

Augmentation of the plasma norepinephrine response to exercise in patients with congestive heart failure

C.A. Chidsey, D.C. Harrison, E. Braunwald

N Engl J Med. 1962;267:650-655

Starling expounded his Law of the Heart in 1915. Its almost biblical resonance and authority dominated physiological thought through two world wars. "The mechanical energy set free on passage from the resting to the contracted state depends (...) on the length of the muscle fiber." The Law had, however, the characteristic defect of a purely benchtop experiment extrapolated into the complex world of a man's body in action. And, eventually, Sarnoff and Berglund in the 1950s showed that a whole family of Starling's curves relating cardiac output to filling pressure could be derived at different degrees of sympathetic stimulation. By 1965, Hamilton and Richards could state: "Without the coordinating stimulus of the central nervous system and the hormonal control governed by this system, the truly isolated heart seems to vary its pumping function between that of a normal resting animal and that of a heart in an animal moribund in the last stages of shock."

In normal life, the greatest increases in cardiac output are to be found during physical exercise, so that it was reasonable to imagine that this increase would be made possible by increased sympathetic activity. In 1952, von Euler and Hellner showed that the excretion of norepinephrine in the urine was increased during exercise in normal men.

These were also the years in which, following the introduction of cardiac catheterization by Cournand and Richards, the cardiac output was being measured in man under all sorts of conditions. In patients with congestive cardiac failure, the cardiac output was low and did not increase to the normal extent during exercise. Was this because there was an inadequate sympathetic stimulus during exercise? Or was there increased sympathetic outflow, but the damaged heart was unable to respond?

Measurements of norepinephrine in the blood had to wait, as is often the case, for a reliable method; but in 1961, von Euler and Lishajko published their fluorometric technique. Thus, by 1962, when Chidsey had moved from Cournand's laboratory, where we had worked together, to Braunwald's laboratory, the stage was set to investigate the role of the sympathetic in patients with congestive cardiac failure at rest and during exercise. The paper by

Chidsey, Harrison, and Braunwald is a precisely designed and executed study that left no doubts and was to suffer the fate of a classic—always referred to, but seldom read. It is worth reading for its simple and unambiguous writing; and to see what it was like in the good old times when editors had more space for original data than for glossy ads.

They studied five normal subjects and 10 patients with heart disease, of whom 9 had rheumatic heart disease and one cardiomyopathy. Seven of the patients were in congestive cardiac failure.

The normal subjects undertook exercise first at a moderate level for 6 minutes and then at a more intense level for 6 minutes. The cardiac patients undertook only the moderate level of exercise. The oxygen uptake rose from 151 to 477 mL·min⁻¹·m⁻² in normal subjects during moderate exercise, and from 159 to 463 mL·min⁻¹·m⁻² in the patients with congestive cardiac failure. Patients therefore undertook the same moderate exercise as the normal subjects. But the heart rate, which rose from 69 to 104 beats/min in the normal subjects, increased from 88 to 142 beats/min in the patients with congestive cardiac failure. In the normal subjects, the arterial norepinephrine rose from 0.28 to 0.46 g/L; in the patients with congestive cardiac failure it rose from 0.63 to 1.73 g/L. In the patients without failure, the levels of norepinephrine were within the normal range under both conditions. Epinephrine was not affected.

"It is concluded that the excessive augmentation of the plasma norepinephrine during exercise in these patients with congestive heart failure reflects an increased response of the sympathetic nervous system and that this response may have an important supportive role in such patients."

The results were too good for any statistics.

1962

Adolf Eichmann is hanged for his Nazi war crimes;
James Watson, Francis Crick, and Maurice Wilkins
share the Nobel Prize for Medicine;
and Marilyn Monroe dies, aged 36



The renin-angiotensin-aldosterone system in congestive failure in conscious dogs

L. Watkins Jr, J.A. Burton, E. Haber, J.R. Cant, F.W. Smith, A.C. Barger

J Clin Invest. 1976;57:1606-1617

These aptly designed experiments, quoted much less often than their importance warrants, were carried out in the mid-seventies. By that time, a role of the renin-angiotensin-aldosterone system in congestive cardiac failure was suspected, but the measurement of plasma renin activity and aldosterone in patients with the clinical condition had given diverse results. It seemed that the renin-angiotensin-aldosterone system was stimulated in some patients, but not in others.

Watkins and his colleagues had already studied dogs in which congestive cardiac failure had been induced by pulmonary artery ligation and tricuspid incompetence, but they appreciated that, by the time the animals had recovered from the effects of the operation, the initial neurohumoral response to the cardiac damage may well have passed off. They therefore sought to reproduce the hemodynamic conditions of cardiac failure by implanting inflatable balloons around the pulmonary artery or the inferior vena cava of dogs, so that at a later date congestive cardiac failure might be initiated in conscious animals. The cuffs were then maintained inflated for a period of 2 weeks.

The immediate effect of inflating the cuffs was a fall in arterial pressure. This was accompanied by an increase in plasma renin activity, plasma aldosterone, and water intake, and by near total sodium retention. In the days succeeding a moderate degree of inflation, the body weight and plasma volume increased, and ascites and edema developed. As the plasma volume increased, the arterial pressure became restored to normal and plasma renin activity, plasma aldosterone, and renal excretion of sodium also returned to normal values. In animals with more severe constriction, the arterial pressure did not recover, and the levels of plasma renin activity and plasma aldosterone remained high throughout.

In the early days following a moderate degree of constriction, when plasma renin activity was high, the intravenous injection of a converting enzyme inhibitor caused an abrupt decrease in arterial pressure, but later, when the level of plasma renin activity had returned to

normal, this did not happen. Chronic infusion of the converting enzyme inhibitor prevented the restoration of arterial pressure and suppressed the increase in plasma aldosterone, while sodium retention was less than in control experiments.

It was noted that the above effects were much greater in inferior vena caval constriction than in pulmonary artery constriction. It is interesting to follow the way in which authors attempted to explain this. "A growing body of evidence," they write, "suggests that the cardiopulmonary pressures (atrial, pulmonary venous, or ventricular end-diastolic) may modify the release of renin." It wasn't a bad attempt. De Bold's paper (*see review page 220*) on the atrial granules appeared just 3 years later, and subsequent research would point to the influence of atrial natriuretic peptide. The peptide would have been released during constriction of the pulmonary artery as the right atrial pressure rose, but constriction of the inferior vena cava was accompanied by a decrease in right atrial pressure and a decreased stimulus for release of atrial natriuretic peptide.

These studies revealed the feedback mechanism through which the renin-angiotensin-aldosterone system operates in congestive cardiac failure. The initial threat to the arterial pressure evokes an increased plasma renin activity and plasma aldosterone. Angiotensin II is of immediate help in maintaining the arterial pressure by peripheral arterial vasoconstriction. Then, in the period which follows, the expansion of the plasma volume through the sodium-retaining properties of aldosterone and the action of angiotensin II to increase thirst completes the restoration of the arterial pressure and the system shuts off.

1976

The United States celebrates its Bicentennial year;
Milton Friedman (USA) is awarded
the Nobel Prize in Economic Sciences;
and Benjamin Britten, the English composer,
dies, aged 63

Heart atrial granularity: effects of changes in water-electrolyte balance

A.J. de Bold

Proc Soc Exp Biol Med. 1979;161:508-511

The discovery of the function of the atrial granules and their production of atrial natriuretic peptide has been one of the most exciting stories of modern cardiology. Suddenly the heart, thought of since time immemorial only as a pump, became an endocrine organ.

The presence of granules in the atrial myocytes had been described by Jamieson and Palade in 1964 when the heart was first being studied under the electron microscope. They were referred to as “atrial specific granules,” and it was noted that they had the appearance of secretory granules. But it was not until 1976 that Marie, Guillemot, and Hatt proposed that the granules had a function in the volume sensitivity of the atria. To my mind, Pierre-Yves Hatt, who also described the juxtaglomerular apparatus in the kidney, has never been accorded the recognition due to him for this seminal observation.

But it was de Bold who, by applying careful electron microscopical morphometric techniques to the study of the atria of rats under experimental conditions, was able to assert with confidence their relation to salt and water balance. Using these techniques, the granularity of the myocytes could be expressed as the percentage volume occupied by granules. As de Bold pointed out, the distribution of the granules in the cell was so irregular that it would take large changes in their numbers to be evident by simple inspection. Preliminary experiments had shown that “as much as near doubling in granularity as detected by the morphometric method used in the present investigations is not detectable by subjective microscopic evaluation.”

The mathematical basis of such morphometric techniques had been developed by Gomez in the 1950s. That colorful and vulnerable Cuban genius had been found by Cournand in Paris and brought to New York, where he developed the methods of morphometry in order to estimate the surface area of the alveolar membrane and the volume of emphysema in the lungs—and demonstrated its general application by predicting the number of string beans in a frozen packet from a cross section.

In de Bold’s original paper, rats were subjected to a number of different experimental conditions involving salt and

water balance. These comprised: adrenal regeneration hypertension, bilateral adrenalectomy, injections of desoxycorticosterone, water deprivation, adding salt to the drinking water, and salt restriction. Separate control groups were used for each type of experiment.

Neither adrenalectomy nor adrenal regeneration hypertension had any significant effect on the granules. Adding sodium chloride to the drinking water under various other experimental conditions consistently reduced the atrial concentration of granules, but the differences were not statistically significant. However, sodium restriction, which increased the hematocrit from 45% to 52%, caused a significant increase in granularity from an average of 2.95% granules to 3.67%. Water deprivation, increasing the hematocrit from 44% to 54%, also caused a significant increase in granularity from 2.54% granules to 3.62%. In the case of water deprivation, there was a significant correlation between the hematocrit and the granularity. In animals receiving desoxycorticosterone plus salt loading, there was a significant fall in atrial cell granularity from 2.74% granules to 2.03%.

Thus, de Bold started with no more than a general hint from previous workers, and set up a limited number of well-designed fishing experiments to investigate it numerically, being rewarded with the clear-cut answer that was to start a new epoch in cardiology. He ends with the modest comment that this and previous work “suggest that atrial specific granules are likely related to water-electrolyte balance and this appears a useful working hypothesis to further define the physiological role of these organelles.”

1979

Mother Teresa is awarded the Nobel Peace Prize; Maria Pintassilgo becomes Portugal’s first female Prime Minister; and Lord Mountbatten is killed by an IRA bomb blast, aged 79



Atrial natriuretic peptide elevation in congestive heart failure in the human

J.C. Burnett Jr, P.C. Kao, D.C. Hu, D.W. Hesser, D. Heublein, J.P. Granger, T.J. Opgenorth, G.S. Reeder
Science. 1986;231:1145-1147

Following de Bold's discovery of the relation of the atrial granules to water and electrolyte balance, atrial natriuretic peptide was identified, its chemical composition established, and the molecule synthesized. When given to animals, it was found to cause natriuresis, a decrease in arterial pressure, and inhibition of the renin-angiotensin-aldosterone system. Assays for atrial natriuretic peptide were developed, and it could be shown that increasing the intracardiac pressure in conscious dogs led to an increase in the plasma concentration of the peptide.

At this point it was not certain what role atrial natriuretic peptide might play in the pathophysiology of heart disease. One suggestion, which appeared plausible, was that there was a suppression of the production or liberation of the peptide in congestive cardiac failure. After all, this condition was notable for the massive retention of salt and water in the body, so it was difficult to see why the body in its "wisdom" should decide on an increased level of atrial natriuretic peptide in the blood. This paper was the first to investigate such a hypothesis.

The authors were careful first to develop a sensitive radioimmunoassay for human atrial natriuretic peptide, using radioiodinated purified synthetic peptide, and to validate the method in the laboratory. They then used the method to assay the concentration of atrial natriuretic peptide in the plasma of four groups of subjects. These comprised normal controls, patients with cardiovascular disease but normal cardiac filling pressures, patients with cardiovascular disease and raised cardiac filling pressures, and patients with cardiovascular disease and raised cardiac filling pressures and congestive cardiac failure. All cardiac therapy was withheld on the day of investigation.

The results were unequivocal. Instead of the expected diminution in plasma concentration of atrial natriuretic peptide in congestive cardiac failure, there was a striking increase. There is nothing, as Popper would have told us, so convincing as disproving your hypothesis. The mean figures were 45 pg/mL in normals, 52 pg/mL in patients with cardiovascular disease but normal cardiac filling

pressures, 232 pg/mL in patients with cardiovascular disease and raised cardiac filling pressures, and 445 pg/mL in patients with cardiovascular disease and raised cardiac filling pressures.

Taken in conjunction with the preceding experiments on animals, it could be concluded that distention of the cardiac chambers gave rise to an increased release of atrial natriuretic peptide into the plasma.

But what was the role of the mechanism in the pathogenesis of congestive cardiac failure? And, if the action of the peptide is to cause natriuresis and vasodilation, why is it so ineffective in that condition? The authors conclude that their study "establishes that, in human subjects, congestive heart failure reflects not an atrial natriuretic peptide deficiency state, but rather a compensatory increase in peptide release." With hindsight we may now, I think, add that this "compensatory" mechanism is ineffective because the body has been programmed to consider the maintenance of the blood pressure more important than the limitation of the blood volume.

1986

The World Wildlife Fund
celebrates its 25th birthday;
Yellow balls are used for the first time
at the Wimbledon Championships;
and Henry Moore, British sculptor, dies, aged 88

Edema of cardiac origin. Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure

I.S. Anand, R. Ferrari, G.S. Kalra, P.L. Wahi, P.A. Poole-Wilson, P.C. Harris

Circulation. 1989;80:299-305

By the early 1980s, a great deal of fragmented information was available concerning the neurohumoral response in congestive cardiac failure (see review of Harris page 225). The information, however, was incomplete in a number of ways. The first problem was that, in the affluent West, it was rare to find a patient who had not yet received some treatment, and one could not be sure to what extent previous treatment had influenced or even initiated the neurohumoral responses that had been reported. To get round this, therapy could be withdrawn for a few days; but again it was not clear to what extent the observations might be the results of a recovery from chronic diuretic therapy. In addition, nearly all had congestive cardiac failure due to a damaged heart, and there was virtually no information concerning patients with a "high output failure." Would the neurohumoral response be the same in them?

The present study—the first of a series intended to fill these essential gaps in our knowledge—was carried out on eight patients with severe congestive cardiac failure. Two had ischemic heart disease and six had dilated cardiomyopathy. The hemodynamic measurements were a measure of the extreme severity of the condition—cardiac index $1.8 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$, heart rate 115 beats per minute, pulmonary wedge pressure 30 mm Hg, right atrial pressure 15 mm Hg—but the mean aortic pressure was maintained at 100 mm Hg.

In addition to standard hemodynamic procedures, measurements of renal function, plasma volume, total body water, and exchangeable sodium were performed to complete the physiological picture and confirm the presence of retention of saline in the body. There were significant changes in all, which showed that the retention of water in the body was distributed preferentially in the extracellular space, including the blood plasma. Renal plasma flow was greatly diminished, while glomerular filtration rate was diminished to a lesser extent, indicating vasoconstriction of the glomerular efferent vessels. The observations support (but do not prove) the hypothesis that the control mechanisms operating in congestive

cardiac failure are directed to the maintenance of the arterial pressure.

The neuroendocrine measurements in the plasma were aldosterone, vasopressin, growth hormone, prolactin, cortisol, norepinephrine, epinephrine, and renin activity. The values were compared with measurements taken in the same laboratory from normal subjects of the same ethnic population. The findings confirmed that in untreated congestive cardiac failure there is a striking increase in plasma renin activity, aldosterone, norepinephrine, and atrial natriuretic peptide. Unexpected findings were increases in growth hormone and cortisol. Epinephrine, which seems to reflect emotional rather than hemodynamic stress, was not affected. Neither was vasopressin. However, the release of vasopressin is controlled by both baroreceptor and osmotic stimuli. In congestive cardiac failure, these two factors are operating in opposite directions: hyponatremia and hypo-osmolarity reducing vasopressin release, while a decreased baroreceptor stimulus increases it. The level of plasma vasopressin may, therefore, have been abnormally high in relation to the hyponatremia.

The results established a primary database with which to compare other forms of congestive cardiac failure. Subsequent studies using the same techniques were to show a similar neurohumoral response in the "high output failure" associated with chronic respiratory disease or anemia. Together they provided evidence that the response is evoked to maintain the arterial pressure, whether it is threatened by a reduced cardiac output or by a decreased peripheral resistance.

1989

The 200th anniversary of the French Revolution is celebrated in Paris;
Batman celebrates his 50th birthday (31 December);
and San Francisco is devastated by an earthquake that leaves at least 90 people dead



Prostaglandins in severe congestive heart failure: relation to activation of the renin-angiotensin system and hyponatremia

V.J. Dzau, M. Packer, L.S. Lilly, S.L. Swartz, N.K. Hollenberg, G.H. Williams

N Engl J Med. 1984;310:347-352

This paper was published in 1984. That was around the time when atrial natriuretic peptide had appeared on the horizon. Since then, there has been a great deal of interest in atrial natriuretic peptide as a natriuretic and vasodilator liberated in excess into the plasma in congestive cardiac failure. Some of the prostaglandins, which are the subject of this paper, are also vasodilators and promote salt and water excretion by the kidneys, but they have, by contrast, been little followed up.

Underperfusion of the kidneys or the heart releases prostaglandins I_2 (prostacyclin) and E_2 , whose vasodilator activity helps to restore blood flow. The infusion of vasoconstrictor hormones, such as angiotensin II, norepinephrine, or vasopressin, also stimulates prostaglandin synthesis, which attenuates the vasoconstriction.

Prostaglandins E_2 and I_2 are highly unstable, and, in this study, their more stable metabolites were measured in the plasma as an indication of their overall rate of biosynthesis in the body. Such measurements were made in a group of 38 patients with severe congestive cardiac failure, as shown by the cardiac output, pulmonary wedge pressure, and left ventricular ejection fraction. Treatment with diuretics and vasodilators had been withdrawn 3 to 5 days before the study. The measurements of prostaglandin metabolites were related to plasma levels of renin activity and angiotensin II, and to serum sodium concentration.

The stable metabolites used were prostaglandin E_2 -M for prostaglandin E_2 and 6-keto-prostaglandin $F_{1\alpha}$ for prostaglandin I_2 . The mean plasma concentrations of both metabolites were greatly increased in the patients with congestive cardiac failure, as was plasma renin activity. However, individual values of all three ranged from normal to extremely high. Plasma concentrations of E_2 -M correlated directly with plasma renin activity and plasma angiotensin II, while concentrations of 6-keto-prostaglandin $F_{1\alpha}$ correlated with angiotensin II.

Serum sodium concentration had an important bearing on hormonal levels. Patients with hyponatremia ($Na < 135$ mmol) had increased concentrations of E_2 -M, 6-keto-prostaglandin $F_{1\alpha}$ and angiotensin II, and an increased plasma

renin activity. The patients with hyponatremia also had an increased blood urea and creatinine.

Seven patients were placed on a diet of 10 mmol sodium a day, and eight patients were placed on a diet of 80 mmol daily. These dietary manipulations did not affect the above correlations, but the absolute values of the various measurements under these conditions are not given.

To assess the importance of prostaglandins in congestive cardiac failure, the authors studied the effects of indomethacin in 23 patients. This nonsteroidal, anti-inflammatory drug inhibits the enzyme cyclooxygenase that generates the cyclic endoperoxides from arachidonic acid. In this way, it inhibits the synthesis of both E_2 and I_2 . Not all prostaglandins and endoperoxides are vasodilators—some are vasoconstrictors—but Wennalm (*Clin Sci*, 1978) had shown that the infusion of indomethacin in normal man caused a reduction in cardiac output and an increase in systemic vascular resistance.

Indomethacin caused a considerable and significant decrease in cardiac output and increase in pulmonary wedge pressure, systemic arterial pressure, and systemic arterial resistance in those patients with a low serum sodium; in the patients with a normal serum sodium, the effects were in the same direction, but of less magnitude and not statistically significant.

This paper provides impressive evidence of a role played by vasodilator prostaglandins in congestive cardiac failure. It is surprising that its implications have not been explored further. The caveat against the use of nonsteroidal anti-inflammatory drugs in congestive cardiac failure is borne out by clinical experience.

1984

Peggy Ashcroft wins an Oscar
(Best Supporting Actress) for “Passage to India”;
Jayne Torvill and Christopher Dean win an Olympic
Gold for ice-dancing in Sarajevo;
and The Nobel Peace Prize is awarded
to Desmond Tutu, Bishop of Johannesburg

Plasma norepinephrine as a guide to prognosis in patients with congestive heart failure

J.N. Cohn, T.B. Levine, M.T. Olivari, V. Garberg, D. Lura, G.S. Francis, A.B. Simon, T. Rector

N Engl J Med. 1984;311:819-823

In this neat prospective study, Jay Cohn, Gary Francis, and their colleagues show for the first time that, in patients with clinical congestive cardiac failure, plasma norepinephrine is a better predictor of prognosis than hemodynamic measurements.

They studied 106 patients with congestive cardiac failure; 60 had coronary heart disease, while the rest had cardiomyopathy or "volume-overload lesions." The objective was to see if, during follow-up, their prognosis could be related to initial hemodynamic and hormonal measurements, all performed at rest. Any vasodilators had been withdrawn 48 hours before, and digoxin and diuretics were withheld on the day of the study. Mean values for right atrial and pulmonary wedge pressures were abnormally high, while the systemic arterial pressure and cardiac output were low. The mean plasma levels of norepinephrine and of renin activity were abnormally high, and the serum sodium was low. Over a period of 62 months, 60 patients died. Of these, 17 died suddenly and unexpectedly, 11 died suddenly after a worsening of the congestive cardiac failure, and 27 died with progressive congestive cardiac failure.

The main analysis was between the patients dying and those surviving. Plasma norepinephrine ($P<0.001$), plasma renin activity ($P=0.01$), stroke work index ($P=0.03$), serum sodium ($P=0.05$), and heart rate ($P=0.05$) could be identified as potential predictors of survival. But, when the simultaneous predictive utility of these measurements was analyzed, only plasma norepinephrine emerged as an independent factor of importance ($P=0.002$).

Why should plasma norepinephrine be a better predictor than direct hemodynamic measurements of cardiac function? The authors first review evidence that plasma norepinephrine reflects sympathetic activity in the body, and they point to the stability of the measurement of plasma norepinephrine in their patients. Emotional stress, which has immediate hemodynamic effects, influences epinephrine rather than norepinephrine. Hemodynamic measurements are labile, and particularly the arterial pressure may vary widely in patients of middle age and beyond. In a damaged heart, the cardiac output may actually be brought back to normal by an increased sympathetic activity, and sympathetic activ-

ity may be seen as a response "when depression of pump function is perceived by the body as impairing organ function."

In order to determine whether higher plasma levels of norepinephrine are associated with a greater mortality, Cohn et al divide the plasma norepinephrine levels arbitrarily into terciles and show that this results in statistically distinguishable survival curves, with survival decreasing as plasma norepinephrine increases.

Sympathetic activity in the heart itself has been shown to favor arrhythmias, so that the increased sympathetic activity that is revealed by a high plasma norepinephrine may not only be a reflection of a poor cardiac pump function, but may itself be a cause of sudden death. If that were important, one would expect the initial plasma norepinephrine to have been higher in patients dying suddenly than in those dying from progressive congestive cardiac failure. The data do not bear that hypothesis out. In an analysis to distinguish between the patients dying suddenly and those dying from progressive congestive cardiac failure, plasma norepinephrine and renin activity were found to be significantly higher and the stroke-work index significantly lower in the patients dying of progressive congestive cardiac failure. The authors, however, are careful to point out that the limited number of deaths provided only a limited statistical power and that the clinical selection of patients dying of unheralded arrhythmias is much less certain than overall mortality.

To what extent could the level of plasma norepinephrine be influenced by cardiac therapy? We can only tell you, say the authors, that the patients received conventional therapy. For most of them, this consisted of digoxin, furosemide, and a vasodilator drug.

1984

Indian troops storm the Golden Temple of Amritsar, held by Sikh extremists; Band Aid is created by Bob Geldof, to help victims of the Ethiopian famine; and US author and playwright Lillian Hellman dies, aged 77



Congestive cardiac failure: central role of the arterial blood pressure

P. Harris

Br Heart J. 1987;58:190-203

The history of the changing concepts of the mechanisms of formation of peripheral edema in cardiac patients goes back to 1832 when Hope proposed that an overworked ventricle first hypertrophies and then dilates, damming up the blood behind it, resulting in increased venous pressure, which is transmitted ultimately to the capillaries, where edema is formed. This theory convincingly explained the formation of pulmonary edema, but not the massive peripheral edema found in severe congestive heart failure.

By the beginning of our century, Starling and Mackenzie had rejected the “backward failure” theory in favor of a forward failure due to impaired nutrition of the capillaries from a diminished cardiac output. Landis eventually showed that capillary pressure was increased, which made the backward failure theorists happy. But both forward and backward theories implied a diminution in blood volume, and this was shown to be increased. In the 1940s, cardiac catheterization confirmed that the cardiac output in patients with congestive failure was usually decreased. But it revealed a disconcerting group of patients who had an increased cardiac output. Here was disaster for the backward failure theorists and a serious dilemma for the forward failure proponents.

It took a long time for the theorists to realize what was obvious to any clinician: that edema and oliguria implied a retention of water in the body. In the 1940s, attention swung finally to the kidneys, and Merrill showed that reduced urinary volume and lack of urinary sodium were associated with a reduction in renal blood flow. But then a mysterious increase in tubular reabsorption of sodium was found. This led to the discovery of aldosterone and its eventual link to the renin-angiotensin-aldosterone system.

The urine had been known to be highly concentrated for a century. Robinson and Farr showed in 1940 that it contained an antidiuretic substance, but it was not until 1974 that this was identified as vasopressin. The influence of the sympathetic system on the heart was also known in the 19th century, but it took Sarnoff and Berglund in 1954 to show its physiological importance, while its particular importance in congestive failure had to wait a further 6

years to be revealed (*see review of Chidsey et al, page 218*).

Thus, there emerged a combination of neurohumoral agents that together would stimulate the heart and cause peripheral vasoconstriction and retention of saline. Then came the discovery of atrial natriuretic factor (*see review of de Bold, page 220*), a peptide with natriuretic and vasodilator properties that circulated in high concentration in congestive failure. Although it is clear that its influence is quite outweighed by that of the vasoconstrictor agents, one is left with a nagging doubt about how the “wisdom of the body” could have got so mixed up.

The thesis proposed in this article is that the neurohumoral response in congestive failure arose during evolution for preservation of arterial pressure during hemorrhage. In this condition, both the arterial and the venous pressures fall, so that the release of atrial natriuretic peptide is diminished simultaneously with a stimulation of the sympathetic and renin-angiotensin-aldosterone systems, and the total neurohumoral response is coordinated. During evolution, the warm-blooded animals developed a high arterial pressure, which permitted the distribution of blood flow by regional vasoaction. This was essential during exercise when an overriding diversion of blood flow to the limbs might be necessary. The threat to the system was leakage from the high pressure, and the responses that we see in congestive failure evolved to deal with that contingency.

The body is not prepared for the threat to the arterial pressure from a damaged heart or from severe sustained vasodilatation that occurs in “high output failure,” and it responds in the way it has been programmed. It maintains the arterial pressure by cardiac stimulation, vasoconstriction, and an increased blood volume, and overrides the opposing neurohumoral influences from the resulting distention of the atria.

1987

Van Gogh’s “Irises” are sold for 53.9 US dollars;
Australian Pat Cash wins
the Men’s Singles at Wimbledon;
and Fred Astaire, US dancer and actor, dies, aged 88

The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure

M. Packer

J Am Coll Cardiol. 1992;20:248-254

This review of the literature concerning the role of neurohumoral stimulation in congestive heart failure attempts to answer the question: do systemic vasodilators or myocardial stimulants reduce mortality?

First to be reviewed are the vasodilators. The Veterans Administration Heart Failure Trial (V-HeFT) showed that prazosin produced a greater decrease in arterial pressure than isosorbide dinitrate, but no effect on mortality, whereas the combination of isosorbide with hydralazine, although relatively ineffective on the arterial pressure, reduced mortality by 28%. Minoxidil and the calcium channel blockers are potent vasodilators, but worsen the prognosis. β -Agonists and phosphodiesterase inhibitors have the advantage of stimulating the myocardium as well as causing vasodilation. However, their long-term use has been associated with an increase rather than a decrease in mortality. Treatment with milrinone in the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial resulted in a 28% increase in mortality.

Packer next explores the hypothesis according to which the progressive deterioration in patients with congestive failure would be due to the direct effects of neurohumoral stimulation. Both norepinephrine and angiotensin II have effects on hemodynamics and water and salt balance that might increase the disability of the heart. Since the 1950s it had been known that massive doses of catecholamines could cause myocardial necrosis, and more recently that angiotensin II had a direct deleterious effect on the myocardium. What then, are the effects of long-term blockade of these systems?

The findings of the North Scandinavian Enalapril Survival Study (CONSENSUS), published in 1987, were striking. Enalapril, which decreased plasma angiotensin II by inhibiting converting enzyme, reduced total mortality by 40% at 6 months and 31% at 1 year. Subsequent trials with this and other converting enzyme inhibitors gave similar results. These beneficial effects could simply have been due to the drugs' potent vasodilatory effects, but two points argue against this. First, the reduction in mortality was greatest in patients with the highest neurohumoral

activation. Second, the Veterans Administration Heart Failure Trial II (V-HeFT II), comparing enalapril and the hydralazine/isosorbide dinitrate combination, showed that the hemodynamic effects were greater with hydralazine/isosorbide dinitrate while the neurohumoral effects were greater with enalapril, and that mortality was significantly lower with the latter.

Physicians were long scared to give β -blockers to patients with congestive failure, since increased sympathetic activity was thought to be necessary to support cardiac output. Eventually, however, trials showed that β -blockers were beneficial, probably by suppression of arrhythmias, since they particularly reduced the risk of sudden death, a risk increased by milrinone. Since phosphodiesterase inhibitors increase intracellular cyclic AMP and β -blockers reduce it, these two types of drugs may be acting on the same biochemical mechanism.

Among the drugs used in the treatment of congestive cardiac failure, a good case is made that relief of the myocardial effects of norepinephrine and renin-angiotensin-aldosterone stimulation is more effective than relief of hemodynamic over-burden. However, the review is based on the treatment of patients with ischemic heart disease. In this disease, the scope for surgery is limited, and treatment relies on drugs. Do the same principles apply to valvular heart disease? Few would deny the effectiveness of surgery in such conditions, but even here there comes a point after which surgery fails to prevent the progression of congestive cardiac failure.

1992

The European parliament celebrates
its 40th anniversary;
Emma Thompson wins an Oscar (Best Actress)
for her role in "Howard's End";
and Anthony Perkins, who starred in "Psycho",
dies, aged 60



Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD)

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This study was a spin-off from SOLVD (Studies of Left Ventricular Dysfunction), a large trial testing the effects of the converting enzyme inhibitor enalapril in patients with a low left ventricular ejection fraction (<35%). Most of the patients had ischemic heart disease.

There were two sections of the trial. The first section, called the "prevention group," consisted of patients with left ventricular dysfunction who did not require diuretics or digitalis for control of clinical congestive cardiac failure. A certain number, however, were being treated with diuretics for hypertension or with digitalis for arrhythmia. In this group, the object of the trial was to see if enalapril prevented the development of congestive cardiac failure and reduced mortality.

The second section of the SOLVD trial, called the "treatment group," consisted of patients with left ventricular dysfunction who had symptomatic congestive cardiac failure requiring treatment with digitalis, diuretics, or vasodilators that were not converting enzyme inhibitors. The object of this section of the trial was to see if enalapril reduced mortality.

There was a placebo division for each section of the trial, and it had been planned to measure plasma renin activity, norepinephrine, atrial natriuretic peptide, and vasopressin in each patient before randomization into placebo or treatment division. This paper gathers together the results of those measurements and compares them in the prevention group and treatment group. In addition, a control group had been studied simultaneously with the recruitment of patients into the trial. Thus, for each measurement there were three groups: prevention group, treatment group, and control. There was a total of 151 patients in the prevention group, 81 patients in the treatment group, and 56 persons in the control group. The results are summarized in *Table I*.

Measurement	Control	Prevention	Treatment
Norepinephrine (g/mL)	317	422	507
Renin activity (ng·mL ⁻¹ ·h ⁻¹)	0.6	0.7	1.4
Vasopressin (g/mL)	1.8	2.2	3.0
Atrial natriuretic peptide (g/mL)	48	103	146

Table I. Median values of neuroendocrine parameters in SOLVD.

In each case, the value for the prevention group was significantly greater than that of the control group, and the value for the treatment group significantly greater again than that of the prevention group. Of these statistical tests for significance, the least impressive was a *P* value of 0.03 in the comparison of plasma renin activity between the control group and the prevention group. Could this be accounted for by the fact that 20% of the patients in the prevention group were receiving diuretics for hypertension?

To look into this, the authors reanalyzed their data according to diuretic use. Whether the patients were on diuretics or not made no significant difference in the results for norepinephrine, atrial natriuretic peptide, or vasopressin; but there was a significant increase in the plasma renin activity in patients taking diuretics in both the prevention group and the treatment group. "It is, therefore, likely," say the authors, "that activation of the renin-angiotensin-aldosterone system (...) is in part related to diuretic use."

Neuroendocrine stimulation, involving both vasoconstrictor and vasodilator systems, "occurs at a symptomless or mildly symptomatic stage of left ventricular dysfunction and therefore is not likely to be a simple consequence of worsening congestion. Our data suggest that there is additional progressive neuroendocrine activation as patients progress from early asymptomatic or mildly symptomatic left ventricular dysfunction to symptomatic heart failure."

The final, prophetic sentence is: "Neuroendocrine activation appears to precede overtly symptomatic heart failure and may therefore contribute to its development."

1990

Macauley Culkin is left "Home Alone";
The Hubble space telescope
is put into orbit around the earth;
and John McEnroe is banished
from the Australian Open for bad behavior