Magnesium in cardiac failure and diuretic treatment

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Summary

A large proportion of the deaths from congestive heart failure (CHF) occur suddenly and unexpectedly. The reason is thought to be the high frequency of electrolyte disturbances observed in treated CHF. Every effort should therefore be made to avoid or correct electrolyte changes in CHF patients. Several hormonal compensatory mechanisms operate in CHF, which influence electrolyte metabolism. Activation of the renin-angiotensin-aldosteron (RAA) system leads to Na accumulation and losses of K and Mg. Increased sympathetic activity stimulates the RAA system and may influence the movement of K and Mg over the cell membrane. Treatment with conventional diuretics and digitalis leads to further losses of K and Mg resulting in low levels of extra- and intracellular K and Mg and intracellular Na accumulation. The low intracellular K cannot be corrected by K supplementation if there is a concomitant Mg deficiency with regard to that Mg is a necessary ion for the Na-K pump function. However, it is possible to correct the electrolyte disturbances by adding an aldosteron antagonist or by the use of other K- and Mg-saving diuretics such as amiloride or triamterene. Studies indicate that Mg supplementation may also have the desired effect. One interesting possibility is treatment with ACE-inhibitors but this also needs further studies.

Résumé

Une grande partie des décès par suite d'insuffisance cardiaque surviennent de façon soudaine et inattendue. On considère que la raison en est la haute fréquence des perturbations électrolytiques observée dans les syncopes traitées. Tous les efforts devront donc être faits pour éviter ou corriger les changements électrolytiques chez les patients. Plusieurs mécanismes hormonaux compensatoires entrent en jeu dans l'insuffisance cardiaque et influencent le métabolisme électrolytique. L'activation du systéme RAA (renin-angiotensin-aldosteron) amène une accumulation de Na et des pertes de K et de Mg. Une activé sympathique accrue stimule le système RAA et peut influencer le mouvement de K et de Mg à travers la membrane cellulaire. Le traitement par les diurétiques conventionnels et la digitaline provoque des pertes supplémentaires de K et de Mg, avec pour résultat des niveaux bas de K et de Mg extra- et intracellulaires aussi qu'une accumulation de Na intracellulaire. Un faible K intracellulaire ne peut être corrigé par apport supplémentaire de K s'il existe une déficience concomitante de Mg dans la mesure ou Mg est un ion nécessaire au fonctionnement de la pompe au sodium. Toutefois, il semble possible de corriger les perturbations électrolytiques par l'addition d'antagoniste à l'aldosterone ou par l'utilisation d'autres diurétiques ménageant K et Mg, tels qu' amiloride ou triamtérène. Certaines recherches indiquent que l'apport supplémentaire de Mg peut aussi avoir l'effet désiré. Une intéressante possibilité est le traitement par inhibiteurs ACE qui, exige cependant, de plus amples recherches.

Zusammenfassung

Ein Großteil der Todesfälle durch Herzmuskelinsuffizienz tritt plötzlich und unerwartet auf. Man nimmt an, daß der Grund dafür die hohe Frequenz von Elektrolytstörungen ist, die bei behandelten Fällen von Herzmuskelinsuffizienz beobachtet wurde. Alles Bestreben sollte deshalb der Vermeidung oder Korrektur von Elektrolytveränderungen bei Patienten mit Herzmuskelinsuffizienz gelten. Bei Herzmuskelinsuffizienz wirken verschiedene hormonelle Kompensationsmechanismen, die den Elektrolytmetabolismus beeinflussen. Die Aktivierung des Renin-Angiotensin-Aldosteron (RAA)-Systems führt zu einer Anhäufung von Na und zum Verlust von K und Mg. Erhöhte sympathische Aktivität stimuliert das RAA-System und kann die Bewegung von K und Mg über die Zellmembran beeinflussen. Eine Behandlung mit konventionellen Diuretika und Digitalis führt zu weiterem Verlust von K und Mg, und das Ergebnis ist ein niedriger Gehalt an extra- und intrazellulärem K und Mg sowie eine intrazelluläre Na-Anhäufung. Der niedrige intrazelluläre K-Gehalt kann durch den Zusatz von K nicht korrigiert werden, wenn ein begleitender Mangel an Mg besteht, da Mg ein notwendiges Ion für die Pumpfunktion der Na-K-ATPase ist. Trotzdem scheint eine Korrektur der Elektrolytstörungen möglich durch den Zusatz eines Aldosteron-Antagonisten oder den Gebrauch anderer K- und Mg-schonender Diuretika wie z. B. Amilorid oder Triamteren. Untersuchungen zeigen, daß auch der Zusatz von Mg die erwünschte Wirkung haben kann. Eine interessante Möglichkeit ist die Behandlung mit ACE-Inhibitoren, die allerdings auch weitere Untersuchungen erfordert.

Hormonal regulation in CHF

In congestive heart failure (CHF) there are several compensatory mechanisms operating, which may in the long run establish a viscious circle leading to further damage (Fig. 1). The reduced cardiac output gives rise to elevated levels of vasoconstrictor and volume-regulating hormones such as catecholamines, renin-angiotensin-aldosteron (R-A-A) and antidiuretic hormone, which will cause an increase in both pre- and afterload. The possible failing counter regulation by the recently described atrial natriuretic factor is a matter for specu-

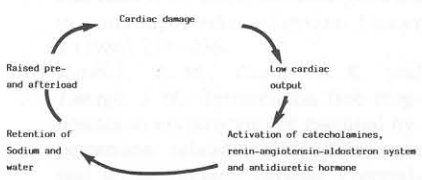

Fig. 1: Viscious circle in congestive heart failure

lation [7, 22]. The most important finding in CHF consists of changes in water and electrolyte balance with sodium retention and accumulation of extracellular fluid in the body. Possible sensory mechanisms are thought to be volume and pressure receports in the atrial and ventricles of the heart and carotid arteries, liver and pulmonary capillaries and also the juxtaglomerular apparatus of the kidney. However, changes in extra-cellular volume proper may not in fact activate the mechanisms but rather the effective arterial blood volume, which means the blood volume in relation to the vascular capacity [17].

The effector organ is the kidney and the effector hormones discussed are noradrenaline, RAA-hormones, antidiuretic hormone, prostaglandines and atrial natriuretic factor.

The low cardiac output evokes an increase in sympathetic activity, which may be reflected in increased circulating levels of noradrenaline. The resulting redistribution of blood flow leads to diminished kidney blood supply and activation of the RAA system. Noradrenaline also has a vasoconstrictor effect pretentially on the efferent arterioles in the kidney. However, angiotensin II is thought to play an even more important role for the changes observed in intrarenal haemodynamics in CHF by increasing the resistance of the efferent arterioli [20]. This effect leads to increased glomerular capillary pressure, decreased plasma flow through the peritubular capillary space and increased filtration fraction. The net effect will be enhanced reabsorption of water and sodium in the proximale tubuli.

There is also a stimulation of the catecholamines of the RAA system. Increased sympathetic activity stimulates renin release via a β_1 agonist action [16]. One of the major effects of angiotensin II is the release of aldosteron, which increases the reabsorption of sodium in the distal tubuli. Impaired sensitivity of stretch receports leads to increased release of antidiuretic hormone causing increased water reabsorption *(De Torrente)*. Prostaglandins may counteract the vasoconstrictor effects of noradrenaline and angiotensin II [1], which explains the deteriorating effect of prostaglandin inhibitors on CHF symptoms.

Hormonal effects on electrolytes in CHF

The R-A-A system

Aldosteron stimulates the resorption of sodium in the distal tubulus in exchange for potassium and hydrogen, the net effect being sodium retention, hypokalemia and alkalosis. Hypomagnesemia may also be added. No direct effects of aldosteron on magnesium have been observed. Acute administration of aldosteron causes no changes in urinary magnesium excretion [24, 28]. However, long-term administration causes increased urinary magnesium excretion [19, 33], which may be explained by the decreased magnesium reabsorption in proximal tubuli observed in conditions with increased extracellular volume [2].

On the tubulus cell and possibly also on other cells aldosteron causes an influx of sodium into the cell and an intracellular potassium loss probably through a direct permeability effect on the cell membrane. The accumulation of intracellular Na and loss of intracellular K may be partly counteracted by an increase of the Na-K pump activity. However, since Mg is a necessary ion for the proper function of Na-K pump activity a Mg deficiency, which may develop through the aldosteron effect, will lead to a further increase in intracellular sodium and loss of intracellular potassium.

In accordance with the expected intracellular changes we have found, in a study of 79 patients with CHF or essential hypertension, a positive correlation between skeletal muscle Na and plasma aldosteron ($p < 0.001$) and a negative correlation between muscle K and plasma aldosteron. Neither the muscle Mg nor the plasma electrolytes showed any correlation to the plasma aldosteron level (unpublished results).

Electrolyte disturbances may in turn affect the RAA system. Renin release is stimulated by low plasma levels of Na, chloride (Cl), K and Mg [6, 27, 38]. Mg deficiency may also in this way, viz. stimulation of the RAA system, lead to further intracellular K and Mg losses. On the other hand, the effect of hypokalemia on renin release is counter regulated by the direct inhibitory effect of low plasma K on aldosteron production. Very low plasma K is even more inhibitory on aldosteron secretion than it is stimulatory on renin secretion [35].

Catecholamines

Catecholamines may influence electrolytes in different ways. Noradrenaline stimulates renin release leading to losses of extra- and intracellular K and Mg and retention of extra- and intracellular Na. Adrenalin elevates plasma glucose and insulin release, which leads to a movement of plasma K from the extra- to the intracellular space. A similar effect will come from the reported stimulatory effect of catecholamines via β_2-receptors on the Na-K pump. However, catecholamines may influence the pump activity differently in different organs and different species e. g. stimulating in frog skeletal muscle and inhibiting in frog cardiac muscle [3].

The effect of catecholamines on Mg is not so well studied. In dogs and rats adrenerg stimulation of α- and β-receptors produced a rapid loss of Mg from the heart muscle which

could be prevented ba α- or β-blockade. However, adrenerg stimulation had no effect on Mg content in skeletal muscle, liver, erythrocytes or bone tissue [15, 23, 37]. An increased uptake of Mg into adipocytes by β-receptor stimulated lipolysis has been suggested [15]. This effect of catecholamines may explain the often observed decrease of serum Mg in patients with acute myocardial infarction.

Other factors

There are also factors other than the hormonal influencing electrolytes in CHF (Table 1). A low daily intake and reduced intestinal absorption of K and Mg may contribute to low levels of these ions in CHF. The daily intake of Mg in particular may be insufficient [18].

Tab. 1: Factors influencing electrolytes in CHF

Nutritional
Low daily intake
Low absorption
Hormonal
R-A-A activator
Catecholamine increase
Antidiuretic hormone increase
Atrial natriuretic factor
Treatment
Diuretics
Digitalis

Diuretic treatment

Treatment with diuretics is a cornerstone in the management of CHF since the intense reabsorption of salt and water is one of the main problems causing the majority of symptoms. Diuretics are very efficient in moving the ventricular function curve to the left relieving congestive symptoms. However, with regard to electrolytes the long term use of diuretics brings with it several problems. Continued use of these agents may lower blood volume leading to a shift down the ascending part of the curve. The decreased cardiac output will stimulate the RAA system counteracting the diuretic effect and also leading to extra- and intracellular loss of K and Mg.

Further, diuretics may have a pronounced effect on the renal handling not only of Na and K but also of Mg. The diuretic induced urinary loss of potassium has been dealt with clinically for a long time. The importance of the increased urinary losses of magnesium has only recently entered clinical discussion. The urinary Mg loss usually increases by 25–50% but may reach up to several hundred %.

Mg deficiency and secondary hyperaldosteronism will act on cellular electrolytes in the same way, a Na increase and a K decrease, the hyperaldosteronism by causing a leaky membrane and the Mg deficiency through impaired function of the Na-K pump.

The amount depends on the type of diuretic, the dose, the dosage interval, the length of treatment and not least the underlying disease. Different types of diuretics exert their renal effects on different parts of the nephron. The main action site of thiazides is from the peritubular site at the cortical dilutional segment and at the distal tubules. In this part of the nephron only 2–5% of filtered Mg is reabsorbed and blocking this may only increase the urinary Mg output to a very small degree. However, the Mg-reabsorption at the distal tubuli is load dependent and if thiazides are combined with loop-diuretics the thiazide-induced Mg-waste may be greater. The Mg losses observed during long-term thiazide treatment may depend on secondary hyperaldosteronism aggravated by the thiazides and possibly also by interaction with calcium metabolism and parathormone. In patients with normoreninemic essential hypertension [5] and in otherwise healty stone-forming patients [5, 26] long term thiazide therapy did not lead to Mg deficiency.

On the other hand loop-diuretics act from the luminal site on the thick ascending part of Henle's loop where the majority (50–60%) of filtered Mg is reabsorbed. Thus, the Mg-waste by loop-diuretics may be explained by a direct tubular effect. The potassium-sparing diuretics — amiloride, spironolactone and triamterene — exert their effect on the distal tubulus and the collecting ducts of the kidney where only 3–5% of the filtered Na is reabsorbed. This explains their limited diuretic effects when they are used alone as therapy. However, when combined with other diuretics that increase the distal tubular load of Na their effect is enhanced. Besides their potassium-sparing properties these diuretics have an additional bonus viz. their magnesium-saving effect [13, 32], which I will present in more detail later.

Digitalis treatment

Treatment with digitalis may also contribute to electrolyte changes. Digitalis is a known inhibitor of Na-K-ATPase. Thus, digitalis therapy, like Mg deficiency, will impair the function of Na-K pump leading to increased intracellular Na and decreased intracellular K. Furthermore, digitalis treatment causes increased loss of Mg by reducing the tubular reabsorption [28], which may lead to Mg deficiency. Mg deficiency may lead to K deficiency and K deficiency completes the vicious circle by reducing the tubular secretion of digitalis [34]. It has also been reported that hypomagnesemia is common in digitalis intoxication [36].

In a study of long-term treatment with conventional diuretics and digitalis in 297 patients with CHF we observed a high incidence of abnormal electrolytes in plasma and even more so in skeletal muscle (Fig. 2).

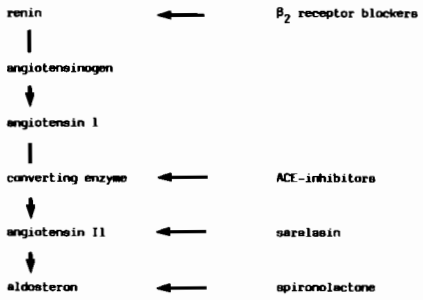

Fig. 2: Inhibitors of the renin-angiotensin-aldosteron system

42% had hypokalemia, 37% hypomagnesemia and 12% hyponatremia. About half the patients had depletion of muscle K and muscle Mg and most of them had muscle Na excess. Compared to controls there was a significant reduction of muscle K and Mg and a significant excess of muscle Na and extracellular water [8].

Dysrhythmias in CHF

Thus, electrolyte disturbances are very frequent in treated CHF patients. The resting potential is build up from the concentration gradient between extra- and intracellular K. Thus, changes in extra- or intracellular K are very likely to induce dysrhythmias. Dysrhythmias are also extremely common in patients with CHF and the risk of sudden death (SD) is even higher for CHF patients than for patients in the first twelve months after an acute myocardial infarction [31].

Treatment with diuretics and digitalis is very effective in releasing the congestive symptoms in cardiac failure. However, no treatment has been shown to be effective in improving the very poor longterm survival rate for CHF. Many CHF patients don't die from progressive circulatory failure but suddenly and unexpectedly. In all probability dysrhythmias is/are the reason for this. It has been estimated that 35–45% of all CHF deaths are sudden and are not related to the severity of congestive symptoms [31]. The cause of dysrhythmias in CHF patients may of course be irreversible underlying structural changes in the myocardium. However, the dysrhythmias may also arise from electrolyte imbalance induced either by the compensatory hormonal mechanisms or by the conventional treatment with diuretics and digitalis. These reasons for dysrhythmias in CHF patients must be counteracted.

K substitution

As K is the key ion for the membrane potential it has long been thought proper to try to replace the K losses by K supplementation. However, it has been shown that low intracellular K cannot be corrected with K substitution when there is a concomitant Mg deficiency as is often the case in patients with CHF. The reason for this is that Mg is a necessary cofactor for Na-K-ATPase. Thus, in Mg-deficiency the pump function of K into the cell and Na out of the cell is impaired. Furthermore, a rise in plasma K induced by K substitution will lead to increased aldosteron secretion leading to further K and Mg losses.

In 79 our patients treated with diuretics the mean plasma K was 3.55 mmol/l before K substitution and 4.30 mmol/l after. However, the muscle K did not increase. The mean value was 40.5 mmol/100 g fat free solids before substitution and 39.2 after [9].

Treatment possibilities

Some possible ways to counteract the K and Mg disturbances in CHF patients are listed in Table II. The effects of the potassium-sparing diuretics are reviewed by *Ryan* [32] in this symposium. Acute [32] and long-term studies [13] have shown that the Na-channel blocker amiloride also saves Mg. We have observed that the addition of 5 mg amiloride to 50 mg hydrochlorothiazide (Htz) for patients already treated with Htz for more than one year increased K and Mg in serum and muscle after 6 months' therapy as compared to patients with continued treatment with Htz alone [13]. We have also observed in a similar study that the addition of the K-sparing agent triamterene also increased Mg in plasma and muscle after six months' treatment as compared to treatment with Htz alone.

Tab. 2: Possible treatments

K-sparing diuretics
Aldosteron antagonists
Converting enzyme inhibitors
Magnesium substitution

As has been pointed out earlier activation of the RAA-system leads to losses of K and Mg. This system may be blocked at different sites (Fig. 2). As far as I know there are no studies on the effect of saralasine on Mg metabolism. The effect of the new ACE-inhibitor enalapril on — among others — serum K and Mg has recently been studied in an extensive placebo controlled cross-over study. The addition of enalapril to 19 CHF patients on diuretics and digitalis reduced the levels of angiotensin II, aldosteron, vasopressin and noradrenalin and increased K and Mg in serum significantly. There was a non-significant increase in body K measured by a whole body count. The effect of ACE-inhibition on tissue electrolytes seems to be missing.

It has been found in several longterm studies that blocking aldosteron with spironolactone saves Mg [19, 25, 30]. We found that the addition of 100 mg spironolactone to 21 patients treated with diuretics increased K and Mg in serum and muscle compared to 23 patients who continued with their ordinary diuretic treatment [13, 14].

Supplementation with Mg offers another possibility for correcting the changes in K and Mg balance. We have shown earlier in acute

studies that i. v. infusion of K did not increase the low intracellular K and had no influence on the number of ectopic beats registered on a Holter ECG. However, the infusion of Mg significantly increased both intracellular Mg and intracellular K as well as reduced the number of ectopics [10]. In patients with severe CHF and hyponatremia we observed that Mg infusion not only increased the low intracellular K and Mg but also reduced the high intracellular Na [11]. We have also found that long-term supplementation with Mg per os to diuretic treated patients for arterial hypertension and/or CHF significantly increased intracellular K and Mg, compared to patients continuing their diuretic treatment without Mg supplementation (unpublished results).

In conclusion, extracellular and intracellular electrolyte disturbances are very frequent in CHF patients. Both hormonal compensatory mechanisms such as raised catecholamine levels and activation of the RAA system and treatment with digitalis and conventional diuretics contributes to these changes which may give rise to serious dysrhythmias. Since more than one third of all CHF deaths occur suddenly and unexpectedly it is urgent that we increase our efforts to avoid or correct the electrolyte disturbances in our CHF patients. There are several different possibilities of achieving this such as the use of aldosterone antagonists or other K-Mg-sparing diuretics. Magnesium supplementation may also be efficient. Another way, which also need further studies, is ACE-inhibition.

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