Section of Experimental Medicine and Therapeutics

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Paper

The Adrenergic Nervous System in the Control of the Normal and Failing Heart

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The contractile activity of the heart is modulated by two major influences: (1) The Frank-Starling mechanism, i.e. the dependence of the mechanical activity of the ventricle on the end-diastolic fibre length. (2) The intensity of stimulation provided by catecholamines, which determine the level of myocardial function at any given ventricular end-diastolic fibre length (Braunwald 1965). The myocardium is richly supplied with postganglionic sympathetic nerves and when these nerves are stimulated their endings release noradrenaline (NA), the neurohumoral transmitter substance, which in turn augments the myocardial contractile state.

The role of the adrenergic system in circulatory regulation can be appreciated by studying the effects of its removal or blockade on cardiovascular dynamics. The cardiac output was found to be normal at rest in intact, conscious dogs which had previously been subjected to total extrinsic cardiac denervation (Glick *et al.* 1964). However, when the circulation was stressed acutely with the induction of severe isovolæmic anæmia, the cardiac output increased significantly more in the intact dogs than in the animals with denervated hearts. Furthermore, while the increase in cardiac output in the intact dogs stemmed predominantly from a rise in heart rate, in the denervated dogs the increase in output tended to be more the result of an augmentation in stroke volume. Thus, in the absence of a functioning autonomic nervous system, the animals appeared to fall back upon what may be looked upon as a reserve mechanism for the augmentation of cardiac output, i.e. elevation of stroke volume.

The role of the adrenergic nervous system in man can now be assessed by using adrenergic blocking drugs. The administration of guanethidine, which blocks adrenergic transmission at the neuroeffector junction, did not influence the cardiac output or arterial pressure of normal subjects studied in the supine position, although it lowered their heart rate. However, during the stress of muscular exercise, the drug resulted in lower levels of cardiac output, mean arterial pressure and left ventricular work than those occurring during the control exercise period (Kahler *et al.* 1962). It was then shown that reflex venoconstriction occurs during exercise, and since this reflex could be blocked with guanethidine, its efferent limb evidently traverses adrenergic fibres (Mason & Braunwald 1964).

To study the effects of blocking the excitatory action of the adrenergic nervous system on only the heart, the beta adrenergic blocking drug propranolol was used instead of guanethidine. This agent had little effect on circulatory dynamics in normal subjects at rest, but it invariably caused a reduction in heart rate, cardiac output, mean arterial pressure, and left ventricular minute work achieved during exercise, while the arteriovenous O_2 difference and central venous pressure were higher than during exercise before beta blockade. Furthermore, the capacity of the subjects to perform strenuous exercise was much reduced (Epstein *et al.* 1965). It was therefore concluded that adrenergic nervous stimulation of the heart plays a significant role in mediating the normal response to exercise in man.

From these studies it appears that the adrenergic nervous system is of relatively little importance to the normal organism in the basal state (Glick & Braunwald 1965). However, when a load is placed on the circulation and a potential imbalance exists between the cardiac output and the perfusion requirements of the peripheral tissues, as occurs during severe anæmia or muscular exercise, the augmentation of cardiac performance provided by the adrenergic nervous system becomes important (Braunwald, Chidsey, Harrison, Gaffney & Kahler 1963).

The adrenergic nervous system plays a particularly prominent role in supporting myocardial function when the latter is depressed in congestive

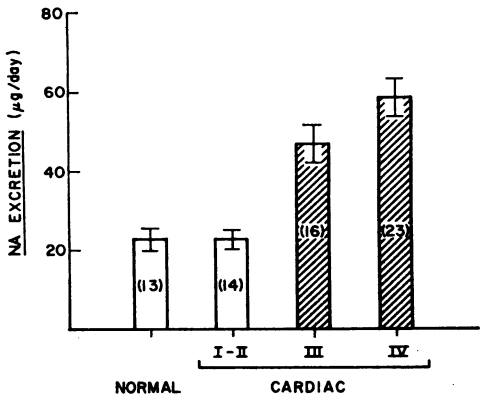

Fig 1 *Urinary NA excretion in normal control subjects, in cardiac patients without failure (Classes I–II, New York Heart Association Classification), and in patients with failure (Classes III and IV). The average values and their standard errors are shown*

heart failure. An index of the activity of this system, at rest and during exercise, was provided by measurements of the concentration of NA in arterial blood (Chidsey *et al.* 1962). No change or very small increases in the NA concentrations were noted during exercise in normal subjects, while much greater increases occurred in patients with congestive heart failure, presumably reflecting an increased activity of the adrenergic nervous system during exercise in these patients.

Measurements of twenty-four-hour urinary NA excretion were made in order to determine whether the activity of the adrenergic nervous system is also augmented at rest in patients with congestive heart failure (Chidsey, Braunwald & Morrow 1965). Normal subjects and patients with heart disease without heart failure on average excreted 22·5±2·6 µg NA/day. However, the NA excretion was significantly raised in patients with heart failure, averaging 46·4 µg/day in patients with moderate disability and 58·1 µg/day in patients with marked disability (Fig 1). Studies on the decline of specific activity of urinary NA following the administration of radioactive NA suggest that the increase in the excretion of NA may not be associated with an alteration of its turnover rate within the intraneuronal pools from which it is derived (Chidsey & Braunwald 1966). From these studies the sympathetic neurone might be pictured as constantly synthesizing NA at a rate which is unrelated to the secretion rate of the neurotransmitter. No change in formation need occur during augmented secretion, but simply more of the formed NA is released and less is destroyed intraneuronally.

The importance of the augmented activity of the adrenergic nervous system in maintaining ventricular contractility when the function of the myocardium is depressed in congestive heart failure is shown by the effects of adrenergic blockade in patients with heart failure. In patients on a metabolic diet guanethidine frequently caused sodium and water retention, as well as intensification of heart failure (Gaffney & Braunwald 1963). Recently, we have made similar observations on the aggravation of congestive heart failure with propranolol (Epstein & Braunwald, in preparation). The adrenergic nervous system thus plays an important compensatory role in the circulatory adjustments of patients to congestive heart failure and caution is needed in the use of anti-adrenergic drugs such as reserpine, guanethidine, and propranolol in the treatment of patients with limited cardiac reserve.

Because of the chronic hyperactivity of the sympathetic nervous system in clinical congestive heart failure described above, we became interested in the effects of heart failure on the cardiac stores of the neurotransmitter. The concentration of NA in atrial tissue removed at operation in 34 patients who had not suffered heart failure averaged 1·77 µg/g; this value was significantly lower, averaging 0·49 µg/g, in 49 patients with heart failure (Fig 2). In 8 of these patients extremely low values were found with NA concentrations less than 10% of the average normal level (Chidsey *et al.* 1963, Braunwald, Chidsey, Mason & Morrow 1963). The NA concentration was also measured in papillary muscles removed from the left ventricles of patients undergoing

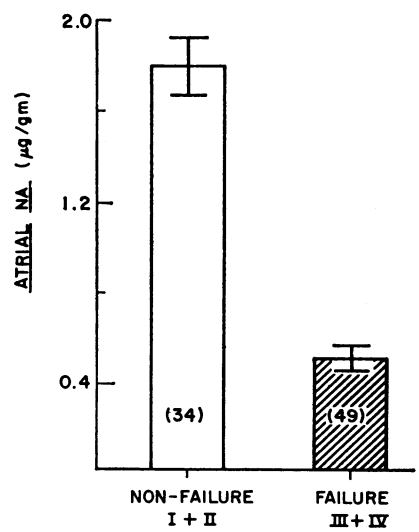

Fig 2 *Concentration of NA in atrial appendage biopsies taken during cardiac operations from 34 patients without heart failure (non-failure, Classes I+II) and 49 patients with heart failure (failure, Classes III+IV). The average values and their standard errors are shown*

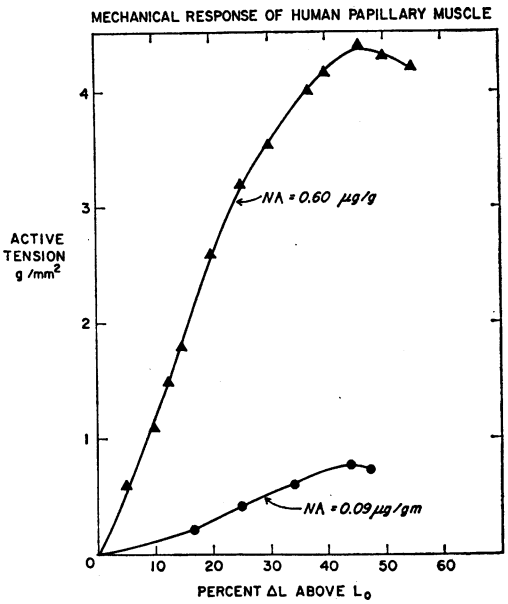

Fig 3 *Length/active tension curves in two human left ventricular papillary muscles determined* in vitro. *The active tension developed isometrically is plotted along the ordinate, at progressively increasing muscle lengths, expressed on the abscissa as percentage increase* (ΔL) *above the muscle length at which no tension was developed* (L_0). *One muscle having only a slight depression of NA concentration, 0·6 µg/g* (▲), *has a maximum active tension of 4·5 g/mm² while the other with a markedly reduced NA concentration, 0·09 µg/g* (●), *has a much lower maximum active tension, 0·9 g/mm². (Reproduced from Chidsey, Sonnenblick, Morrow & Braunwald, 1965, by kind permission of the American Heart Association, Inc.)*

mitral valve replacement, and the levels were found to be markedly depressed in many patients who had been in severe left ventricular failure (Chidsey, Braunwald & Morrow 1965). The function of these papillary muscles was also assessed *in vitro* by measuring the maximum isometric tensions which the muscles could develop. The maximum tensions developed were significantly correlated with the NA concentrations, the muscles with the lowest NA concentrations developing the smallest forces (Chidsey, Sonnenblick, Morrow & Braunwald 1965) (Fig 3). In spite of these correlations there is no evidence to suggest that the reduction of the contractile state of the muscle removed from patients with heart failure is due to a decrease in its NA concentration (Spann, Sonnenblick, Cooper, Willman, Chidsey & Braunwald 1965). The contractile responses of these human papillary muscles to tyramine were also evaluated. Since this amine stimulates cardiac muscle indirectly through the release of stored NA, it served as a pharmacological tool for assessing the functional capacity of the chemically measured NA. In the muscles in which the NA concentration exceeded 0·3 µg/g and averaged 0·53 µg/g, tyramine increased the maximum isometric tension by an average of 21%; on the other hand, in muscles with a concentration less than 0·3 µg/g and which averaged 0·16 µg/g, tyramine caused no increase or an actual reduction of tension.

Since the changes in cardiac NA concentration occurring in some patients with heart failure were thus shown to be severe enough to affect adrenergic function, we attempted to define the mechanism by which this depletion occurred, using dogs with right ventricular failure produced by creating tricuspid insufficiency and pulmonary stenosis (Chidsey *et al.* 1964). The cardiac NA concentrations were greatly reduced and this reduction was not the result of a simple dilution of sympathetic nerve endings in a hypertrophied muscle mass, since the total ventricular NA contents were lowered, both in the right and left ventricles (Fig 4). When the papillary muscles obtained from the failing hearts were compared *in vitro* to those obtained from normal dogs, their contractions in response to added NA were normal, but their responsiveness to tyramine was markedly impaired, providing evidence for the functional significance of the NA depletion.

After the production of heart failure in the guinea-pig by constricting the aorta, the left ventricular NA concentration fell to values approximately 30% of normal (Spann *et al.* 1964). We wondered whether a repletion of the cardiac NA stores could be achieved, since such repletion might provide a valuable therapeutic approach to heart failure in man. The infusion of a large dose of NA (2 µg/kg) raised cardiac NA to 3·2 µg/g in normal animals, but only to 1·0 µg/g in guinea-pigs with heart failure (Spann, Chidsey, Pool &

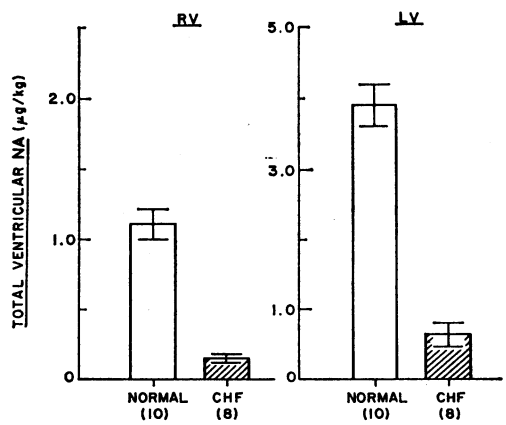

Fig 4 *Total ventricular noradrenaline* (*NA*) *content in normal dogs and in dogs with pulmonary stenosis, tricuspid insufficiency and congestive heart failure* (*CHF*). *The average values are given with their standard errors.* RV, *right ventricle.* LV, *left ventricle*

Braunwald 1965). Lesser reductions in the uptake of trace quantities of radioactive NA were demonstrated in both dogs and guinea-pigs with experimental heart failure (Chidsey *et al.* 1964, Spann, Chidsey, Pool & Braunwald 1965). We thought that this altered capacity to retain administered NA might be due either to a reduction in the total number of nerves in the myocardium or to a diminution of the intraneuronal binding sites. However, heart failure was found not to alter the intracellular distribution of endogenous NA in the guinea-pig heart (Spann, Chidsey, Pool & Braunwald 1965), indicating that preferential depletion of intraneuronal binding particles does not occur. The subcellular distribution of administered radioactive NA in the NA-depleted, failing dog heart was studied and again it was observed that, when markedly reduced but still measurable quantities of endogenous NA were present, both the fraction of the administered radioactive NA in the microsomal bound fraction and its distribution in the sucrose gradient were essentially normal (Chidsey & Braunwald 1966). Thus, there is no evidence for any qualitative abnormality in the distribution of the reduced catecholamine stores in the failing heart, nor for any abnormality in the distribution of the reduced quantities of NA taken up by it.

The rate of formation of NA was estimated by measuring the turnover of the radioactively labelled amine in the guinea-pig heart (Spann, Chidsey, Pool & Braunwald 1965). After administration of radioactive NA similar rate constants of decay were found in both groups of hearts. Since the turnover rate was not altered in the hearts of animals with heart failure in which the NA pool size was reduced, the synthesis of NA must be diminished in proportion to the change in pool size.

Although the mechanism ultimately responsible for the striking changes in the concentration, content, uptake, and rate of formation of NA in the myocardium in congestive heart failure remains to be elucidated, some of the consequences of these changes are already clear. In collaboration with Dr James Covell we have observed that on supramaximal stimulation of the right cardiac accelerator nerve much smaller increments of heart rate and contractile force occurred in animals with heart failure than in normal dogs. Thus, it is likely that when congestive heart failure is accompanied by depletion of cardiac NA stores, the quantity of NA released by the sympathetic nerve endings in the heart is deficient relative to the impulse traffic along the adrenergic cardiac nerves. In view of the strongly positive inotropic effect exerted by the NA released from these nerves, the adrenergic nervous system may be considered to provide potential support to the failing myocardium. However, if the reduction of NA stores in some instances of heart failure is associated with a diminished release of neurotransmitter, as now appears to be the case, then this depletion of NA may be responsible for loss of the much-needed adrenergic support to the failing heart and so intensify the severity of congestive heart failure.

Conclusions

The adrenergic nervous system provides one of the major control mechanisms of myocardial function. This system is relatively inactive in the normal heart when the organism is in the basal state. However, the adrenergic nervous system plays a progressively more important role as the normal circulation is stressed, or as the contractile state of the myocardium deteriorates in congestive heart failure. There is pronounced overactivity of the adrenergic nervous system in patients with heart failure, both at rest and during muscular exercise, and this is often associated with profound depletion of cardiac NA stores. Marked reductions, both in the concentration and total content of cardiac NA stores occur in animals with experimental heart failure, and abnormalities in the rate of formation, uptake and binding of NA in these failing hearts have also been documented. The reduction of cardiac NA stores diminishes the quantity of NA released by nerve stimulation and this defective function may then further intensify the congestive heart failure state by removing the support to myocardial function provided by release of NA in the heart.

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