Myocardial Performance after Excision of the Extrinsic Cardiac Nerves in the Dog

By David E. Donald

The performance of the heart in the intact subject is determined by the complex interplay of cardiac and extracardiac factors; the initial length of the myocardial fibers and the state of activity of the cardiac autonomic nerves are most important. The profound changes in cardiac behavior that attend excitation of the cardiac autonomic nerves have led to the concept of neurogenic dominance in the control of cardiac output, particularly in situations that strongly constrain the cardiovascular system. This concept is basic to an evaluation of the mechanisms by which the heart responds to changes in the peripheral circulation and has important implications in clinical cardiac transplantation. In this review, the behavior of the denervated heart in different stressful situations is considered; the presentation is limited to studies in which dogs have been chronically deprived of both sympathetic and parasympathetic nerves. The role of cardiac receptors and their afferent innervation has recently been reviewed and is not discussed in this paper (1, 2).

TECHNIQUES OF CARDIAC DENERVATION

The four major techniques of cardiac denervation currently used are described briefly, because the method of denervation will influence the results obtained.

(1) According to the methods of Gasser and Meek (3) and of Ashkar and Hamilton (4), the stellate ganglia and thoracic paravertebral sympathetic chains are bilaterally excised from T-1 to T-4. The right vagus nerve is sectioned distal to the right recurrent laryngeal nerve. During a second operation, the left vagus nerve is sectioned in the neck. Some cardiac sympathetic fibers remain biable but decentralized, and the myocardial content of catecholamines is reduced to a varying degree. Supersensitivity to catecholamines does not develop. The lungs and viscera are vagally denervated, resulting in altered respiratory dynamics, gastrointestinal disturbances, and loss in body weight. Vagal cardiopulmonary afferent nerves are interrupted.

(2) Complete cardiac denervation is assured after orthotopic autografts or allografts. This technique requires cardiac bypass and results in significant morbidity and mortality. Sympathetic denervation is postganglionic, and the heart is depleted of and becomes supersensitive to catecholamines. Pulmonary afferent fibers are preserved, but afferent fibers that course along the aorta, the main pulmonary artery, or the superior vena cava are interrupted. Depending on the technique used, afferent fibers from receptors in the pulmonary veins, posterior atrial wall, and ostia of the vena cava may (5) or may not (6) be preserved. After transplantation, variability in the functional integrity of the donor sinus node has been noted.

(3) The technique of regional neural ablation (7) involves stripping the aorta, the main, right, and left pulmonary arteries, the pulmonary veins, the atria, and the vena cava. The pericardium is removed, and the efferent and afferent fibers in the regions named are interrupted. Enough pulmonary afferent fibers are preserved to maintain a normal respiratory pattern at rest and during exercise. Sympathetic denervation is postganglionic. The heart is depleted of and becomes supersensitive to catecholamines. Sinus rhythm remains with no disturbance in the conduction of the excitatory impulses. This surgery results in significant mortality due primarily to pulmonary complications, presumably from mechanical distortion of the stripped and unsupported pulmonary veins.

(4) Recently, Geis and colleagues (8) have described a two-stage modification of the technique of excision and reimplantation. In the first stage, the entire free wall of the left atrium is transected and reanastomosed. The adventitias of the...
main pulmonary artery and aorta, along with areolar tissue and nerves, are transected circumferentially. At the second stage, the free wall of the right atrium, the interatrial septum, and the superior vena cava also are transected and reanastomosed. The new suture lines join those made previously to complete the circumferential division. Sympathetic denervation is postganglionic; the heart is depleted of and becomes supersensitive to catecholamines. Pulmonary afferent fibers are preserved as is the neural continuity of the posterior wall of the left atrium with its mediastinal connections. Immediately after the second stage of the procedure, acute bradycardia, atrial arrhythmia, and hypotension occur. These conditions are reversed after the intravenous infusion of isoproterenol for 30–120 minutes. Once there is recovery from the anesthetic, the pacemaker activity is maintained without support. After denervation, complications are absent, and the mortality rate is less than 10%.

TESTING FOR COMPLETENESS OF DENERVATION AND FOR REINNervation

Two separate studies in which excision and reimplantation of the heart were used have reported that vagal or sympathetic reinnervation can occur as early as 20–33 days after surgery (9, 10). Rigorous testing for completeness of denervation, therefore, is essential in chronic studies, even when the technique employed ensures total denervation immediately after surgery. During the experimental period frequent tests should be made with atropine, tyramine, and hypertensive drugs. Sinus arrhythmia should be completely absent when the dog is resting, and sudden startling of the dog should not induce any immediate change in heart rate. On completion of the study, more demanding test procedures should be used. Geis and colleagues (8) have suggested that direct stimulation of cardiac nerves provides the most reliable criterion for assessment of denervation and have pointed out the necessity for determining changes in inotropism in all four cardiac chambers. Diencephalic stimulation has also been used (9), but Noble and colleagues (11) have pointed out that such stimulation releases catecholamines from the adrenal medulla and the noncardiac sympathetic nerve endings, thus producing a humoral effect on the denervated heart. There should be absence of myocardial catecholamines (7, 12).

The demonstration of an inotropic or a chronotropic response to stimulation of the cardiac autonomic nerves does not necessarily mean that the predenervation state of the heart has been regained. The sinus node, for example, may be preferentially reinnervated. Ebert and Sabiston (13) found positive responses to stimulation of the stellate ganglia in 15 of 16 dogs 8 months after cardiac denervation by autotransplantation or neural ablation; however, myocardial catecholamine content averaged on 16% of that found in normal control hearts. Gilmore and Michaelis (14) and Thames et al. (15) presented evidence for continuing afferent denervation when reinnervation by efferent nerves had taken place.

REST

The characteristic features of the denervated heart at rest are its constant frequency and the complete absence of the respiratory sinus rhythm typically observed in the conscious quiescent dog (16, 17). Resting heart rates range from 90 to 140 beats/min, and there is no immediate response to somatic or emotional stimuli (18). Values for cardiac output, stroke volume, left ventricular systolic pressure, left ventricular dp/dt, and left ventricular maximal ejection rate are not different from those recorded from normally innervated hearts (11, 19). Left atrial mean pressure either is within the normal range or is slightly elevated.

RESPONSE TO STRESS

Exercise.—After excision of the extrinsic cardiac nerves, the ability of the dog to exercise on the treadmill seemingly is unimpaired. Cardiac output increases substantially and in proportion to the work load as measured by the increase in oxygen consumption. In contrast to the normally innervated heart, an increase in stroke volume makes a major contribution to the increase in cardiac output, particularly at moderate work loads (two- to threefold increases in cardiac output and oxygen consumption) and during the early moments of severe exercise (18, 20). The increases in left ventricular end-diastolic pressure and internal diameter suggest that increased initial fiber length is the responsible mechanism (19). Normal dogs also increase cardiac output by increasing stroke volume if the heart rate is increased by atrial pacing prior to the beginning of exercise (21). Although an increase in stroke volume contributes extensively to the increase in cardiac output seen in the denervated dogs, the maximal stroke volume is not very different from that measured in conscious dogs at rest with heart rates of 50–70 beats/min or in dogs with chronic atrioventricular block.

A feature of the cardiac response to exercise in the normal dog is the immediate, rapid change in
heart rate at the onset of exercise; this change often results in an initial overshoot. In contrast, after denervation, heart rate increases slowly, requiring 1-2 minutes to reach steady-state values. The increase in cardiac output at the beginning of exercise is slower in the denervated heart than it is in the innervated heart, although steady-state values for cardiac output and oxygen consumption are similar (19, 20). Thus, the dog with the denervated heart may be at a disadvantage in situations in which rapid changes in heart rate contribute extensively to the total cardiovascular response.

The increase in heart rate with exercise after cardiac denervation is still proportional to the work load. At each level of exercise, the increase in frequency is one-half to one-third of that observed prior to denervation, and, in the laboratory, the maximal heart rate rarely exceeds 180 beats/min. The tachycardia caused by exercise persists after bilateral adrenalectomy, is unrelated to the temperature of the blood, and cannot be mimicked by the infusion of saline or dextran into the right atrium. This tachycardia is still present after beta-receptor blockade (propranolol 1 mg/kg); as yet there is no explanation for this intrinsic response of the denervated heart (22).

The findings of Gasser and Meek (3) and of Ashkar and Hamilton (4) that the dog suffers a severe reduction in capacity for exercise after cardiac denervation contrast with the previous observations. However, the technique used by these workers denervated the lungs and the abdominal viscera in addition to interrupting the nerve supply to the heart, and, as suggested by Gasser and Meek (3), the reduced capacity for exercise was of pulmonary rather than of cardiac origin.

Maximal Capacity for Exercise.—In exercise studies, the treadmill generally is set at a submaximal work load for the dog because of the difficulty that the dog has in retaining its footing on the fast moving, steeply inclined platform. The cardiac output is then less than maximal; therefore, the Starling mechanism is capable of compensating for the reduction in heart rate. As circulatory demands are further increased by increases in work load, a level is reached at which cardiac output cannot be augmented solely by the Starling mechanism: Bishop and Horwitz (23) have shown that stroke volume depends not only on initial fiber length but also on an increase in the velocity and the extent of cardiac fiber shortening caused by sympathetic stimulation. To obtain adequate cardiac performance at and above this work level, the denervated heart thus requires the inotropic and chronotropic actions of circulating catecholamines. It seems to be an almost too perfect accommodation that, shortly after denervation, the heart becomes supersensitive to the adrenergic neurotransmitter (24-26).

The role of circulating catecholamines is clearly demonstrated by studies in racing greyhounds—dogs that are bred, trained, and highly motivated to run at maximal effort (27, 28). In these dogs, racing times and maximal heart rates are only slightly less after cardiac denervation. However, when the cardiac effect of circulating catecholamines is prevented by beta-receptor blockade, the greyhound with a denervated heart shows a marked reduction in racing performance and in heart rate.

The exact point at which the Starling mechanism becomes maximal and the addition of adrenergic stimulation becomes necessary varies considerably. The training and motivation of the dog, the type of exercise, and the intensity of the stress are obvious factors.

The previously cited studies suggest that, if the stress is such that maximal response requires participation of the cardiac sympathetic nerves in addition to the intrinsic length-tension mechanism, the denervated heart performs at a disadvantage unless it is also stimulated by circulating catecholamines. Lesser circulatory demands are met equally by the denervated and the normally innervated heart, although each increases cardiac output in a different manner.

Ventricular Function Curves.—The ability of denervated hearts to pump blood has been assessed by comparing the responses of normal and denervated hearts to acute volume loading. Studies in anesthetized dogs (29, 30) indicated that the ability of a dog with a denervated heart to augment ventricular performance in response to stress was unimpaired. Volume loading in conscious dogs (31) increased both the rate and the stroke volume in innervated hearts but increased only the stroke volume in the denervated hearts. The mean plateau value of ventricular output in the denervated hearts was 83% of that in the hearts of normal dogs but was not significantly different from the value obtained in normal dogs treated with propranolol. This difference is explained by the finding in a later study (23) that the increased stroke volume observed during acute volume loading partly depends on increased discharge in the cardiac sympathetic nerves.

These studies support the conclusion that the denervated heart only performs at a disadvantage...
when (1) the stress is such that the length-tension mechanism cannot fully compensate for the absence of both neural and humoral adrenergic stimulations and (2) an immediate increase in heart rate is an essential component of the cardiovascular response.

**Arterial Hypotension and Hypertension.**—The responses of anesthetized normal dogs and dogs with cardiac denervation to mild (15 ml/kg) (32) or severe hemorrhage (40-50 ml/kg) (33) were essentially similar except for the increases in heart rate shown only by the innervated group. Maintenance of systemic blood pressure seemed to depend more on the choice of anesthetic and the severity of the bleeding than it did on the presence or absence of the cardiac autonomic nerves.

However, when hypotension was produced in anesthetized dogs by an intra-arterial infusion of acetylcholine (34), cardiac output and heart rate increased less (87% and 11%, respectively) in the denervated dogs than they did in the similarly treated group of normal dogs (194% and 145%, respectively). With heart rate controlled by electric pacing, both groups showed similar increases in cardiac output (113% denervated and 124% normal).

Whether arterial hypertension was produced in anesthetized dogs by an intra-aortic infusion of angiotensin (34) or in conscious dogs by bilateral carotid occlusion (35), the increase in pressure load was sustained as well by the denervated hearts as it was by the innervated hearts (36).

Thus, the presence of the extrinsic cardiac nerves does not seem to be essential to the maintenance of cardiac output when the afterload is increased. When hypotension is accompanied by excitation of the cardiac sympathetic nerves, however, absence of the neurally induced tachycardia results in a significantly smaller increase in cardiac output and a less well-maintained systemic arterial blood pressure.

**Hypoxia and Anemia.**—Glick and colleagues (37) stressed conscious normal dogs and cardiac-denervated dogs by exposure to acute generalized hypoxia (ambient oxygen concentration 8%). Both groups showed similar minimal changes in heart rate, cardiac output, and stroke volume; oxygen delivery to the tissues was similarly reduced. Anesthetized, open-chest dogs were studied by Greenfield and Ebert (38) during ventilation with 10% oxygen. During hypoxia, normal dogs showed moderate increases in systemic arterial blood pressure, heart rate, and myocardial contractile force (Walton-Brodie strain gauge). Dogs with cardiac denervation responded in a similar but less pronounced fashion.

Severe acute anemia was produced in trained conscious dogs by exchange transfusion with dextran (39). Substantial increases in cardiac output were seen both in normal (119%) and in cardiac-denervated dogs (77%). In the normal dogs, the increase in heart rate was larger (83%) than that in stroke volume (21%); however, in dogs with denervated hearts the increase in stroke volume (44%) was larger than that in heart rate (23%). In both groups, right atrial pressure was increased, suggesting an increase in cardiac filling pressure, although the cause of the increase was not determined. Oxygen delivery to the tissue decreased in all dogs in both groups. The average decrease of 42% in the dogs with denervated hearts was significantly greater than the 22% decrease observed in the normal dogs. In three dogs with cardiac denervation, beta-receptor blockade did not prevent the hemodynamic responses to anemia.

These studies offer further support for the conclusion that, when a neurally induced tachycardia constitutes an important part of the cardiac response to stress, the response of the denervated heart may be less than maximal.

**Cardiac Arrhythmia**

Because the cardiac sympathetic nerves are involved in the arrhythmias that almost invariably follow acute occlusion of a coronary artery, the behavior of the denervated heart in this situation is of interest. Studies in dogs by Ebert and colleagues (40) and by Schaal and colleagues (41) have demonstrated that, after ligation of the left anterior descending coronary artery, the chronically denervated heart does not develop the arrhythmia and ventricular fibrillation observed in the normal dog. In contrast to the normally innervated heart, the chronically denervated hearts had minimal or zero levels of myocardial catecholamines and exhibited no elevation in the concentration of potassium in the coronary sinus blood in the first 20 minutes after coronary artery ligation. However, when octylamine, a potassium-releasing agent, was infused directly into the left anterior descending coronary artery, both control and denervated hearts lost potassium (42). All control dogs developed ventricular fibrillation within 3-6 minutes; none of the chronically denervated hearts developed any arrhythmia, although the electrocardiogram showed changes resembling those of marked
ischemia. The authors concluded that, although the exact mechanism by which chronic cardiac denervation protects the heart from ventricular fibrillation is not known, a direct relationship between rhythm disturbance and myocardial catecholamines appears to exist.

METABOLISM AND CHEMICAL COMPOSITION OF THE DENERVATED HEART

There are only a few studies about the metabolism and chemical composition of the denervated heart, and the findings are controversial. Techniques of cardiac denervation have been varied, different species have been used, and the time between surgery and study has not been constant. The preparations used have been isolated papillary muscles, dogs on right heart bypass, anesthetized dogs, and conscious dogs at rest and during exercise. Most authors agree, however, that after cardiac denervation there is an absence of catecholamines in heart muscle and that this absence is related to denervation of the terminal adrenergic nerve fibrils.

After determining myocardial energy utilization at rest and during isometric and isotonic contractions for cat papillary muscles from normal and denervated cat hearts, Coleman and associates (43) concluded that the denervated heart has a normal basal metabolism and an unimpaired ability to convert a given amount of energy into mechanical work. Daggett et al. (29) also found no increase in myocardial oxygen consumption per 100 g of left ventricle when hemodynamic conditions were controlled in autotransplanted hearts; however, since the total amount of oxygen consumed was greater than that in the control group, they suggested that the autotransplanted heart was less efficient. More recently, Gregg et al. (44), in a study of conscious normal dogs and dogs with cardiac neural ablation, suggested that the denervated heart functions at a lower metabolic level than does the heart with intact cardiac nerves. At rest and during exercise to equivalent levels of cardiac work, left circumflex coronary flow and myocardial oxygen consumption were about half the values obtained in normal dogs.

Different findings were reported by Barta et al. (45–47), who studied anesthetized dogs before and 14–18 days after cardiac denervation. These authors found substantial decreases in coronary blood flow, in myocardial usage of oxygen and other energy-yielding substances, and in left ventricular work and efficiency. They suggested that hypoxia of the myocardium, changes in myocardial ultrastructure, and decreases in myocardial catecholamines resulted in an inability of the denervated myocardium to produce a sufficient quantity of chemical energy. Jellinek et al. (48) and Willman et al. (49) found disturbances in fat and carbohydrate metabolism in dogs after stellate and caudal cervical ganglionection and after cardiac autotransplantation; they suggested that the glycogen accumulation was due to impairment of phosphorylase activation resulting from loss of myocardial catecholamines. These data conflict with those of Daggett et al. (29), who could not demonstrate alterations in substrate utilization by the autotransplanted heart from measurements of glucose lactate and pyruvate across the coronary bed and from calculations of respiratory quotients. The observations by Barta et al. (45–47), Jellinek et al. (48), and Willman et al. (49) also disagree with recent findings by Noble et al. (11), who denervated the heart by regional neural ablation and found that intracellular enzyme function and lipid, glycogen, RNA/DNA, and water content were normal, as judged by quantitative histochemical studies and interference microscopy.

It is difficult to make adequate comment on this aspect of cardiac denervation. The general impression is that there are no major alterations in myocardial metabolism in the long-term surviving animal. The findings of Gregg et al. (44) merit further investigation, since studies in anesthetized dogs report both an increase (29, 50) and a decrease (45) in coronary blood flow. The studies by Barta and colleagues (45–47) were conducted in dogs that had evidence of gastrointestinal disturbance, required great postoperative care, and had a mean weight loss of 4 kg.

The value of any investigation may lie more in the questions it raises than in those it answers. Animal studies and later clinical experience seem to have satisfied the initial question of the competence of the transplanted heart to meet the demands of everyday activity. The heart deprived of extrinsic cardiac nerves adequately meets the demands of pressure and volume loading by the length-tension mechanism and a limited intrinsic tachycardia or, if the stress is sufficiently severe, by the additional excitatory effect of circulating catecholamines.

One would like to postulate, however, that it was the initial interest in cardiac denervation that led to further knowledge of the terminal innervation of the heart (51), of the function and the anatomy of the regional distribution of cardiac autonomic
nerves (52), and of the interplay of initial fiber length and cardiac autonomic nerves in the control of stroke volume (23).

One area of possible future interest is the role of cardiac receptors and their afferent nerves in homeostasis of blood volume, release of renin, and reflex control of the peripheral circulation since abnormalities in these functions have been reported after cardiac denervation (15, 53–55). It is, however, the opinion of this reviewer that total cardiac denervation is much too blunt a technique, and inquiry here would demand accurate identification of the afferent pathways involved and the development of methods permitting denervation of precisely defined, limited areas of the heart.

The recent observation of Gregg et al. (44) that the denervated heart appears to function at a lower metabolic level than does the heart with intact nerves should be pursued further, since in that study myocardial oxygen consumption was equated only with external cardiac work. The studies of Coleman and associates (43) allowed a more precise definition of myocardial energy requirements and indicated that the basal metabolism of the noncontracting muscle and the conversion of energy to mechanical work were normal in the denervated heart. However, the papillary muscle at a temperature of 29°C and beating at a frequency of 30/min may not totally represent the metabolic situation of the in situ heart. Further studies, therefore, should be made in which the requirement and utilization of energy by the denervated heart, beating at normal temperature and frequency, are defined in terms of the mechanical events during contraction.

Another area of interest is the resistance of the denervated heart to the arrhythmias and the ventricular fibrillation that follow coronary occlusion (56). The fact that myocardial catecholamines are directly involved in the genesis of this ventricular ectopic activity is suggested by the failure of cardiac sympathectomy and treatment with propranolol (56, 57) to afford substantial protection. Thus, metabolic alterations within the myocardium, possibly in particular anatomic locations (55), may be major factors in the arrhythmias of coronary occlusion.

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