EDEMA AND DYSPNEA OF HEART FAILURE*

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THE chief symptoms of congestive failure are weakness, swelling and shortness of breath. All authors agree that weakness occurs because the heart cannot normally increase its output in response to the stimulus of exercise. There has been less general agreement as to the cause of the edema and dyspnea.

The amount of blood pumped per minute in patients in heart failure is less than that pumped under similar conditions by patients without heart failure. The separation of patients with heart failure into two groups, those with high output failure and those with low output failure, has caused considerable confusion. The cardiac output at rest varies considerably from person to person. In the same patient it varies greatly in different physiologic and pathologic states. Exercise, eating, apprehension and epinephrine increase the cardiac output; motionless standing decreases it. In a person with a normal heart the resting cardiac output will be decreased if the subject has myxedema, and increased if he has anemia, thyrotoxicosis, beriberi or arteriovenous fistula. There are no absolute levels of the circulation above which circulatory failure does not occur and below which it always occurs. The amount of blood pumped must be considered in terms of the immediate needs of the body rather than as an absolute value.

In the natural history of slowly progressive congestive heart failure it is the rule rather than the exception for symptoms to occur during periods when the cardiac output is above the resting level. Fatigue develops during the day when the subject is active. The output is increased above the resting value, but is below the level that is reached by a normal heart.

During sleep the cardiac output falls from a subnormal exercising level to a normal value for rest, and the output becomes sufficient for

the resting needs, causing symptoms to disappear. As the heart becomes weaker, signs and symptoms of congestive failure persist at rest. In these patients the cardiac output is consistently below the resting value unless complicating physiologic or pathologic states are present.

Patients with advanced pulmonary disease, anemia, thyrotoxicosis, beriberi and arteriovenous fistula have a high resting cardiac output. In them circulatory failure usually develops before the resting cardiac output falls below the value for normal subjects. The significant fact is the fall in cardiac output to a value below that found in the diseased state in the absence of heart failure.

Stimuli which normally cause a rise in cardiac output frequently cause a fall in output in congestive failure. The reverse is also seen, and stimuli which cause a fall in the normal subject cause a rise in the patient with failure. Any stimulus, such as exercise or excitement, which normally increases the output may decrease the output in a fatigued heart. As fatigue increases the ability of the heart to empty decreases. Anything which decreases the activity of the patient and normally decreases the output may increase the output of the fatigued heart.

In uncomplicated heart failure which persists at rest, blood flow has been reduced in all areas where it has been studied.[1] The reduction in splanchnic blood flow and cerebral blood flow is proportionate to the decrease in cardiac output; the reduction in renal blood flow is much greater. Fasting splanchnic oxygen consumption is maintained at a normal level by widening of the arterio-venous oxygen difference. Cerebral oxygen consumption is usually normal but may be reduced slightly in severe failure. The reduction in blood flow to the various areas studied is related to the change in cardiac output and does not correlate with changes in venous pressure.

Edema in heart failure may be divided into two types: 1) that caused by a redistribution of fluid normally present in the body; 2) that caused by a gain in weight indicating an abnormal accumulation of salt and water. The first type, that produced by redistribution of normal fluid, is seen in pure form in patients who develop a massive infarct of the left ventricle without previous symptoms of heart failure.[2] These patients may rapidly develop massive pulmonary edema. Blood is pumped into the lungs by the right ventricle, and it is not removed by the left ventricle. The pulmonary capillary pressure rises sharply, and fluid is pushed into the lungs. Fluid enters the blood stream from the extracellular areas supplied by the systemic circulation, and thus becomes available

for increasing the pulmonary edema. The hematocrit reading and plasma protein concentration indicate a slight to moderate fall in blood volume. The weight of the patient is unchanged.

In the second type of edema, fluid is retained in the body and weight gain occurs. For some reason related to heart failure, the kidneys are excreting less water than the patient is drinking. The exact reason why the kidneys retain fluid has not been agreed upon.

In chronic heart failure there is a striking disturbance in the circulation to the kidney. The renal blood flow is reduced to a value only one-third to one-fifth that of normal and the glomerular filtration rate is reduced to a value one-half to one-third of normal.[3] This reduction in renal blood flow and filtration rate is related to the level of cardiac output, but shows no obvious correlation with the level of venous pressure. Tubular function remains good. The author believes that this reduction in filtration rate, secondary to the reduced renal blood flow in the presence of relatively well-functioning tubules, is the primary cause of the edema in congestive failure. According to this theory, the normal tubules are unable to depress their sodium reabsorbing function enough to allow the escape of large quantities of sodium in the urine when the amount of sodium presented to them is reduced to the degree seen in heart failure. This thesis emphasizes that the reabsorptive ability of the tubules in both normal subjects and patients with heart failure can be altered by various agents acting on the tubule, but it emphasizes also that the amount of sodium retention produced by these factors acting on the tubules is influenced in a quantitative rather than a qualitative way by the reduced filtration rate. In other words, both normal subjects and patients with heart failure retain sodium during light exercise, but the amount of sodium retained by the cardiac exceeds that retained by the normal subject. This quantitative difference is believed to be the result of the low filtration rate in the presence of reasonably well-functioning tubules.

Other investigators believe that the retention of salt and water is caused by a rise in renal venous pressure. Still others feel that a rise in systemic venous pressure causes loss of fluid into the tissue and that this loss of fluid from the blood stream in some way causes retention of fluid by the kidney. Many other persons think that the circulatory disturbance in the kidney is not very important, and that the sodium retention of heart failure is caused by the action of various hormones on the renal tubules. There is evidence that urinary corticoid excretion is

increased in heart failure.

Our chief difficulty in settling the question of edema in heart failure lies in our ignorance of the factors which control sodium excretion in normal subjects. We know that sodium excretion is increased on a high sodium intake and lowered on a decreased sodium intake. More sodium is excreted during the day than during the night. Lowering the blood volume by bleeding and motionless standing increases sodium retention. Cortisone and desoxycorticosterone cause sodium retention. Whether these hormones are important in the hourly and daily variations in excretion of sodium in normal subjects is not known.

In this discussion we have blithely assumed that the primary cause of cardiac edema is sodium retention and that retention of water and chloride are secondary phenomena. This is based on the clinical observations that 1) the sodium ion when given as bicarbonate, lactate or chloride increases edema formation; 2) chloride ion when given as calcium chloride or ammonium chloride does not increase edema; and 3) when sodium is rigidly restricted, patients with heart failure excrete water relatively well. In patients with sudden heart failure the concentrations of sodium and chloride in the plasma are normal. In many patients with chronic failure the sodium and chloride concentrations in the plasma are low. This has led many people to wonder if too much emphasis is not put on sodium retention, and they raise the question of whether in certain instances water retention may not be the primary defect.[4] Let us consider what we know about low sodium concentrations in the serum and about the regulation of water metabolism.

Data collected in many laboratories have shown a surprising number of patients with occurrence of low sodium and chloride concentrations in the plasma.[4-6] In any chronic illness, with or without edema, we are apt to find the plasma sodium below 120 mEq. Many of these patients have none of the signs of circulatory difficulty of the type we are accustomed to see in patients in addisonian crisis. Indeed, we may well blame our friends in endocrinology for making us believe that patients always appear acutely ill when the sodium concentration becomes low. We forget that the addisonian appears very ill not because the electrolytes are out of balance but primarily because his entire body homeostasis is upset by the lack of a functioning adrenal cortex.

These data indicate that in such chronic illnesses, the osmotic activity of the cells is decreased. In the past we have been taught that cellular osmolarity is rigidly defended, but the finding of low electrolyte con-

centrations in the plasma can only mean that the osmotic activity of the cell is also low. Cellular osmolarity can also increase as shown by observations after electric shock therapy.[7] These data are compatible with 1) retention of an abnormal quantity of water because of a disturbance in the mechanisms controlling water secretion, with subsequent dilatation of electrolytes; 2) lowering of osmotic activity of the cells so that water is retained by normal rather than abnormal function of the water-regulating mechanism. Any fluid-regulating mechanism which was set to fluctuate around the osmotic pressure of cells would give an invariable level of electrolyte activity in the plasma, but would regulate the plasma to correspond to the variable osmotic activity of the cell. This has been suggested by Welt et al. as a possible explanation for certain hyponatremic states.[7]

When a normal person drinks a large quantity of water, the level of electrolytes in the blood and extracellular fluid is lowered. The water passes into the cells to restore the osmotic equilibrium between intra- and extracellular fluid. This fall in electrolyte concentration acts on osmoreceptors in the area supplied by the internal carotid artery and causes an inhibition of secretion of the anti-diuretic hormone of the posterior pituitary gland (ADH). When the renal tubules escape from the action of ADH, absorption of water in the distal tubules is decreased and water diuresis occurs. If hypertonic saline is now injected intravenously, the electrolyte activity of the blood and extracellular fluid is increased and water passes out of the cells to restore osmotic equilibrium. Immediately the osmoreceptors respond to the cellular dehydration with stimulation of the post-pituitary gland to produce ADH. Tubular reabsorption of water in the distal tubule is increased, and the water diuresis is checked.

If ADH is supplied exogenously by giving pitressin repeatedly in small doses, water drinking results in a considerable increase in intra- and extracellular water, and the sodium and chloride concentrations in the plasma are considerably decreased. May not such a mechanism be the cause of edema in patients with heart failure and low concentrations of chloride and sodium? May not the water retention itself result in a secondary retention of sodium and chloride? We do not think so, because the administration of pitressin to normal subjects over a 24-hour period does not cause the characteristic retention of sodium, so typical of heart failure. Water is retained, but not the salt.[8]

Let us consider more closely the findings in chronic illness with low

sodium and chloride concentrations. The patients do not show signs of peripheral circulatory failure. If sodium chloride intake is increased, either edema occurs because of expansion of the extracellular fluid volume or the salt is excreted in the urine. In either instance the concentrations of sodium chloride may change little. If salt is restricted in the diet, the excretion in the urine becomes greatly reduced and the fall in concentration in the plasma is slowed down. If desoxycorticosterone or ACTH is given salt retention occurs, but this results in an expansion of extracellular fluid and not in a rise in concentration in the plasma. If water is given a diuresis occurs. If hypertonic salt is given intravenously the diuresis is broken. We thus have evidence of a new level around which function the osmoreceptors regulating pituitary ADH secretion function. These observations suggest that in chronic illness cellular osmolarity changes and, therefore, the concentration of electrolytes in extracellular fluids is altered. Water is not retained to dilute the electrolytes because of the over-activity of post-pituitary ADH. The pituitary mechanism functions normally, but it is working around a new osmotic setup.

We believe, then, that we have three common situations in which the serum sodium and chloride fall to low levels. Water intoxication is a fourth and rare cause. The most common situation is the one resulting from changes in cellular osmolarity. Administration of salt can only expand the volume of extracellular water. It cannot raise the concentration in extracellular water because this would cause cellular dehydration.

Less common is the acutely occurring low salt syndrome in which the concentration of sodium and chloride is low because of constant loss of sodium chloride from the body either from the gastrointestinal tract or through kidneys whose tubules are injured by disease or temporarily paralyzed by the influence of mercurial diuretic. The acute renal low sodium syndrome has the following characteristics: On a low sodium chloride intake, the loss in the urine is greater than the intake of salt. Regardless of the level in the plasma, this loss continues, and does not stop until death or anuria occurs. It cannot be prevented by the use of desoxycorticosterone or ACTH. It is eventually associated with peripheral circulatory failure. Giving hypertonic sodium chloride solution results in dramatic clinical improvement.

The third common low sodium syndrome is a combination of low cellular osmolarity and excessive loss of sodium from the body. Let us consider an example. A patient with chronic illness has been placed on

a low sodium intake. After a time he does not do well; the sodium concentration is determined and found to be very low. He is given a little sodium chloride intravenously with dramatic improvement. Repeat laboratory examination shows that the sodium has risen only a little and is still much below the normal value. More sodium is given. The patient does not improve further; the extracellular volume rises and clinical edema occurs. If one insists on treating such a patient until the sodium concentration returns to normal, death frequently occurs from drowning.

A fourth, but less common cause of low sodium syndrome is the fall in electrolytes produced by water intoxication. In post-operative patients who receive only glucose and water and who have lost some salt by sweating, a syndrome characterized by confusion, rise in blood pressure, and reduced urine output may occur. Sodium, potassium and chloride concentrations in the plasma are low. Hypertonic salt solution given intravenously results in dramatic improvement. These same findings are seen in patients with Addison's disease who are being treated with desoxycorticosterone. If they force water, stop eating and discontinue their extra salt, the syndrome of water intoxication develops. In severe congestive failure where marked discomfort is present, or where infection or pulmonary infarction has occurred, one may retain water because of the repetitive neurogenic discharge of post-pituitary ADH. Hypertonic saline in these patients usually aggravates the edema.

So much for generalized edema. The cardiac retains salt and water because the kidneys do not excrete sodium normally. The retained fluid is of normal tonicity as long as cell tonicity is normal, but will change as cellular tonicity changes.

The third great symptom of cardiac failure is dyspnea. The basis for cardiac dyspnea is the structural changes which occur in the lung as a result of heart failure. Characteristically, the left heart is more damaged than the right and blood accumulates in the lungs. The pulmonary capillary pressure rises. Early in the course of heart failure, any fluid retained in the body by the kidneys tends to be dumped preferentially in the lungs. This tendency may become less marked as advanced heart failure occurs, and both ventricles fail equally.

When the patient with congestive failure is dyspneic at rest, he is pumping more air in and out of his lungs than do normal subjects. His dyspnea is a combination of decreased breathing space and increased ventilation. The cause of the increase in volume of air respired has never been fully determined.

The overbreathing causes a fall in the carbon dioxide content of the arterial blood and serves to maintain oxygenation of the arterial blood. The fact that the increased breathing is essential to maintaining full oxygenation is easily demonstrated by the use of morphine. As the ventilation is brought to a normal level by the action of morphine, the arterial oxygen content decreases to a point well below the normal level.

It has been stated repeatedly that in many patients with dyspnea from heart failure, the arterial oxygen saturation is normal and that need for oxygen is not the stimulus for increased ventilation. It is true that the cardiac patient has nearly normal saturation and that the slight fall in arterial oxygen saturation characteristic of the cardiac has no easily detectable effect on the breathing of a resting normal subject. But can these data from the resting normal be applied to the dyspneic cardiac?

We know that a normal subject at rest can breathe 100 per cent oxygen with little effect on his breathing. If he is doing heavy exercise, however, breathing 100 per cent oxygen causes a sharp fall in ventilation. Will the cardiac patient's response to changes in oxygen tension be like that of the man at rest or like that of the exercising man?

Data collected by Hickam[9] show that the orthopneic cardiac has a sharp fall in ventilation when he breathes 100 per cent oxygen, and that this fall is much greater than will occur in normal resting subjects with a corresponding change in oxygen tension. The cardiac who is dyspneic at rest responds to minor changes in oxygen tension in a way similar to that of a normal subject doing heavy exercise. The mechanism for this increased sensitization to oxygen remains to be determined.

Cheyne-Stokes respiration is one of the dramatic clinical findings in patients with heart failure.

Pryor[10] has recently described one of the mechanisms responsible for this type of breathing. These patients have large hearts and a long circulation time. The irregularity in breathing occurs without any evidence of disturbance in the carotid sinus or respiratory centers. The breathing follows closely the changes in arterial blood gases and their response to a given change in arterial blood is a normal one. Coordination between the lungs and the medulla is lost because of the large sac of blood placed in the heart between the lungs and the medulla. Overbreathing does not affect the medulla until the entire heart is filled with aerated blood. When this red, overventilated blood reaches the medulla, apnea occurs. The blood entering the left side of the heart becomes ven-

ous as it perfuses through the motionless lungs, but the blood leaving the heart remains arterial until the entire dilated heart is filled with venous blood. When venous blood finally reaches the medulla, marked overbreathing occurs, but this can have no effect on the respiratory centers until the venous blood empties out of the heart. This is only one of the mechanisms for Cheyne-Stokes breathing.

The tools for a study of respiratory stimulation in various disease states are now available and during the next few years our knowledge of the mechanisms of dyspnea is certain to be greatly increased.

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