Neural Responses Following Autotransplantation of the Canine Heart


We have excised and reimplanted the heart in its original location in 50 dogs in order to assess the effect of the transplantation procedure on cardiac function and long-term survival. It is apparent that the procedure completely divides the extrinsic nerves to the heart. The total effect of dividing these nerves is not yet clear, but we have observed certain alterations in neural responses of the heart which constitute the basis of this report.

Methods

Total cardiac excision and orthotopic replacement has been performed in 50 mongrel dogs by a previously described technique. We divided both venae cavae, the aorta, pulmonary artery, and left atrium at the confluence of the pulmonary veins. These were sutured in their original positions. During the three-hour procedure, cardiopulmonary bypass with hypothermic cardioplegia averaging an hour was employed.

All survivors of the operative procedure required supportive therapy for cardiac decompensation. As controls, four animals had a sham procedure involving cardiopulmonary bypass with hypothermic cardioplegia for an hour, but the heart was not separated from its attachment. The surviving three animals required no special treatment. In all animals, physiological responses were measured at frequent intervals by conventional methods.

Results

Of 50 dogs, 15 survived longer than 3 days. All survivors developed cardiac failure, and a number of them died despite intensive treatment. The three survivors of the sham procedure did not develop cardiac failure.

Immediately after autotransplantation, there was a fixed tachycardia of 140 to 160/min. Blood pressure remained at preoperative levels. During the first three weeks after operation, there was gradual slowing of the rate to a level of 100 to 110/min. (fig. 1). The electrocardiogram showed a sinus rhythm, but the sinus arrhythmia usually seen in dogs was not present. The inverted T waves seen in the immediate postoperative period became upright in the next few days.

There was negligible alteration of rate in response to sudden noise, mild exercise, eating, or light anesthesia (fig. 2). Stimulation of the vagus nerve failed to slow the heart (fig. 3). Instead, there was a pressor response which could be eliminated by injecting 1 per cent procaine into the nerve central to the point of stimulation, thus blocking vagal afferent impulses.

Stimulation of the stellate ganglion failed to elicit cardiac acceleration or augmentation. The resulting pressor response presumably was caused by stimulation of extra-arterial sympathetic fibers (fig. 4).

Intravenous injection of small amounts of l-norepinephrine (0.25 μg./Kg. body weight) resulted in cardiac acceleration, increased ventricular contractile force, and an increase in arterial blood pressure (fig. 5). Myocardial biopsies showed extremely low levels of catecholamines.

Two animals have been studied one year after autotransplantation. Parasympathetic innervation has been re-established, as indicated by prompt bradycardia in response to vagal stimulation (fig. 6). There is also evidence of sympathetic reinnervation, as indicated by prompt cardiac acceleration and augmentation on stimulation of the stellate ganglion (fig. 7). Myocardial biopsies contain normal levels of catecholamines (left atrium:

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0.90 μg./Gm.; left ventricle: 0.58 μg./Gm.). Injection of small doses of l-norepinephrine (0.25 μg./Kg. body weight) at this time caused negligible change in cardiac rate (fig. 8).

Discussion
These studies demonstrate that excision and reimplantation of the heart eliminates, for a substantial interval, extrinsic neural regulation of the heart. The alterations in neural responses and in tissue catecholamine content after orthotopic transplantation of the heart are quite similar to those recorded after apparently complete extrinsic denervation by mediastinal neural ablation. The autotransplantation technique assures complete severance of all extracardiac neural connections. Donald and Shepherd3 have demonstrated, in

Figure 1
Electrocardiograms (lead II) obtained from unanesthetized dog after cardiac autotransplantation. Heart rate was 160/min. immediately after autotransplantation. The rate progressively slowed and stabilized at 100/min. after three weeks. The usual sinus arrhythmia was not evident.

Figure 2
Electrocardiograms taken 45 days after cardiac autotransplantation. There was no alteration in rate or rhythm with induction of intravenous thiopental anesthesia.

Figure 3
Responses of arterial blood pressure and ventricular contractile force after supramaximal electrical stimulation of left vagus nerve in the neck 45 days after cardiac autotransplantation. There was no slowing of cardiac rate.

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orthotopic autotransplantation of the canine heart is followed by loss of direct sympathetic and parasympathetic neural regulation. Stimulation of the vagus nerve or stellate ganglion fails to alter cardiac rate.

Myocardial catecholamines are depleted and exercised dogs, an altered mechanism for regulation of cardiac output after complete extrinsic denervation. Such an altered regulatory mechanism may be important in causation of the increased venous pressure and edema encountered in the early days after autotransplantation. We need to clarify the role of neural impulses from the heart in the central nervous regulation of the circulation and in the hormonal control of body water.

Depletion of myocardial catecholamines and increased sensitivity to exogenous l-norepinephrine is a striking abnormality of these denervated hearts. One year after operation, there is evidence of reinnervation and return of normal responses to catecholamines. This suggests that adequate physiological regulatory mechanisms might be regained in a cardiac homograft if immunological tolerance could be achieved.

**Summary**

Orthotopic autotransplantation of the canine heart is followed by loss of direct sympathetic and parasympathetic neural regulation. Stimulation of the vagus nerve or stellate ganglion fails to alter cardiac rate.

Myocardial catecholamines are depleted and

hypersensitivity to exogenous l-norepinephrine is present for months.

One year after the operation, there is evi-
Figure 7

Responses of arterial blood pressure and ventricular contractile force to electrical stimulation of the left stellate ganglion in a dog one year after cardiac autotransplantation. There was a prompt increase in rate and contractile force as well as increased blood pressure and pulse pressure. This indicated re-establishment of sympathetic innervation to the heart.

Reference

Figure 8

Responses of arterial blood pressure and ventricular contractile force to intravenous injection of L-norepinephrine (0.25 µg/Kg. body weight) in a dog one year after cardiac autotransplantation. There was no alteration in cardiac rate. Blood pressure and contractile force increased. This indicates loss of the hypersensitivity to catecholamines present in the early months after operation.

References
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