# The Effect of Vagal Stimulation on the Myocardium in the Cat[1] (37709)

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(Introduced by E. C. Hoff)

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The participation of the autonomic innervation of the heart in the production of pathologic lesions of the myocardium is well-established, but the relative contribution of the parasympathetic and sympathetic components remains unclear. Sympathetic stimulation or norepinephrine infusion may produce myocardial hemorrhages and fuchsinophilia (7, 8). Although parasympathetic activation by means of vagal stimulation has been reported to produce similar histological changes in the myocardium (2, 6), the effects of acetylcholine infusion are conflicting. Hall *et al.* (4) reported myocardial degeneration and hemorrhages with acetycholine infusion, but Horswell (5) repeated this experiment and was unable to replicate these results. Furthermore, none of the studies in which myocardial necrosis was induced as a result of parasympathetic stimulation have eliminated the possibility that such pathology may be secondary sympathetic effects resulting from the parasympathetic activation. The present experiments were performed to study possible myocardial pathology produced by parasympathetic stimulation while abolishing the possibility of simultaneous sympathetic influences.

*Method.* Adult cats (2.4–3.6 kg) were anesthetized with iv administration of Na thiamylal. A tracheal cannula was inserted, the spinal cord sectioned at $C_2$ after infiltration with procaine, and the animal artificially ventilated. Both vagi were cut, and electrodes placed on their distal-cut end. Femoral arterial pressure and standard Lead II ECG were continuously monitored. Propranolol (1–2 mg/kg) was administered either intraperitoneally before spinal cord section or intravenously immediately after spinal cord section to abolish beta-receptor effects within the myocardium. Propranolol at this dose blocked the hemodynamic effects of isoproterenol (3 $\mu$g/kg), thus established the adequacy of beta-blockade (8). In 11 experimental cats, electrical stimulation from a Nuclear-Chicago constant-current stimulator was applied to the electrodes positioned on the vagus. The stimulus parameters used (30 Hz, 0.5 msec, 0.05–2.0 mA) were sufficient to reduce the heart rate approximately 45% without lowering mean blood pressure below 50 mm Hg. This stimulation was continued for 15–60 min intervals and produced a sustained bradycardia lasting for 1–4 hr. At the conclusion of the experiments, the hearts were immediately removed and immersed in 10% formalin. After fixation and paraffin embedding, three 5-$\mu$m sections from each cat (atrium and lower midventricles) were stained according to H and E, Gomori, and Masson trichrome methods. These sections were compared with myocardial tissue obtained from two cats not subjected to any aspect of the experiment, and three cats subjected to all aspects of the experiment except vagal stimulation.

*Results.* The cardiovascular and morphological data from 16 cats are tabulated in Table I. Right or left vagal stimulation effectively reduced the heart rate without appreciable change in blood pressure. Although the cardiovascular data elicited by both right and left vagal stimulation were

[1] This study was supported by U.S. Public Health Service Grant HE-13454. The technical assistance of Paul Carmichael, Andrew Browe, and F. T. Grove are gratefully acknowledged.

TABLE I. Effects of Vagal Stimulation.

| Cat[a] | Stimulation time (min) | Heart rate (beats/min) | | | Av mean blood pressure (mm Hg) | | |
|---|---|---|---|---|---|---|---|
| | | Before | During | % Change | Before | During | Lesions[b] |
| ER-1 | 60 | 140 | 81 | 42 | 53 | 35 | 1 |
| ER-2 | 60 | 169 | 68 | 60 | 60 | 53 | 0 |
| ER-3 | 60 | 123 | 75 | 40 | 62 | 57 | 2 |
| ER-4 | 60 | 176 | 105 | 40 | 82 | 68 | 1 |
| ER-5 | 60 | 200 | 114 | 43 | 59 | 57 | 1 |
| ER-6 | 60 | 157 | 84 | 46 | 93 | 71 | 0 |
| ER-7 | 60 | 133 | 70 | 55 | 83 | 66 | 0 |
| ER-8 | 120 | 167 | 89 | 47 | 60 | 51 | 1 |
| EL-1 | 240 | 184 | 94 | 48 | 83 | 45 | 0 |
| EL-2 | 240 | 119 | 82 | 31 | 103 | 85 | 1 |
| EL-3 | 240 | 138 | 98 | 44 | 87 | 50 | 0 |
| HC-1 | | | | | | | 0 |
| HC-2 | | | | | | | 1 |
| C-1 | | | | | | | 0 |
| C-2 | | | | | | | 1 |
| C-3 | | | | | | | 1 |

[a] ER: Experimental cat with right vagal stimulation, EL: experimental cat with left vagal stimulation, HC: histological control cat not exposed to any aspect of the experiment, C: control cat exposed to all aspects of the experiment except vagal stimulation.

[b] Lesions: 0, no tissue changes; 1, isolated fuchsinophilia (or myocytolysis); 2, isolated fuchsinophilia and myocytolysis; 3, extensive fuchsinophilia (or myocytolysis); 4, extensive fuchsinophilia and myocytolysis.

comparable, the threshold for the effect was lower in the right vagus. While the effects were obtained from the right vagus with currents between 0.05 and 0.5 mA, the level for the left vagus was between 0.9 and 2.0 mA. This difference in effectiveness between the two vagi may be subject to more than one interpretation related to either the differential innervation of the atrial and ventricular musculature by the vagus or the quantitative release of acetycholine at the neuroeffector site.

The myocardium from these cats was examined for myofibrillary degeneration of the type which has been associated with CNS disturbances of cardiovascular function (9). These changes are fuchsinophilia related to selective affinity of portions of myocardial cells for fuchsin stain and myofibrillary disintegration indicated by cell loss and vacuole formation. A grading system based on a comparison of the extent of these lesions with those observed in other experiments (1, 3) was developed, and the myocardial tissue from the cats in the present experiment was rated from 0 to 4 (Table I). Fuchsinophilia was observed most often in the subendocardial tissue of the ventricles. In the myocardium, the fuchsin stain was occasionally seen to involve either the entire cell, a portion of its length, or a distribution forming segmental transverse bars. In comparison with control animals, the extent of fuchsinophilia was no greater with than without vagal stimulation. While some myofibrillary disintegration was also evident, no distinction of myocardial change could be made between control and experimental cats. Furthermore, no hemorrhages normally associated with myocardial infarction were observed in the myocardial or subendocardial tissue.

*Discussion.* These experiments appear to indicate that parasympathetic stimulation alone fails to elicit myocardial degeneration. Although vagal stimulation produced marked bradycardia, this alteration and associated release of acetylcholine did not produce significant morphological changes in the myo-

cardium. These data are contrary to the observations of Manning *et al.* (6) and Groover and Stout (2). Both of these studies reported that vagal stimulation in anesthetized animals resulted in subendocardial and myocardial hemorrhages and hyaline degeneration. Because the intact vagi were stimulated, secondary sympathetic activation via vagal afferents to the CNS also occurred. Furthermore, the myocardial necrosis was similar to that attributed to CNS sympathetic activation (7) and infusion of norepinephrine (8). Because the sympathetic effect was abolished in the present experiments by vagal section, cordotomy, and propranolol, the absence of myocardial changes substantiates that a sympathetic mechanism plays a dominant role in myofibrillary degeneration observed by previous investigators. Furthermore, pure parasympathetic stimulation appears to be incapable of producing morphological myocardial alterations.

*Summary.* In spinal cats vagotomized and administered sufficient propranolol to block cardiac beta-receptors, the effect of vagal stimulation of the myocardium was studied. With this stimulation, a bradycardia was sustained for 1- to 4-hr intervals. Examination of the myocardial tissue from atria and ventricles revealed, however, no myofibrillary or vascular changes. Since these results indicate that this vagal stimulation did not produce myocardial necrosis, alterations in cardiac tissue attributed by other investigators to parasympathetic activation would appear to involve secondary sympathetic effects.

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Received Mar. 20, 1973. P.S.E.B.M., 1973, Vol. 144.