140 and 200 beats per minute. With one exception the grafts remained within this rate range until interruption. In one graft the rate rose from 185 to 300 on the fourth postoperative day and remained at this rate until interruption on the fifth day after operation. The viability of the grafts could be easily followed by direct palpation of a beat through the skin of the recipient's neck. Viability was checked by electrocardiography. At the time of interruption of the grafts a typical picture was encountered. The epicardium of the graft was surrounded by loose fibrin deposit. The sur-
rounding recipient tissues were swollen and edematous. Graft necrosis became more marked as the age of the graft increased. The six day graft, which still pulsed visibly and possessed electrical activity, showed necrosis of more than 50 per cent of the total myocardium.

Electrocardiographic Observations

Electrocardiographic tracings were recorded from the recipient animal before and directly after the grafting procedure, and daily thereafter until interruption of the graft. The follow-

(1) there are many more QRS complexes appearing in the left neck tracing than in the right neck tracing; (2) there are two types of QRS complexes occurring at two different and regular rates; (3) the two types of QRS complexes occur in one another's absolute refractory periods; and (4) the complexes add algebraically when occurring simultaneously. (See fig. 2.) If the anterior surface of the puppy heart is superficial the electrocardiographic complexes are upright (fig. 3); if the posterior surface of the heart is superficial the complexes are inverted (fig. 2).

On the first day of the graft the voltage amplitude of the graft QRS complex is comparable to a normal canine limb lead II. As the graft age increases the voltage markedly diminishes, probably because of the accumulation of edema fluid and fibrin around the graft. At the time of interruption of the graft, when the incision is opened and the fibrin is cleared away, the QRS amplitude is restored. In the single experiment where the graft was encased in a plastic sleeve, it was noted that the plastic prevented the propagation of the graft electrical activity to the overlying skin. However, complexes of good amplitude could be obtained by inserting the exploring electrode through the drain with no diminution of QRS amplitude during the four days that the graft was allowed to function.

Pathologic Observations

Gross Pathology. The two- and three-day hearts showed very little except a thick fibrin deposit on the epicardial surface and rare petechial bleeding into the endocardium. They were well contracted and free of thrombosis. The four-, five- and six-day hearts showed much more marked changes. Foci of softening and bleeding were grossly visible in the ventricular musculature. The right heart assumed a dilated character. Thrombi appeared in the atria. The six-day heart showed practically complete degeneration of the ventricular and atrial myocardium which was yellowish tan in color and had a tendency to fragment into lamellae. The vascular anastomoses were free of microscopic thrombi, except for the two excluded

![Fig. 1. Drawing illustrating the technic of vivipерfusion of the puppy heart.](http://circ.ahajournals.org/)

(1) proximal end of transected recipient left external jugular vein anastomosed to the puppy heart main pulmonary artery to receive the output of the right ventricle. (2) Distal end of transected recipient left common carotid artery anastomosed to puppy heart aorta for supply of the puppy heart coronary circulation. Solid arrows depict the blood flow during vivipерfusion; the dotted arrows show the direction of the interrupted blood flows in the left external jugular vein and common carotid artery.
grafts already mentioned; both of these hearts weighed less than 20 Gm.

Microscopic Pathology. The earliest change observed is in the one- and two-day hearts which show marked cellular infiltration beneath the endocardium. The reacting cells

cell infiltration into, the epicardium. On the third day small patchy areas of myocardial necrosis are seen in the midportion of the myocardium. There is now a diffuse, cellular infiltration of the myocardium and more marked intercellular edema. The infiltrate is

are chiefly histiocytes with an occasional eosinophil. This infiltrate has a tendency to extend into the underlying myocardium along the larger thebesian channels. The myocardium at this time shows a variable degree of serous edema without appreciable cellular reaction. There is fibrin deposition upon, and round

most marked about large and small vessels. On the fourth, fifth and sixth days the changes are largely quantitative. The patchy areas of necrosis become larger, more numerous, confluent and eventually involve large areas of the myocardium. The myocardial fibers show successively swelling, fatty vacuolization, de-
crease in prominence of and loss of cross striations, loss of sarcoplasm with collapse of the sarcolemmal sheath. There is a marked cellular reaction to the necrotic fibers with many polymorphonuclear leukocytes phagocytizing debris, and ectasia and dilatation of capillaries with intense congestion and petechial hemorrhage. At six days an estimated one-third of the ventricular myocardium is microscopically viable. Within the atria, which show changes at least as severe as the ventricles, mural thrombosis sets in on the damaged endocardium. Typical microscopic changes in a four day graft are illustrated in figure 4.

The pattern of myocardial necrosis is progressive in the chronologically interrupted hearts. This progression can be summarized as follows:

One- to two-day grafts: Serous edema separating the fibers but with the fibers still well preserved; cellular infiltration mostly confined to the endocardium and the perivascular area about larger blood vessels.

Three-day graft: More marked cellular infiltration involving much of the myocardium but still radiating out from vascular channels; more edema richer in protein; small areas of necrobiosis of centrally located muscle fibers.

Four- to six-day grafts: Marked cellular infiltration most severe about epicardium and endocardium but also diffusely present in atrial and ventricular myocardium; increase in number and size of areas of infarction, confluence of areas of infarction; widespread degeneration and necrobiosis of muscle fibers. The presence of the plastic sleeve did not change the four-day histologic picture.

Seven- to ten-day grafts: Complete degeneration with necrosis and liquefaction.

DISCUSSION

In correlating these observations with those of Medawar, it would appear that a homografted canine heart exhibits an initial “take” period of up to six days as evidenced by a palpable beat and the presence of electrical activity. Beginning on the third day there is microscopic evidence of necrosis in the graft. That this necrosis is on the basis of homologous tissue incompatibility seems likely. There is the possibility that the heart graft failure may be a late manifestation of the period of 45 to 90 minutes anoxia that the heart is subjected to while the anastomoses are being made. However, Marcus, Wong and Luisada observed failure of homografted hearts in spite of a continuous perfusion of the heart by means of a third dog while anastomoses were being performed. These hearts were beating constantly without any period of anoxia during the entire transplantation procedure and yet failed following an initial “take” period.

There are two possible sites of incompatibility; that is, incompatibility of host to the donor vascular network with resultant vascular occlusion and myocardial infarction, or an incompatibility acting directly upon the myocardium. If the necrosis observed in this series of grafts were on the basis of ischemic myocardial infarction, then the earliest involved areas should be the areas of poorest blood supply, namely the subendocardial myocardium. But the first areas of necrosis seen were small patches of degeneration in the midportion of the ventricular myocardium.
There was observed no gross or microscopic arterial lesions to account for the necrosis. The central location of the patchy myocardial necrosis is evidence against the operation of a localized or generalized cellular response; the fact that the necrosis followed the same pattern when the graft was isolated by means of a plastic sleeve fairly well rules out this possibility. These findings, therefore, suggest that the necrosis of the homografted canine heart is primarily caused by humoral factors acting directly upon the myocardium.

**Fig. 4.** Photomicrographs of right ventricular wall of four-day interrupted homograft showing typical microscopic changes. A is a low power view and B, C, and D are high power views. A shows the entire thickness of the right ventricular wall with characteristic central necrobiosis of the myocardium, thickened endocardium and epicardium and fibrin deposit on the surface of the epicardium. B illustrates the character of the endocardial infiltration. C demonstrates the central myocardial necrobiosis. D shows the diffuse epicardial infiltration.

**Summary**

1. The feasibility of experimental homotransplantation of the canine heart as described by Mann, Priestley, Markowitz and Yater has been confirmed.
2. Of 11 transplants attempted, nine were
technically successful. The two failures are attributed to thrombosis at the arterial anastomosis. The successful transplants beat for at least 48 hours; those that were not interrupted beat for four to six days. All eventually failed after an initial “take” period. Viability was confirmed by electrocardiography.

3. From study of grafts removed at various times after implantation, a definite pattern of graft failure was observed.

**Sumario Español**

Una serie de corazones de cachorro fueron homoinjertos en los cuellos de perros adultos. Los injertos fueron estudiados para viabilidad por medio de palpación y electrocardiogramas. De los injertos estudiados ninguno funcionó por más de una semana. Otros removidos en días sucesivos a la transplantación reveraron un patrón de fracaso que sugirió la incompatibilidad al homoinjerto canino ser de origen sanguíneo.

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