Reduction of the Cardiac Response to Postganglionic Sympathetic Nerve Stimulation in Experimental Heart Failure

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ABSTRACT

The functional significance of the reduction of the heart's norepinephrine stores which occurs in experimental heart failure was studied. The responses to right and left cardio-accelerator nerve stimulation were studied in normal dogs and in dogs with chronic congestive failure and reduced myocardial norepinephrine stores. Both the chronotropic and inotropic responses to nerve stimulation were found to be markedly reduced in the animals with congestive failure. Since the myocardium of the dogs with heart failure responded normally to exogenously administered norepinephrine, it was concluded that the norepinephrine depletion reduces the quantity of neurotransmitter released per nerve impulse. Thus, norepinephrine depletion interferes with the ability of the adrenergic nervous system to support the failing myocardium and in this manner it may intensify the congestive heart failure state.

ADDITIONAL KEY WORDS

cardiac norepinephrine stores myocardial contractile force adrenergic nervous system inotropic response chronotropic response anesthetized dogs

Recent studies have demonstrated that the norepinephrine (NE) concentration in cardiac tissue is markedly reduced in some patients with congestive heart failure, and similar reductions have also been observed in experimentally produced right and left ventricular failure. In the latter studies it was established that the changes in NE concentration are not simply due to a dilution of a normal complement of the adrenergic neurotransmitter in hypertrophied myocardial tissue, but reflect a true depletion of the total store of cardiac NE. Furthermore, this depletion of cardiac NE was sufficient to reduce markedly the response of isolated papillary muscles to tyramine, both in the tissues removed from experimental animals and from patients with heart failure. These chemical and pharmacological observations suggested the possibility that an interference with terminal adrenergic transmission may occur in congestive heart failure.

The positive inotropic influence of cardiac sympathetic nerve activity has been well established, and it has been postulated that this activity may play an important role in supporting the function of the failing heart. The reduction of NE stores in failing hearts has suggested that interference with sympathetic transmission may occur in congestive heart failure. If such an alteration in sympathetic function does exist, it would remove an important compensatory mechanism and it might contribute to the further deterioration of cardiac function. The present investigation was done to study this problem by comparing the chronotropic and inotropic responses to graded stimulation of the sympathetic nerves in dogs with chronic right ventricular failure with the responses of normal animals.

Methods

The responses to right stellate ganglion stimulation were studied in thirteen normal mongrel
dogs weighing between 16 and 22 kg, and in six dogs with experimentally produced heart failure and weighing between 19 and 23 kg. Tricuspid insufficiency and pulmonic stenosis were produced in six dogs using the technique described by Barger and associates and subsequently employed by other investigators, or by a modification of this technique, using a one-stage procedure in which the tricuspid valve is approached through the right ventricle. All animals were studied five to seven weeks following thoracotomy and all had developed ascites three to four weeks prior to study.

The dogs were anesthetized with Na pento-barbital (30 mg/kg); respiration was maintained with 100% O₂, a cuffed endotracheal tube, and Harvard respiratory pump. The right stellate ganglion and right ventricle were exposed through a right thoracotomy; the descending sympathetic chain and associated ganglia were excised from the stellate ganglion to the level of the sixth thoracic vertebral body; the accelerator branch was dissected free and stimulated with impulses of 5 msec duration and 8 volts intensity.* The frequency of stimulation was varied from 0.25/sec to 9/sec and the nerves were stimulated for 15 seconds at each frequency. Right ventricular contractile force was measured with a Walton-Brodie strain gauge arch sutured to the ventricular wall, and was recorded along with the electrocardiogram and aortic pressure. Relative changes in peak contractile force were expressed as per cent change above control.

In the right ventricle of the dogs with heart failure, which form the basis of the present report, both the concentration and total quantity of NE were markedly reduced, averaging respectively 0.18 ± 0.07 μg/g heart weight (±SE) and 0.29 ± 0.13 μg/kg body weight compared to 0.84 ± 0.09 μg/g and 1.14 ± 0.12 μg/kg in a group of control dogs studied previously in this laboratory. Similar reductions of these NE values were seen in the left ventricle of the dogs with heart failure, in which the concentration and total quantity averaged 0.28 ± 0.07 μg/g and 0.77 ± 0.22 μg/kg respectively compared to 0.86 ± 0.07 μg/g and 3.89 ± 0.30 μg/kg in the control dogs. The ratio of right ventricular to left ventricular weight was significantly elevated in the dogs with right ventricular failure, averaging 0.54 compared to 0.33 in control dogs (P < 0.01). The concentration of NE in the right atrium tended to be re-

**Results**

In the right ventricle of the dogs with heart failure, which form the basis of the present report, both the concentration and total quantity of NE were markedly reduced, averaging respectively 0.18 ± 0.07 μg/g heart weight (±SE) and 0.29 ± 0.13 μg/kg body weight compared to 0.84 ± 0.09 μg/g and 1.14 ± 0.12 μg/kg in a group of control dogs studied previously in this laboratory. Similar reductions of these NE values were seen in the left ventricle of the dogs with heart failure, in which the concentration and total quantity averaged 0.28 ± 0.07 μg/g and 0.77 ± 0.22 μg/kg respectively compared to 0.86 ± 0.07 μg/g and 3.89 ± 0.30 μg/kg in the control dogs. The ratio of right ventricular to left ventricular weight was significantly elevated in the dogs with right ventricular failure, averaging 0.54 compared to 0.33 in control dogs (P < 0.01). The concentration of NE in the right atrium tended to be re-

*American Electronic Laboratories stimulator, model 104A.
SYMPATHETIC STIMULATION IN HEART FAILURE

Mean percentage increases in right ventricular contractile force at 5 frequencies of right cardio-accelerator nerve stimulation in control and failure animals.

The responses of heart rate and right ventricular contractile force to stimulation of the right cardio-accelerator nerve were reduced in the dogs with heart failure when compared to the responses in control animals (figs. 1 to 3). In the latter, the basal heart rate with the dog anesthetized and the chest open, averaged $152 \pm 3.2$ beats per minute (bpm), and the mean maximal increment in heart rate with nerve stimulation was $76 \pm 4.3$ bpm. This response was achieved at a frequency of stimulation of 5 impulses/sec, with no further augmentation of heart rate occurring as the frequency of stimulation was increased to 9 impulses/sec. In these dogs the increase produced even more strikingly than in the ventricles, and averaged 0.13 µg/g in the dogs with heart failure, compared to the normal level of 1.97 µg/g in control dogs previously reported from this laboratory.\(^{11}\)

Records showing the effect of right cardio-accelerator stimulation in a normal dog (panel A) and a dog with congestive failure (panel B).

\(\text{FIGURE 2}\)

\(\text{FIGURE 3}\)
in heart rate occurring with 1.0 impulse/sec was \(37 \pm 5.0\) bpm. In the six animals with heart failure, the basal heart rate averaged \(122 \pm 4.2\) bpm and the average increment in rate reached a maximum of only \(26 \pm 7.7\) bpm, a change which was significantly \((P < 0.01)\) less than that observed in the control dogs; this maximum response occurred with 9 impulses/sec. Only four of these six dogs exhibited any increase in heart rate when stimulated at the rate of 1.0 impulse/sec, and in these four animals the increase averaged only 6 bpm.

In the control dogs the peak systolic right ventricular contractile force increased by a maximum value which averaged \(27.8 \pm 5.8\)\% of control with stimulation of the right cardio-accelerator nerve and this occurred at 2 to 10 \((\text{avg} = 4.8)\) impulses/sec. In the dogs with heart failure a significantly \((P < 0.01)\) lower response was observed, with the maximum increment averaging only \(10.4 \pm 4.3\)\% above the prestimulatory level and this occurred at 2 to 10 \((\text{avg} = 5.5)\) impulses/sec. All control animals responded to stimulation at 1 impulse/sec with an increment in contractile force averaging \(14.4 \pm 2.9\)\%. Only two of the five dogs in which force was measured at a frequency of stimulation of 1.0 impulse/sec showed an augmentation of contractile force, and in these two animals the increments averaged only 5\% of control (fig. 3). The normal chronotropic and inotropic responses to stimulation of the left cardio-accelerator nerve were also found to be absent in the single animal with heart failure tested (fig. 4).

In the three control dogs in which heart rate was increased progressively by electrical stimulation of the right atrium, the changes in right ventricular contractile force were \(-18, -7, \) and 0\% of control respectively, with increments of rate averaging 74/min. When exogenous NE \((3 \mu g/kg)\) was administered, right ventricular force increased by an average of 105\% in the control dogs and by 98.7\% in the animals with heart failure, a difference which was not significant \((P > 0.1)\).

**Figure 4**

Records showing the effect of left cardio-accelerator stimulation in a normal dog (panel A) and a dog with congestive failure (panel B).
Discussion

It is well established that the intraneuronal pool of NE is not homogeneous, and is divided into at least two major functional compartments. Crout and associates observed that atria removed from reserpine-treated, NE-depleted, guinea pigs did not respond to tyramine, but that the functional response could be restored by repleting only 1 to 2% of the normal NE stores. In intact dogs the chronotropic response to cardioaccelerator nerve stimulation was shown to be preserved after reserpine treatment, with reductions of NE stores by as much as 85% of normal. Similarly, Anden et al. have reported that a response to adrenergic nerve stimulation can be elicited in reserpine-treated animals with only a small fraction of the normal store of the neurotransmitter. From these considerations it is clear that it would be hazardous, on the basis of cardiac NE measurements alone, to conclude that heart failure is associated with a disturbance in transmission at the adrenergic neuro-effector junction. The findings of the present study, however, indicate that experimental heart failure is associated with marked reductions in the inotropic and chronotropic responses to electrical stimulation of the cardiac sympathetic nerves. It is notable that the impulse frequency-response curve was not simply shifted to the right, but showed an overall depression of the maximal response.

Consideration was given to the possibility that the difference in the increases in force resulting from nerve stimulation observed in the two groups of animals could be accounted for by the larger increases in heart rate which occurred in the control dogs. However, this was excluded by experiments in which increments in rate similar to those observed during cardioaccelerator nerve stimulation were produced by electrical stimulation of the atrium, and either no change or a small decrease in contractile force occurred. Furthermore it was shown that the myocardium of the dogs with heart failure responded normally to exogenously administered NE. From these observations it may be concluded that the amount of neurotransmitter released per nerve impulse is reduced markedly in experimental heart failure with cardiac NE depletion. Since the maximum responses to nerve stimulation were very small, it would appear that even an abnormal increase in the impulse traffic along the cardiac sympathetic nerves will not augment the contractile state of the failing myocardium substantially. These findings indicate that the functional defect in the cardiac sympathetic nerves involves either a depression of NE contained in each sympathetic nerve ending and/or a reduction in the number of functional nerve endings. The results of other studies lend support to the second explanation.

When the results of this investigation are considered together with those of other recent studies, the following sequence of events may be postulated to occur in congestive heart failure: A decrease in myocardial contractility occurs, as has been shown in the reduced peak tensions developed by the papillary muscles removed from patients with congestive heart failure. In order to maintain circulatory function at an appropriate level, sympathetic activity is augmented. This is reflected in the increased basal excretion of NE as well as in the excessive elevations of circulatory NE during exercise in patients with heart failure. Persistence of heart failure is associated with depletion of cardiac NE stores. This depletion does not appear to depress the intrinsic contractility of the myocardium, since both the peak tension as well as the maximum velocity of shortening of isolated papillary muscles removed from chronically denervated NE-depleted cats have been shown to be normal. However, as noted in the present study, the NE depletion certainly interferes with function of the adrenergic neuro-effector junction and hence reduces the ability of the adrenergic nervous system to support the function of the failing myocardium. In this manner the abnormality of cardiac sympathetic function may intensify the severity of congestive heart failure.
References


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