REVIEW

Cardiovascular effects of aldosterone

Murin J

*1st Department of Internal Medicine, Faculty of Medicine, Comenius University, University Hospital, Bratislava, Slovakia.***murin@ faneba.sk**

Abstract

Aldosterone plays an important role in the pathophysiology of sodium/potassium and water homeostasis of the body. It is nowadays clear that aldosterone contributes also to the development of cardio-vascular diseases, such as hypertension, left ventricular hypertrophy, heart failare, renal failare and others, by direct effets on vesels and the heart. The global view on pathophysiology, on harmful effects of aldosterone and on aldosterone in hypertension and heart failare is presented. ***(Tab. 2, Fig. 1, Ref. 132.)***
Key words: aldosterone, cardiovascular diseases, congestive heart failure, hypertension, spironolactone.

For several decades aldosterone has been recognized as playing a role in the pathophysiology of heart failure and spironolactone – an aldosterone antagonist – has been available for over three decades.The importance of aldosterone has, however, been underestimated and conversely, the risk of serious adverse effects (like serious hyperkalaemia) associated with the use of spironolactone, overestimated. We have now not only better clinical experience with blocking of harmful effects of aldosterone but also useful results of clinical studies, such as RALES (the Randomized ALdactone Evaluation Study) and EPHESUS (the Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SUrvival Study) in congestive heart failure and studies with eplerenone (a derivative of spironolactone devoided of androgen and progesterone activities) in hypertension patients.

Physiology and pathophysiology

Synthesis and metabolism of aldosterone

Aldosterone is a steroid hormone synthesized from cholesterol molecule in the mitochondria of the zona glomerulosa cells of the adrenal glands. Recent research shows that other, extra-adrenal sites of aldosterone production occur, such as within cardiovascular tissue (1).

Aldosterone content of the adrenal glands is in the range of 1–2 μg, while its secretion rate is 70–250 μg/day, yielding plasma aldosterone levels of 5–100 pg/ml. So adrenal glands do not store aldosterone but are capable of rapidly synthesizing it in mitochondria.

Unlike for glucocorticoids, there is no specific aldosterone binding protein in the circulation and therefore more than 50 % of circulating aldosterone is no protein bound. Because of its weak binding to plasma albumin, the volume of distribution of aldosterone is considerable, nearly 35 l (2).

Cholesterol represents the backbone molecule to the generation of aldosterone, the most potent mineralocorticoid hormone. Critical enzymes and co-factors are required for the sequential production and conversion of steroid molecules that eventuate in aldosterone synthesis (2) (Fig. 1).

A number of factors (Tab. 1) can regulate aldosterone synthesis by zona glomerulosa cells: (a) Angiotensin II (ang II) is the most potent stimulus to aldosterone synthesis. Its effects is mediated by AT1 receptors which are located on the zona glomerulosa cells. Ang II is also a potent trophic substance and may promote growth of zona glomerulosa. (b) ACTH (adrenal corticotropin hormone), a stress hormone, also stimulates aldosterone secretion (3). Its effect, however, is temporary, with aldosterone secretion returning to baseline values despite persistent elevations in plasma ACTH. Levels of ACTH have not been measured in patients with chronic myocardial failure and its short-

1st Department of Internal Medicine, Faculty of Medicine, Comenius University, University Hospital, Bratislava, Slovakia

Address for correspondence: J. Murin, MD, PhD, 1st Dept of Internal Medicine, Faculty of Medicine, Comenius University, University Hospital, Mickiewiczova 13, SK-813 69 Bratislava 1, Slovakia.
Phone: +421.2.52921388, Fax: +421.2.52925875

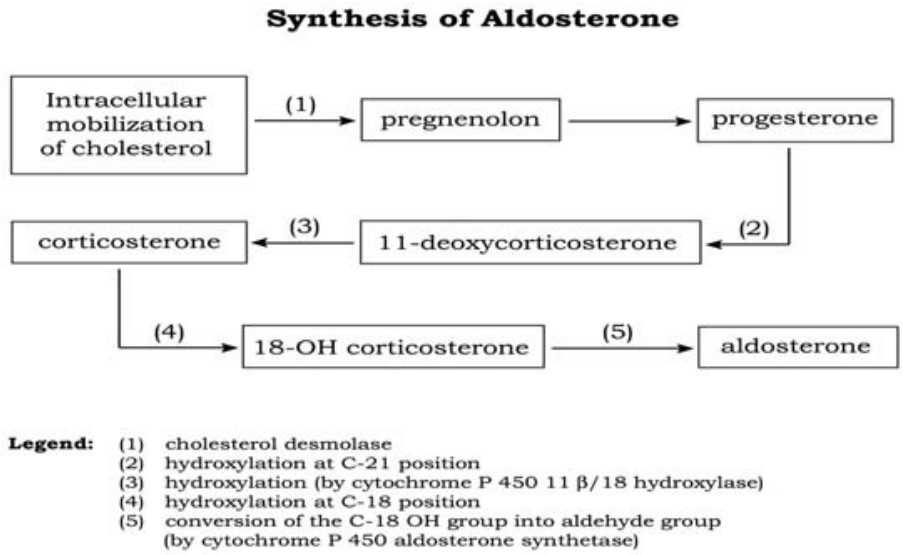

Fig. 1. Synthesis of aldosterone.

term and long-term contribution to aldosterone synthesis is therefore unknown. However, plasma cortisol levels, also regulated by ACTH, are known to be increased in congestive heart failure, providing indirect information that ACTH may be elevated in such patients (2). (c) Potassium ion (mainly hyperkalaemia) has been shown to increase aldosterone synthesis, while hypokalaemia suppresses it. Interestingly, ouabain can block this response, suggesting that Na^+/K^+-ATPase activity may be involved in this process. Even very small changes in plasma K+ concentrations can alter aldosterone synthesis. (d) There are also several other (minor) stimulators of aldosterone synthesis: endothelin, prolactin, vasopressin, catecholamines, acetylcholine, prostaglandins, nitric oxide – all these substances are affected during the development and the course of congestive heart failure. (e) Conversely, there are substances which inhibit aldosterone synthesis: 1) ANP (atrial natriuretic peptide) with its generation of cGMP inhibits aldosterone biosynthesis by reducing mitochondrial cholesterol uptake. In addition, this response is amplified through the concurrent inhibitory effect of ANP on renin secretion. 2) heparin, which acts by occupying the ang II receptors in the zona glomerulosa cells and thus preventing the stimulating action of ang II. The ACTH-induced aldosterone biosynthesis remains unimpaired. Long-term heparin administration is associated with an involution of the zona glomerulosa. 3) ouabain, a digitalis glycoside which inhibits aldosterone synthesis both under baseline conditions or in response to increased plasma potassium. The exact mechanism of this action is unknown but it is likely to reflect the inhibition of the membrane-bound sodium-potassium ATPase. This is a Na+ pump which actively extrudes intracellular Na^+ and transports K^+ into cell. As a result of inhibition of this pump, intracellular Na^+ gradually increases and K^+ decreases. Aldosterone synthesis by zona glomerulosa cells is exquisitely sensitive to intracellular Na^+ and K^+ levels. Increased intracellular K^+ and decreased Na+ markedly stimulate aldosterone synthesis, probably through the induction of the synthesis of the enzyme aldosterone synthetase. Reversal of these electrolyte levels by digitalis probably inhibits aldosterone synthetase and, thereby, aldosterone production (2). 4) adrenomedullin which is a peptide produced mainly in the peripheral circulation which not only inhibits aldosterone secretion but also has vasodilatory and natriuretic actions (4). 5) Blockade of 11-beta- and 18-hydroxylations of precursor steroids in zona glomerulosa cells. This could be done by various compounds, such as metyrapone and others.

There was recently a report on the presence of aldosterone receptors on left ventricular and atrial myocytes, as well as on smooth muscle cells of large arteries (1). Human vascular endothelial and smooth muscle cells express and synthesize aldosterone and its cytoplasmic receptor (6, 7). The whole aldosterone synthesis pathway is present in the myocardium and in the isolated heart, and is sensitive to a low sodium and a high potassium environment. Myocardial aldosterone concentrations are 17-fold higher than mean plasma values suggesting that cardiac aldosterone generation has autocrine or paracrine properties. Therefore, it is likely that aldosterone synthesis in the heart is controlled by pathways similar to those described in the adrenocortical cells.

Metabolism of aldosterone occurs primarily within the liver, where more than 85 % is inactivated during the single passage. Therefore, the rate of aldosterone degradation is related to hepatic blood flow and its extraction by parenchymal cells, both processes being potentially impaired in congestive heart failure (5). Tetrahydroaldosterone is the major urinary metabolite and it is conjugated with glucuronic acid to impart water solubility. Urinary excretion of this metabolite requires 24 to 36 hours. An 18-glucuronide conjugate represents 10 % to 20 % of metabolized aldosterone and is formed in both the liver and kidneys. Ninety percent of this acid-labile conjugate is excreted in urine within 6 hours.

In heart failure, aldosterone secretion may reach 4 to 5 mg/day. Impaired hepatic metabolism alone can account for a three- to

Tab. 1. Factors regulating aldosterone synthesis.

Stimulators
– angiotensin II
– adrenal corticotropin hormone
– potassium ion (hyperkalaemia)
– minor stimulators: endothelin, prolactin, vasopressin, catecholamines, acetylcholine, prostaglandins,
– nitric oxide
Inhibitors
– atrial natriuretic peptide
– heparin
– ouabain
– intracellular hypokalaemia
– intracellular hypernatremia
– adrenomedullin
– blockade of 11-beta- and 18-hydroxylations of precursor steroids (metyrapone, androgens, others)

four-fold rise in plasma aldosterone concentration. This is further underscored by the fact that the normal half-life of plasma aldosterone is 30 to 35 minutes. In heart failure, where hepatic blood flow and aldosterone degradation are impaired, averaging only 25 % to 50 % of normal values, plasma aldosterone half-life rises to 70 to 100 minutes.

Actions of aldosterone

Aldosterone acts on the distal renal tubule where it enhances sodium reabsorption, creating an electrical gradient which favours the transfer of potassium and hydrogen ions towards the lumen.

Aldosterone increases the urinary excretion of magnesium.

Aldosterone increases sodium transport by increasing Na-K pump activity (9).

It has recently been reported that aldosterone can also have some rapid, non-genomic effects in the heart and in the vessels. This rapid effect has been described in several cell types, including cardiac myocytes. So aldosterone infusion can cause changes in systemic vascular resistance and cardiac output within 10 minutes in humans, which is not compatible with its action at the level of the kidney. All these effects are probably mediated by an as yet unknown membrane receptor and they (probably) do not involve protein synthesis (10). Also spironolactone does not block these effects.

When sodium load is presented to a cell in the presence of aldosterone, there is recruitment and increased expression of sodium pumps (1). Alterations in the expression of sodium-pump isoforms may affect the excitability and conctractility of cardiac myocytes, the reactivity of vascular smooth-muscle cells, the growth of fibroblasts and turnover of collagen, the vasodilative and angiogenic potential of endothelial cells and the exchange of sodium for potassium and magnesium in epithelial cells. Antagonism of aldosterone receptors could attenuate such changes in cell function and improve the outcome for patients with congestive heart failure.

Aldosterone receptors

It is nowadays clear that aldosterone contributes to the development of cardio-vascular diseases (such as hypertension, left ventricular hypertrophy, heart failure, microalbuminuria, renal failure and others) not only via an increase of renal sodium reabsorption – which is the classical renal mineralocorticoid effect – but also by a direct effects on vessels and the heart. This implies that mineralocorticoid receptors (MRs) also exist in the heart and/or vessels.

Aldosterone receptors are located in the renal tubules where aldosterone-MR complexes migrate into the nucleus to interact with specific DNA sequences. This stimulates the synthesis of the messenger RNAs which encodes for aldosterone-inducing proteins that allow the entry of sodium from the urinary lumen into the tubule cells. In parallel, the sodium-potassium pump extrudes sodium from the cell into the interstitial space (5).

Aldosterone receptors are located also in the human heart: (a) Lombés et al (1995) evaluated the presence of MRs in the human heart using specimens removed during surgery for cardiac valve replacement or myocardial biopsies performed for the assessment of transplant tolerance in heart transplant recipients (11, 12). Cardiomyocytes, but not intramyocardial vessels, display MRs. This evidence for MRs was more consistent in biopsies from patients subjected to cardiac valve replacement than from transplanted hearts. It is possible that the latter situation can be explained by profound histological alterations of heart tissue due to therapy with immunosuppressive agents and/or glucocorticoids. (b) At present we can only speculate about aldosterone's mechanism of action in cardiac and/or vessel tissues. It is possible that the intracardiac effect of aldosterone (analogous with the kidney's effect) involves regulations of ion exchange and these changes might affect contractility and excitability of the myocytes – the likely target could be sodium-potassium ATPase (12). Recently there has been a report of an effect of aldosterone on the chloride-bicarbonate exchange and the sodium-hydrogen exchange in cultured neonatal rat cardiomyocytes (13). Other group studied the mechanism for cardiac fibrosis in aldosterone-salt sensitive rats and their data suggests that aldosterone does not directly modulate cardiac collagen synthesis through cardiac sodium-potassium ATPase (14). These animal studies have suggested that aldosterone's cardiac effects may be mediated through upregulation or increase of the level (or density) of ang II type 1 receptors in the heart and in vessels – which means that aldosterone may enhance the effects of ang II (1). This increase of density of AT1 receptors by influence of aldosterone is preventable by spironolactone or losartan (an angiotensin II AT1 receptor blocker) (14). This suggests that cardiac ang II receptors may be a target for aldosterone, possibly leading to increased responsiveness to angiotensin II. It is also possible that MRs are present in some interstitial cells such as cardiofibroblasts and that this may be the cause of the direct effect of aldosterone on the development of cardiac fibrosis (13).

Aldosterone escape phenomenon

The traditional view is that it is the angiotensin II which is the principal culprit in the renin angiotensin aldosterone system (RAAS). However, it is now appreciated that aldosterone is a second culprit and that the harmful effects of aldosterone are additional to the harmful effects of angiotensin II. This is important because the chronic suppressive effects of ACE inhibitors on aldosterone levels in heart failure are weak, variable and unsustained. It was recently shown that both plasma angiotensin II (some 15 % of treated congestive heart failure, CHF patients) and plasma aldosterone (but as much as 40 % of treated CHF patients) are elevated in many patients with congestive heart failure who are being treated with chronic ACE inhibitors (15). This blocking action on the production of ang II and consecutively on the production of aldosterone is greater with higher doses of ACE inhibitors (16). Studies of the long-term effects of ACE inhibitors on aldosterone concentrations in congestive heart failure are scarce. Cleland et al (1984) showed in patients with congestive heart failure that despite a good dose of captopril the aldosterone concentration increased above baseline values after several weeks to months of treatment (8). The clinical point here is that there is plenty of residual aldosterone around for this to be a potential problem, even in the presence of an ACE inhibitor (17). In the RESOLVD Pilot Study enalapril (ACE inhibitor) or candesartan (the AT1 receptor antagonist) were administered to heart failure patients, either alone or in combination for a period of 43 weeks. Although plasma aldosterone levels had dropped significantly in patients treated with enalapril and candesartan after 17 weeks of treatment, after 43 weeks of treatment aldosterone levels returned to pretreatment values or rose above baseline with prolonged therapy. The rise in aldosterone occured even when maximal doses of enalapril and candesartan were administered (18).

The reason for the secondary increase in plasma concentrations of aldosterone despite ACE inhibition is unclear, but it could be an ‚escape phenomenon“ from ACE inhibitors (17). Alternative pathways of ang II formation (chymase) may lead to an increased ang II production since increased levels of ang II occur when the converting enzyme is blocked (18). However, the increase in aldosterone does not seem to be always matched by an increase in ang II. From studies with angiotensin-II receptor blockers it does not appear that these drugs are much more effective than ACE inhibition in suppressing aldosterone secretion in congestive heart failure. The proportion of congestive heart failure patients who have plasma aldosterone levels increase despite treatment with ACE inhibitors is uncertain, but in a study by Dahlstrom and Karlsson it was as high as 24 % of patients with severe heart failure receiving low doses of captopril (19). Van Vliet et al (1993) found in their study that aldosterone escape with ACE inhibition is reversible by spironolactone (20).

Harmful effects of aldosterone

Nearly all of the harmful effects of angiotensin II with which we are familiar also occur with aldosterone. There is now compeling evidence that aldosterone mediates significant deleterious cardiovascular effects via the action of this hormone on mineralocorticoid receptors (MRs) outside the kidney, namely in the heart, vasculature and in the brain too (21). Furthermore, the enzymes responsible for extra-adrenal aldosterone biosynthesis have been identified in these same tissues (22, 23, 24). It is now postulated that many of the deleterious effects of aldosterone are mediated through MR activation in these ‚non-classical‘ target tissues (Tab. 2).

Magnesium and potassium loss

Aldosterone independently causes magnesium loss from the body by increasing urine magnesium output. ACE inhibition during the course of congestive heart failure increases serum magnesium by 2 % but spironolactone (aldosterone receptor blocker) increases serum magnesium by 13 % (25). The same is true also for potassium.

Calcium (ion) current changes

In adult rat cardiomyocytes aldosterone exposure increases Ca^{2+} current and spironolactone could prevent this (26).

Dysfunction of autonomous nervous system

Aldosterone has the ability to potentiate the effects of catecholamines and so it stimulates the sympathetic activation. One of the contributing mechanisms is blocking of catecholamine’s uptake in tissues. Barr et al (1995) found in an animal experiment that aldosterone blocks noradrenaline uptake in the heart in vivo (25).

Aldosterone may also reduce parasympathetic activity: (a) it directly reduces baroreceptor discharge from the carotid sinus but it also reduces the heart rate (HR) response to blood pressure changes in acute and chronic administration of aldosterone (tested in dog experiments) (27, 28). (b) In man aldosterone halved the reflex bradycardic response to an equivalent pressor stimulus (and this effect was not due to changes in sympathetic activity or angiotensin II levels) (29).

Myocardial fibrosis

Experimental studies (rats with experimentally induced chronic mineralocorticoidism) demonstrated an association between chronic inappropriate elevations in plasma aldosterone and a structural remodelling of the heart, arterial vasculature and systemic organs (30).

Aldosterone stimulates fibrosis in the myocardium, but the same is true also for angiotensin II (31). Brilla et al (1993) showed that aldosterone induces biventricular extensive perimyocytic and perivascular myocardial fibrosis in the rat and that myocardial fibrosis could be prevented by spironolactone at a dose which was too low to alter the blood pressure itself (31). The recent work from Rocha et al (2000) suggests that the primary damaging effect of aldosterone may be the induction of vascular inflammation and fibrinoid necrosis of the small arteries and arterioles, which leads to a reparative fibrotic prosess (32). It is very difficult to study myocardial fibrosis in the man, but recently it was proposed that plasma levels of procollagen type III amino-

Tab. 2. Harmful effects of aldosterone.

- Magnesium/potassium loss
- Increase Ca^{2+} current in cardiomyocyte
- Sympathetic activation/parasympathetic inhibition
- Myocardial/vascular fibrosis
- Myocardial hypertrophy
- Vascular changes
  - reduction of large artery compliance
  - reduction of baroreceptor function
  - induction of endothelial dysfunction
  - vascular injury (renal, cardiac damage)
- Inhibition of fibrinolysis
- Induction of arrhythmias
- QT dispersion prolongation
  - induction of recurrent myocardial ischemia (mainly in patients with LVD)
- Hypertension by stimulation of brain's aldosterone receptors (experiments)

Legend: LVD - left ventricular dysfunction

terminal peptide (PIIINP) may be a useful index of myocardial collagen turnover (33, 34). So we can expect that aldosterone causes patchy myocardial fibrosis, which is a cause of increased myocardial stiffness and which could also lower the treshold for malignant ventricular arrhythmias, mainly in the setting of a patient with congestive heart failure.

Myocardial hypertrophy

Aldosterone has been shown to be important in the development of ventricular hypertrophy (35).

Vascular changes

Aldosterone exerts harmful effects at the level of the peripheral vasculature: (a) There is an inverse relationship between plasma aldosterone and large artery compliance (36). This could be due to the induction of fibrosis and vascular remodelling or to other negative effects of aldosterone. Aldosterone seems to be a mediator of the aortic collagen accumulation that occurs during the development of hypertension in the spontaneously hypertensive rats (37). This finding is supported by clinical evidence that an inverse relationship exists between aldosterone levels and large artery compliance in late stage heart failure patients (36). (b) Aldosterone in animals depresses baroreceptor function which is thought to be related to large artery compliance (29). (c) Aldosterone levels are one of the four determinants of insulin resistance in heart failure (38). It is important to remind that insulin sensitivity is probably related to the ability of vessels to release nitric oxide in response to insulin and it is quite likely that artery compliance is also related to the ability of vessels to release nitric oxide. So aldosterone could be the link between compliance and insulin sensitivity, by acting on nitric oxide. Aldosterone also may be a mediator of endothelial dysfunction because the blockade of aldosterone by spironolactone in patients with congestive heart failure improves endothelial dysfunction and increases nitric oxide bioactivity (39). (d) In patients with primary hyperaldosteronism there is (in comparison to normal individuals) always a presence of endothelial dysfunction, as evidenced by a decrease in forearm vascular response to the administration of acetylcholine (40). Removal of the aldosterone-producing tumour restores endothelial function in these patients. Endothelial dysfunction is probably also a mechanism for the reduced vasodilating capacity of patients with congestive heart failure and this is a way how aldosterone contributes here to the generalized vasoconstriction.

Inhibition of fibrinolysis

Aldosterone appears to disrupt fibrinolytic balance. Aldosterone inhibits fibrinolysis by increasing (upregulation) plasminogen activator inhibitor levels (PAI-1) which is the major physiological inhibitor of plasminogen activation (41, 42).

Induction of (ventricular) arrhythmias

Aldosterone could induce (ventricular and atrial) arrhythmias by a combination of the described effects – magnesium and potassium depletion, autonomic dysfunction (sympathetic activation and parasympathetic inhibition) and myocardial fibrosis. These effects are highlighted in patients with heart failure who usually take diuretics. Arora and Somari (1962) performed coronary ligation in dogs and then studied ventricular arrhythmias produced when adrenaline or aldosterone was infused: adrenalin was arrhythmogenic as expected but aldosterone displayed an even more striking and prolonged arrhythmogenic effect with a distinct dose-response relationship (43). Both hypokalaemia and hypomagnesaemia predispose (heart failure) patients to recurrent ventricular arrhythmias, digitalis toxicity and eventually to sudden cardiac death (44, 45). Aldosterone may also predispose patients to ventricular arrhythmias through its ability to potentiate the effects of catecholamines by blocking the norepinephrine uptake (46). Recently, aldosterone has been demonstrated to produce proarrhythmogenic effects in cardiac myocytes in that exposure of adult rabbit cardiomyocytes to aldosterone produces increases in Na^+ influx and Na^+/K^+ pump activity (47). Sudden cardiac death is only marginally prevented by treatment with ACE inhibitors. Antiarrhythmic drugs (type I of Vaughan-Williams classification) failed completely to reduce mortality in patients with heart failure (48). We are therefore in need of better medicamentous strategies to prevent ventricular arrhythmias and sudden cardiac death in these patients. The results of the RALES study (49) suggest that anti-aldosterone therapy may be useful here.

Aldosterone and QT dispersion

The already mentioned effects of aldosterone produce the kind of cardiac abnormalities which are thought to underlie QT dispersion. It is important to remind that there are a lot of data to suggest that QT dispersion is a marker for those who are at high risk of cardiac death (50–54). The cardiac abnormalities associated with QT dispersion are ischemia, left ventricular dilatation and/or dysfunction, autonomic abnormalities, low serum potassium/magnesium and myocardial fibrosis – all except ischemia (but see later on) are common to both prolonged QT dispersion and aldosterone.

Recurrent ischaemia

High aldosterone levels could also favour the occurence of recurrent ischaemic events in patients with left ventricular dysfunction. This effect can be induced by causing endothelial dysfunction, by magnesium loss (which contributes to the increased coronary resistance), by enhancing the process of atherosclerosis and also by reducing HDL-cholesterol concentration (55).

Aldosterone and renal vascular injury

Stroke-prone spontaneously hypertensive rats (SHR-SP) on 1 % NaCl drinking solution develop severe hypertension and glomerular and vascular lesions characteristic of thrombotic microangiopathy seen in malignant nephrosclerosis. In a study Rocha et al (1999) (56) examined whether chronic (2 weeks) infusion of aldosterone can reverse the renal vascular protective effects of captopril in SHR-SP. These animals received vehicle (n=8), captopril alone (50 mg per kg per day orally) (n=10), aldosterone infusion alone (40 μg per kg per day subcutaneously) (n=7) or captopril (previous dose orally) and aldosterone at 20 (n=6) or at 40 (n=7) μg per kg per day subcutaneously. Systolic blood pressure was markedly elevated in all groups. Vehicle- and aldosterone-infused SHR-SP developed severe proteinuria and comparable degrees of renal injury (21±3 % and 29±3 %, respectively) manifested as thrombotic and proliferative lesions in the arterioles and glomeruli. Captopril treatment reduced plasma aldosterone levels concomitant with marked reductions in proteinuria and the absence of histologic lesions of malignant nephrosclerosis. Aldosterone substitution at 20 or 40 μg per kg per day subcutaneously in captopril-treated SHR-SP resulted in the development of severe renal lesions (16±3 % and 21±2 %, respectively) and proteinuria comparable with that observed in SHR-SP given either aldosterone or vehicle alone. So, these findings support a major role for aldosterone in the development of malignant nephrosclerosis in saline-drinking SHR-SP, independent of the effects of blood pressure.

To determine the role of aldosterone in mediating cardiovascular damage the same group (Rocha et al, 2000) (57) performed ablation/replacement experiments with aldosterone in a rat model of cardiac injury. Administration of angiotensin II and N-omega-nitro-L-arginine methyl ester (L-NAME, nitric oxide synthesis inhibitor) to male rats drinking 1 % saline caused hypertension, severe biventricular myocardial necrosis, proteinuria and fibrinoid necrosis of renal and cardiac vessels. Removal of aldosterone by adrenalectomy or through administration of the selective aldosterone antagonist ‚eplerenone' markedly reduced the cardiac and renal damage without significantly altering blood pressure. Aldosterone infusion in adrenalectomized, glucocorticoid-replaced L-NAME/angiotensin II-treated animals restored damage. Thus, aldosterone is a critical mediator of L-NAME/angiotensin II induced vascular damage through mechanisms apparently independent of its effects on systolic blood pressure.

Aldosterone activities in the brain

In rodents aldosterone activation of MRs in the brain can lead to hypertension, as it was shown that intracerebroventricular administration of aldosterone (at doses too low to raise systemic concentrations) slowly increases blood pressure over several weeks (58). In SS/jr (Dahl salt sensitive) rats on a high-salt diet, blood pressure rises slowly over time despite suppression of the RAAS with high salt intake and when these animals are administered RU28318 (a selective aldosterone receptor antagonist) into the brain, the rise in blood pressure is attenuated (59). This means that endogenous levels of aldosterone can elevate blood pressure via effects on aldosterone receptors in the brain.

Diurnal profile of aldosterone

Aldosterone displays a marked diurnal pattern (60), it peaks during the early morning even while lying supine in bed. What are the consequences of such a dawn surge in aldosterone? It is also well known that adverse cardiovascular events also display a marked diurnal profile with a breakfast time peak in their frequency (like myocardial infarction, sudden cardiac death, arrhythmias, stroke and others) (61). The reason for this diurnal profile is unknown. We know from clinical experience that beta-adrenoceptor blockers reduce the morning peak of mentioned and others cardiovascular events. The dawn increase in aldosterone could contribute to the morning peak of mentioned cardiovascular events by way of increasing sympathetic activity, by way of inhibiting parasympathetic activity, by way of increasing heart rate and hence myocardial ischemia. Spironolactone reduces the normal morning (from 6:00 AM to 10:00 AM) increase in heart rate of patients with CHF (62) and spironolactone increases parasympathetic activity plus decreases sympathetic activity in CHF patients during mentioned morning time period (63).

Aldosterone and hypertension

Heart disease and stroke are the first and the third leading causes of death, respectively (64). Although the percentage of hypertensive patients receiving treatment has increased and blood pressure is now better controlled, the incidence of end-stage renal disease and the prevalence of heart failure continue to increase (65). This suggests that blood pressure reduction alone is not sufficient to prevent end-organ damage and that the additional control of local and/or hormonal factors might be essential. Abnormal activation of the RAAS correlates directly with the incidence and extent of end-organ damage (66, 67). Moreover, numerous clinical and experimental studies have demonstrated that blockade of the RAAS with either angiotensin – converting enzyme (ACE) inhibitors or ang II receptor antagonists provides significant cardiovascular protection (66, 68–71). Therefore, it has been proposed that overactivation of the RAAS represents a cardiovascular risk factor (72). Although many of the mechanisms involved in ang-II-induced cardiovascular injury have been elucidated, little is known about the contribution of aldosterone to the development of pathological changes in the kidney, brain and heart (73).

Novel concepts of aldosterone biology

The classic mineralocorticoid receptor (type I corticosteroid receptor) forms part of the steroid/thyroid/retinoid/orphan – re-

ceptor family of nuclear transactivating factors (74). When unbound, these receptors remain in an inactive but ligand – friendly conformation associated with a multiprotein complex of chaperons (75). Upon binding aldosterone, chaperones are released and the receptor-hormone complex is translated into the nucleus. The complex then binds to hormone-response elements on DNA and interacts with transcription-initiation complexes and other transcription factors to modulate gene expression. Activation of mineralocorticoid receptors by aldosterone induces the rapid expression of serum and glucocorticoid inducible kinase 1 which, when phosphorylated, activates the epithelial Na+ channel (76). This initiates a cascade of events, leading to a rapid increase in Na^+ and water reabsorption and promoting the tubular secretion of K^+. Importantly, under normal conditions, this increase is transient and a rapid return to Na+ balance occurs, even in the presence of continued stimulation of the tubular epithelium by aldosterone (77).

Non-epithelial effects of aldosterone have also been demonstrated in the brain. Aministration of low doses of aldosterone into the cerebral ventricles in rats induces hypertension, whereas the same doses administered systematically have no effect (58). Similarly, intracerebroventricular infusion of non-diuretic doses of the mineralocorticoid receptor antagonist RU 28 318 prevented the development of hypertension in aldosterone/salt hypertensive rats (78), an intervention that did not prevent the pathological effects of aldosterone in the heart (79). Thus, multiple lines of evidence indicate that aldosterone can activate non-epithelial mineralocorticoid receptors. However, the physiological or pathophysiological significance of these effects remains to be clarified.

Role of aldosterone in cardiovascular end-organ damage

Experimental evidence

It has long been known that combined administration of the mineralocorticoid deoxycorticosterone acetate and sodium chloride to rats induces the development of severe hypertension and produces lesions in the kidneys, brain and heart (80). Interestingly, these lesions are virtually identical to those seen in hypertensive models that display an abnormal activation of the RAAS, such as ang II/salt hypertensive rats or stroke – prone spontaneously hypertensive rats (SP-SHR) (81–83). In studies to determine the contribution of aldosterone to vascular lesion development in SP-SHR, it was noticed that administration of aldosterone antagonists or adrenalectomy markedly reduced the incidence of stroke and the development of proteinuria and renal microvascular lesions in saline-drinking SP-SHR (84–87).These vascular protective effects of aldosterone antagonism were not associated with significant reductions in blood pressure.These studies indicate that aldosterone plays a pivotal role in vascular lesion development in the brain and kidnyes, which is unrelated to an effect on blood pressure.

In recent studies the role of aldosterone in the development of cerebral lesions in SP-SHR was studied. Rats were placed on a 1 % NaCl/stroke-prone rodent diet at nine weeks of age. At the same time, treatment with either eplerenone (selective aldosterone receptor blocker) (100 mg per kg per day perorally, n=7) or vehicle (0.5 % methylcellulose, n=8) was started. SP-SHR were maintained on these treatments until 19 weeks of age, at which time the animals that survived were sacrificed. Tail-cuff systolic blood pressure measured before death was similarly raised in the two groups. Starting at 13 weeks of age, vehicle treated SP-SHR began to show neurological signs of stroke and subsequently died. All of the vehicle-treated SP-SHR were dead by 18 weeks of age. In contrast, none of the eplerenone-treated littermates exhibited signs of stroke and all survived to 19 weeks of age, with the exception of one animal which developed stroke signs and died at 18 weeks of age. Histopathological scoring of the brains revealed severe cerebral vascular and parenchymal lesions characteristic of ischemic and hemorrhagic stroke in untreated SP-SHR, whereas cerebral injury in animals receiving eplerenone was markedly reduced (88). Thus, aldosterone seems to play a major role in the development of end-organ damage not only in the kidney but also in the brain.

The effects of aldosterone on the heart have also been studied extensively. Several groups have demonstrated that hypertensive rat models in which ang II and/or aldosterone is elevated display cardiac hypertrophy, with severe myocardial damage, which has been mostly characterized as myocardial fibrosis. When the aldosterone receptor was blocked with a low dose of spironolactone or canrenone, blood pressure was not significantly lowered although the development of myocardial fibrosis was markedly attenuated (79, 89–92). The role for aldosterone in the development of vascular injury in the heart and kidneys of rats with ang II-induced hypertension was recently identified (32). This effect was prevented by either eplerenone or adrenalectomy, independent of blood pressure reductions. The vascular injury observed included lesions of segmental or circumferential fibrinoid necrosis of the media, panarterial inflammation and small foci of ischemic and necrotic damage in the myocardium, or glomerular injury in the kidney (32). Similar vascular lesions have been reported in the heart of rats made hypertensive by aldosterone/salt treatment after four weeks (90). Thus, it is possible that the interstitial fibrosis induced by aldosterone in the heart is a secondary event in response to ischemic/necrotic damage resulting from the vascular inflammatory injury. Whether aldosterone causes this injury solely by its effect on epithelial tissues or whether activation of non-epithelial receptors also participates remaines to be elucidated.

Clinical evidence

There is still scepticism about a role for aldosterone as an independent risk factor for cardiovascular disease. However, several clinical studies have shown that plasma aldosterone levels correlate with end-organ damage. Hene et al (1982) studied 28 patients with varying degrees of chronic renal failure but similar levels of plasma K^+ and plasma renin activity. Interestingly, as creatinine clearance fell below 70 ml per minute, plasma aldosterone level tended to increase (93). Duprez et al (1993) found a significant correlation between plasma aldosterone levels and left ventricular mass in a population of patients with essential hypertension (94). Other groups have also reported correlations be-

tween plasma aldosterone levels and left ventricular hypertrophy (95). A recent report demonstrated an inverse correlation between plasma aldosterone levels and arterial compliance in a population of essential hypertensive subjects, which was independent of blood pressure or age (96). Thus, several studies have shown that aldosterone correlates with the severity of end-organ damage, and is probably an independent risk factor for cardiovascular events.

Aldosterone may promote renal dysfunction in hypertensive patients. Epstein et al (2002) investigated whether the selective aldosterone receptor antagonist eplerenone reduces proteinuria in hypertensive patients with type 2 diabetes mellitus and albuminuria. After 2 to 4 weeks on placebo, 215 patients with diabetes mellitus type 2, hypertension and albuminuria were randomized to forced-titrated doses of eplerenone (50 mg up to 200 mg daily, 74 patients), enalapril (10 mg up to 40 mg daily, 74 patients) or eplerenone plus enalapril in combination (enalapril:10 mg/eplerenone 50 mg up to 200 mg daily, 67 patients) for 24 weeks. If diastolic blood pressure was >90 mmHg at >8 weeks, hydrochlorothiazide or amlodipine was added to control blood pressure. The primary end-point was the mean percent change in urinary albumin to creatinine ratio (UACR) at 24 weeks. Secondary end-points were blood pressure changes and tolerability. Eplerenone reduced UACR by 62 % (from baseline 611.4 mg/g to 248.8 mg/g at 24 weeks) versus 45 % (from baseline 483.3 mg/g to 285.3 mg/g at 24 weeks) with enalapril (difference was significant, $p=0.015$) and combination (from baseline 470.9 mg/g to 120.8 mg/g at 24 weeks) was even more effective (74 %, $p=0.018$ versus eplerenone and $p<0.001$ versus enalapril). Blood pressure decreases were not different between eplerenone (-19.5/-13.2 mmHg) and enalapril (-20.4/-15.0 mmHg) and combination (-21.8/16.2 mmHg). Both drugs were well tolerated also in combination: no gynecomastia and incidence of hyperkalaemia (>6.0 mmol/l) was 8 patients with eplerenone, 2 patients with enalapril and 8 patients with combination. Differences in proteinuria reduction despite similar blood pressure lowering indicate that renal protection is independent of blood pressure reduction. This is consistent with the hypothesis that selective aldosterone antagonism is renoprotective (97).

Unlike other types of hypertension, primary aldosteronism is associated with elevated aldosterone levels and suppresion of other components of the RAAS (98). In general, it has been assumed that these patients do not display significant cardiovascular complications, an assumption that is not supported by the available data. Recently, Nishimura et al (1999) have investigated the incidence of cardiovascular complications in a population of patients with primary aldosteronism secondary to aldosterone-producing adenomas. They identified cardiovascular complications in 34 % of the patients – stroke was found in 16 % and proteinuria in 24 %. In addition, 78 % of the patients in whom left ventricular mass index was evaluated had evidence of left ventricular hypertrophy (99). Grady et al (1996) published a report of 32 renal biopsies obtained from patients with aldosterone-producing adenomas and showed that 56 % had mild to severe arteriolar sclerosis and 46 % presented with interstitial fibrosis and tubular atrophy (100). Thus, there is a significant body of evidence that cardiovascular injury is common in patients with chronic primary aldosteronism.

Cardiovascular events in patients with primary aldosteronism have usually been explained by the presence of accompanying hypertension. To determine the relative contribution of aldosterone in cardiovascular pathogenesis, independent of blood pressure, clinical studies have compared the incidence of cardiovascular events in patients with either primary aldosteronism or essential hypertension. Halimi and Mimran (1995) found an increased prevalence of albuminuria in a population of patients with primary aldosteronism compared with matched subjects presenting with essential hypertension (101). Another study compared 224 cases of primary aldosteronism with a similar number of patients with essential hypertension, in two groups matched by sex and age. The results showed that patients with primary aldosteronism had a significantly higher incidence of cerebral hemorrhage than did those with essential hypertension (102). This incidence was greater in patients with primary aldosteronism, despite the higher levels of diastolic blood pressure and longer duration of hypertension in patients with essential hypertension. Another study compared the level of left ventricular hypertrophy in patients with primary aldosteronism or essential hypertension who displayed similar levels of blood pressure. Despite similar levels of blood pressure and comparable age and gender distribution, primary aldosterone patients demonstrated more severe and more frequent left ventricular hypertrophy and remodeling of left ventricle than did those with essential hypertension (103). Left ventricular hypertrophy is also more common and severe in patients with primary aldosteronism than in patients with other types of secondary hypertension. Denolle et al (1993) showed that left ventricular hypertrophy was more frequent in patients with primary aldosteronism than in those with renovascular hypertension or phaeochromocytoma (104). Thus, clinical evidence is now available that is consistent with the findings from animal studies suggesting a major role for aldosterone in the development of cardiovascular disease and stroke.

Aldosterone and congestive heart failure

Clinical data evidence

The association between elevation of levels of circulating effector hormones of the renin-angiotensin-aldosterone system (RAAS) and the progression of congestive heart failure is now irrefutable. So ACE inhibitors have been shown to be effective in reducing the incidence of hospitalization and the rate of mortality and morbidity in patients with systolic left ventricular dysfunction (105–107). Despite the development of a number of active drugs for the treatment of chronic heart failure this disease is still associated with high mortality rates: from pump failure in 60 %, from sudden cardiac death in 30 % and from associated diseases (as pneumonia, pulmonary embolism, others) in 10 % (107). In the past it was assumed that ACE inhibitors besides inhibiting the conversion of angiotensin I to angiotensin II also suppress the production of aldosterone. We now know that

this (suppression of aldosterone production) is not true. In fact, the currently recommended and usual doses of ACE inhibitors do not completely suppress aldosterone production (15, 17, 108). Aldosterone escape could be due both to non-ACE-dependent angiotensin II production and to the fact that aldosterone production is regulated not only by angiotensin II but also by other factors.

In patients with congestive heart failure plasma aldosterone concentrations may reach 20 times the normal level. Two pathophysiologic mechanisms contribute to the increased concentrations: (a) an increase in the rate of aldosterone production by the adrenal glands, largely as a result of increased plasma angiotensin II concentrations, which stimulate adrenal zona glomerulosa cells by binding to AT1 receptors and (b) a decreased rate of hepatic aldosterone clearance, which causes plasma aldosterone concentrations to triple or quadruple. The primary determinant of aldosterone metabolism is hepatic blood flow. In patients with congestive heart failure, the rate of aldosterone clearance by the liver falls to 25–50 % of the normal rate, with commensurate reductions in hepatic perfusion (109, 110).

It is not established whether ACTH increases in congestive heart failure, but Anand et al (1980) have shown an increase of cortisol levels which were modulated by ACTH, thus providing indirect information that ACTH may be elevated in such patients (3).

Nowadays used treatment of congestive heart failure (mainly diuretic treatment by natriuretic activity of loop diuretics) can stimulate the production of renin by the juxtaglomerular apparatus, thereby stimulating ang II and aldosterone secretion. Loop diuretic treatment seems to be the main cause of increased plasma levels of renin and ang II in heart failure's patients (111).

During the development of congestive heart failure there is at the very beginning arterial underfiling (due to heart failure) which activates sensor elements, called baroreceptors – renal (juxtaglomerular apparatus) and extrarenal (high-pressure receptors in sinus body and aortic arch and low pressure receptors in left atrium and in thoracic veins). This activation triggers the release of many neurohormones – catecholamines, ang II, endothelin and in advanced heart failure also arginin-vasopressin – which are strong vasoconstrictors and induce renal sodium and water retention. This neurohormonal response is counterbalanced by vasodilatory and natriuretic properties of compounds such as natriuretic peptides, adrenomedullin, nitric oxide and prostaglandins. The synthesis of prostaglandins in patients with heart failure increases with rising levels of ang II and noradrenalin (112). Also ANP (atrial natriuretic peptide, mainly synthesized in the atria) and BNP (brain natriuretic peptide, primarily synthesized in the ventricles) are increasingly released into the circulation in patients with congestive heart failure (112). Plasma levels of BNP are elevated in proportion to the degree of haemodynamic compromise and the same is also true for adrenomedullin (4).

Interstitial fibrosis detrimentally affects the failing heart by several mechanisms: (a) subendocardial ischaemia occurs because of the increase in intercapillary distance which increases the diffusion distance of oxygen, limiting the intramyocardial vessels' ability to vasodilate. (b) It also induces ventricular arrhythmias by rendering the conduction velocities among myocardial cells inhomogeneous. (c) Fibrosis alters the systolic and diastolic functions of the left ventricle and (d) extensive fibrosis can reduce ventricular muscle distensibility (35). However, this fibrotic effect of aldosterone on myocardial tissue has mainly been reported in experimental models of hypertension or myocardial infarction and not in congestive heart failure (7). It seems to be true that myocardial fibrosis development is closely dependent on the experimental conditions, necessitating the requirement for a sodium-rich diet and pressure overload as well as an increased aldosterone production (113). But most of heart failure patients suffer from long-term hypertension.

As the baroreceptor response in congestive heart failure is altered with baroreceptor desensitization, aldosterone may contribute to the disequilibrium between the sympathetic and parasympathetic systems in these patients (29).

The SOLVD study found that ACE-inhibition was effective in reducing deaths in patients with congestive heart failure. It influences deaths due to pump failure but had little effect on arrhythmic deaths and on deaths due to associated diseases such as pneumonia and others (107).

The importance of spironolactone (or eplerenone) to retain magnesium and potassium in the body is very important during the course of heart failure treatment because it causes a fall in the incidence of ventricular arrhythmias (114, 115) but also a reduction in cardiovascular (atherosclerotic) events (116).

Spironolactone is able to increase myocardial noradrenaline uptake in patients with congestive heart failure (detected by MIBG scanning) (25). It lowers concentration of catecholamines in the circulation and decreases arrhythmogenicity of congestive heart failure state and in this way it reduces the incidence and prevalence of sudden cardiac death in these patients.

Spironolactone reduces in CHF patients heart rate and increases heart rate variability despite reducing also blood pressure of these patients. This means an evidence that aldosterone has also parasympatholytic effects (62). This aldosterone's reduction in parasympathetic activity could contribute to cardiac death. For example in myocardial ischemia vagal stimulation reduces frequency of reperfusion arrhythmias, mainly of ventricular fibrillation (from 60 % to 7 %) and abolishes ventricular tachycardia completely (117).

The recent UK Heart trial showed that autonomic dysfunction (sympathetic activation and parasympathetic depression) as measured by heart rate variability changes was a strong independent predictor of mortality in heart failure (118).

MacFadyen et al (1997) found that spironolactone reduces serum procollagen type III N-terminal-amino peptide (PIIINP) levels in CHF patients, which is the clinical evidence that aldosterone promotes myocardial collagen formation (62). In a similar study more than 30 patients with congestive heart failure treated with an ACE inhibitor plus furosemide were randomized to spironolactone or placebo: there was no significant difference in serum PIIINP levels in the two groups at entrance into the study, nor did the levels change in the placebo group after 8 weeks of therapy. However, there was a 15–20 % reduction in serum

PIIINP levels in the spironolactone-treated group after 8 weeks of therapy. So the results suggest that spironolactone is capable of reducing collagen synthesis (33). The spironolactone-treated group showed a significant increase in heart rate variability, particularly in the early morning hours, suggesting a decreased risk for sudden death (33).

Yee et al (1998) found recently that spironolactone markedly reduced QT dispersion in patients with congestive heart failure (63).

Evidence by clinical trials data

Thus an important question is whether the use of aldosterone antagonists in patients with congestive heart failure can counter or eliminate the harmful effects of aldosterone that are clearly related to high mortality of these patients (119).

The CONSENSUS study (120) showed a correlation between mortality and increased plasma aldosterone concentrations at baseline, independent of initial haemodynamic status. The improved prognosis associated with enalapril was accompanied by a reduction in plasma levels of aldosterone, ang II and renin (121). The SAVE (122) and the SOLVD (123) trials have confirmed that aldosterone plasma concentrations are increased in congestive heart failure. The relationship between increased plasma aldosterone and outcome suggests that a detrimental role of aldosterone in congestive heart failure may result from one of the following mechanisms: increased load on the heart secondary to sodium retention; hypokalaemia and hypomagnesaemia promoting arrhythmias; increased sympathetic tone accompanied by blocking of neuronal norepinephrine re-uptake which increases myocardial toxicity of catecholamines, and/or myocardial fibrosis. It thus appear mandatory to block increased aldosterone secretion in congestive heart failure.

The Randomized ALdactone Evaluation Study (RALES) trial provides well-controlled clinical evidence of beneficial effect of aldosterone antagonism with spironolactone in patients with congestive heart failure. Let us bring you here the most important information from this trial.

Selection criteria required that patients should have a history of NYHA class IV heart failure and a left ventricular ejection fraction ≤35 % within the last 6 months prior to enrollment into the trial. At the time of randomization the patients were in either class III or IV of congestive heart failure, while maintained on standard therapy (an ACE inhibitor, loop diuretic with or without digoxin). The dose of spironolactone was chosen on the basis of a prior carefully performed parallel dose-finding study in which it was shown that 25 mg of spironolactone was pharmacologically effective and did not result in significant hyperkalaemia (124).

The investigators were allowed to reduce the dose of study medication to 25 mg every other day if they saw any tendency toward hyperkalaemia. However, if after eight weeks there was no evidence of hyperkalaemia but there was still evidence of progressive heart failure, so the dose of spironolactone could be increased to 50 mg daily.

The patients were to have been followed for three years with the end-point of total all-cause mortality. However, the trial was prematurely stopped at the end of two year's mean follow-up because the Data Safety Monitoring Committee found that there was a significant mortality benefit in patients who were randomized to spironolactone.

The baseline characteristics of the patients in the trial are as follows. The mean age was 65 years. Approximately 75 % of enrolled patients were male. They were normotensive and had a normal heart rate. Seventy-five percent were in NYHA class III and about 25 % in class IV (however, all had a history of class IV congestive heart failure). The mean left ventricular ejection fraction was approximately 25 %. Slightly more than half of the patients had ischaemic cardiomyopathy. All of the patients were on a loop diuretic. Three-quarters were on digoxin and about a quarter of the patients received potassium supplementation. Only about 11 % of patients were on a beta-blocking agents (but the trial was carried out before reports of recent exciting data concerning the efficacy of beta-blockers in patients with congestive heart failure) (125, 126). Most of patients were on an ACE inhibitor and the mean dose of enalapril was approximately 15 mg a day (which is a reasonable dose according to a nowadays clinical practice).

The average dose of spironolactone in this trial was 26 mg a day and of placebo it was 31 mg/day, which suggests that more of the patients in the placebo group had evidence of progressive heart failure. Seventy percent of patients randomized to spironolactone remained on the 25 mg dose, in 18 % of patients the dose was reduced to 25 mg every other day because of a trend toward hyperkalaemia, and in 12 % the dose was increased to 50 mg a day after eight weeks of treatment because of evidence of progressive heart failure. This increase in study medication occured more frequently in the placebo group.

There was no significant effect on blood pressure with this dose of spironolactone/placebo but there was a significant increase in serum potassium levels on spironolactone, but the increase was relatively small (clinically non-significant).

The results were astonished: (a) with this low dose of spironolactone there was a significant 30 % reduction ($p<0.001$) of all-cause mortality (49). It is also important to remember that the mortality rate in the placebo group on standard therapy (included ACE inhibitor, loop diuretic and digoxin) was over 20 % per year – and it was almost twice that found in the recent beta-blocker trials (125, 126): in CIBIS II trial (125) the annual mortality rate was about 13 % and in the MERIT-HF trial (126) it was about 11 %. So the RALES patients appear to be more severely ill than those in recent beta-blocker trials. (b) The effect of spironolactone on mortality was fairly uniform across various predefined subsets of patients. Let us have a brief look at one predefined group of patients, patients on betablocker therapy at baseline (approximately 11 % of patients). Here was the mortality reduction with spironolactone even greater – 60 % – in comparison for the whole study group. The confidence limits in this subgroup were wide, but there was no reason to suppose here a negative drug interaction of "spironolactone-betablocker". (c) There was a 35 % reduction in the total number of hospitalizations and a 30 % reduction in the number of patients hospitalized for congestive heart failure (since many of these patients

had multiple hospitalizations for worsening of heart failure). (d) The changes in NYHA class of patients treated by spironolactone – more patients improved and fewer deteriorated in comparison with placebo treatment group.

Safety of spironolactone treatment: (a) There were slightly more patients who had adverse effects on spironolactone. (b) The incidence of severe hyperkalaemia (K≥6.0 mmol/l) was 1.7 % in the spironolactone group compared to 1.2 % of placebo group and the difference was not statistically significant. The one patient who died in this study due to hyperkalaemia was a placebo patient. (c) The one placebo-patient dropped out of the study because of hypotension and no spironolactone-patient dropped for this symptom. (d) The only significant side effect encountered with spironolactone was an excess of gynaecomastia (10 % versus 1.5 % in placebo-patients) and breast pain in males (these are known ‚adverse effect' of spironolactone). In the future even this side effect should not be a concern since there is now in clinical studies (with good results and safety) a new aldosterone antagonist, eplerenone – that has similar mineralcorticoid blocking effects but binds less avidly to androgen and progesterone receptors (therefore should result in less gynaecomastia and breast pain) (127).

A sample of 261 patients from RALES trial were randomized to placebo or spironolactone (12.5 to 59 mg per day) and in this substudy serum procollagen type I carboxy-terminal peptide, serum procollagen type I amino-terminal peptide and procollagen type III amino-terminal peptide (PIIINP) were assessed at baseline and at 6 months. Baseline PIIINP >3.85 μg/l was associated with an increased risk of death (RR=2.36, 95 % CI 1.34–4.18) and of death + hospitalization (RR=1.83, 95 % CI 1.18–2.83). At 6 moths, markers decreased in the spironolactone group but remained unchanged in the placebo group. The spironolactone effect on outcome was significant only in patients with above-median baseline levels of markers. RR (95 % CI) values for death among patients receiving spironolactone were 0.44 (0.26–0.75) and 1.11 (0.66–1.88) in subgroups of PIIINP levels above and below the median, respectively. Similarly, RR (95 % CI) values for death + hospitalization among patients receiving spironolactone were 0.45 (0.29–0.71) and 0.85 (0.55–1.33), respectively (128). It can be stated, that high baseline serum levels of markers of cardiac fibrosis synthesis are significantly associated with poor outcome and decrease during spironolactone therapy. The greater benefit from spironolactone was associated with higher levels of collagen synthesis markers. The limitation of the excessive extracellular matrix turnover may be one of the various extrarenal mechanisms contributing to the beneficial effect of spironolactone in patients with congestive heart failure.

Another very important study the Eplerenone Post-Acute

Myocardial infarction

Heart Failure Efficacy and Survival Study (EPHESUS) tested the hypothesis that treatment with eplerenone, an aldosterone blocker that selectively blocks the mineralocorticoid receptor and not glucocorticoid, progesterone, or adrogen receptors, reduces overall mortality and cardiovascular mortality or hospitalization for cardiovascular events among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure who are receiving optimal medical therapy (133).

EPHESUS was a multicenter, international, randomized, double-blind, placebo-controlled trial. Patients were randomly assigned to receive eplerenone (25 mg per day) or matching placebo for four weeks, after which the dose of eplerenone was increased to a maximum of 50 mg per day. Randomization occured 3 to 14 days after acute myocardial infarction. Left ventricular dysfunction was documented by a left ventricular ejection fraction of 40 % or lower on echocardiography, radionuclide angiography, or angiography of the left ventricle after the index acute myocardial infarction and before randomization. Heart failure was documented by the presence of pulmonary rales, chest radiography showing pulmonary venous congestion, or the presence of a third heart sound.

Patients received optimal medical therapy, which included ACE inhibitors, angiotensin-receptor blockers, diuretics, and beta-blockers, as well as coronary reperfusion therapy.

Important criteria for exclusion were the use of potassium-sparing diuretics, a serum creatinine concentration of more than 220 mol per liter, and a serum potassium concentration of more than 5.0 mmol per liter before randomization.

Patients provided written informed consent before enrollment.

Follow-up visits occurred at one and four weeks, three months, and every three months thereafter until the termination of the study. The serum potassium concentration was measured 48 hours after the initiation of treatment, at one, four, and five weeks, at all scheduled study visits, and within one week after any change of dose. All patients who underwent randomization were followed for vital status and hospitalizations every three months until the termination of the study.

The two primary end points were time to death from any cause and time to death from cardiovascular causes or first hospitalization for a cardiovascular event, including heart failure, recurrent acute myocardial infarction, stroke, or ventricular arrhythmia. The major secondary end points were death from cardiovascular causes and death from any cause or any hospitalization. All end points were adjudicated by a blinded critical-events committee.

A total of 6642 patients underwent randomization at 674 centers in 37 countries between December 1999, and December 2001. A total of 3313 were assigned to placebo, 3319 were assigned to eplerenone. There were no significant differences between the two groups at base line (age: 64 ys, race: 90 % whites, 72 % males, blood pressure: 119/72 mmHg, left ventricular ejection fraction: 33 %, 7.3 days to randomization from index myocardial infarction, reperfusion therapy/revascularization: 45 %, symptoms of heart failure: 90 % patients, serum potassium: 4.3 mmol/l, serum creatinine: 1.1 mg/dl, creatinine clearance: 79 ml/min, medical history – acute myocardial infarction: 27 % of patients, diabetes: 32 %, heart failure: 14 %, hypertension: 60 %). The majority of patients were receiving standard therapies for acute myocardial infarction complicated by left ventricular dysfunction and heart failure, including ACE inhibitors or angiotensin –

receptor blockers (in 87 % of patients), beta-blockers (in 75 %), aspirin (in 88 %), diuretics (in 60 %) and statins (in 47 %).

The study continued until 1012 deaths occured. The mean duration of follow-up was 16 months. The mean dose-equivalent of study medication was 43.5 mg in the placebo group and 42.6 mg in the eplerenone group. A total of 478 patients in the eplerenone group (14.4 %) and 554 patients in the placebo group (16.7 %) died (relative risk, 0.85; 95 % CI: 0.75–0.96; p=0.008). Kaplan-Meier estimates of mortality at one year were 11.8 % in the eplerenone group and 13.6 % in the placebo group. Death from cardiovascular causes or hospitalization for cardiovascular events was reached by 885 patients in the eplerenone group (26.7 %) and 993 patients in the placebo group (30.0 %) (relative risk, 0.87; 95 % CI: 0.79–0.95; p=0.002). A total of 407 deaths in the eplerenone group (12.3 % of patients) and 483 deaths in the placebo group (14.6 % of patients) were attributed to cardiovascular causes (relative risk, 0.83; 95 % CI: 0,72–0.94; p=0.005). The reduction in cardiovascular mortality was similar for the most comon causes – sudden death from cardiac causes, acute myocardial infarction, and heart failure (range of relative risks, 0.79 to 0.82). Of these reductions, the reduction in the risk of sudden death from cardiac causes was statistically significant (relative risk, 0.79; 95 % CI: 0.64–0.97; p=0.03). There was a relative reduction of 15 % in the risk of hospitalization for heart failure with eplerenone (relative risk, 0.85; 95 % CI: 0.74–0.99; p=0.03), and there were 23 % fewer episodes of hospitalization for heart failure in the eplerenone group than in the placebo group (relative risk, 0.77; p=0.002).

The rate of death from any cause or any hospitalization was 8 % lower in the eplerenone group than in the placebo group (relative risk, 0.92; 95 % CI: 0.86–0.98; p=0.02).

Reductions in the rate of death from any cause and the rate of death from cardiovascular causes or hospitalization for cardiovascular events were consistent among subgroups (both sexes, elder and younger than 65 ys, serum potassium over and under 4.0 mmol/l, serum creatinine over and under 1.1 mg/dl, diabetics and non-diabetics, hypertensives and no-hypertensives, ejection fraction over and under 35 %, coronary revascularization: yes or no, use of ACE inhibitors/angiotensin-receptor blockers and betablockers: none-one-both, use of diuretics: yes or no, use of aspirin: yes or no, use of lipid-lowering drugs: yes or no).

After week 1, the mean systolic and diastolic blood pressure increased in both groups from base line to each time point throughout the remainder of the trial. The magnitude of these increases in the eplerenone group was significantly smaller than that in the placebo group at every point. At one year, the mean blood pressure had increased by 8/4 mmHg in the placebo group and by 5/3 mmHg in the eplerenone group (p<0.01). Also at one year, the heart rate had decreased by 6 beats per minute in the placebo group and by 7 beats per minute in the eplerenone group (p=0.32).

Potassium levels had increased in both groups at one year (by 0.2 mmol per liter in the placebo group and 0.3 mmol per liter in the eplerenone group, p<0.001). Serious hyperkalemia (serum potassium concentration, ≥6.0 mmol per liter) occurred in 5.5 % of patients in the eplerenone group, as compared with 3.9 % of those in the placebo group (p=0.002). In each treatment group, the incidence of hyperkalemia was higher among patients with a lower base-line creatinine clearance. The rate of hypokalemia was 8.4 % in the eplerenone group and 13.1 % in the placebo group (p<0.001). It should also be pointed out that the risk of hypokalemia was more than twice as high as the risk of serious hyperkalemia and that eplerenone significantly reduced this risk.

The addition of eplerenone to optimal treatment at a maximal dose of 50 mg once daily (mean dose, 43 mg per day) in patients assigned to treatment 3 to 14 days (mean, 7) after acute myocardial infarction resulted in additional reductions in overall mortality and the rate of death from cardiovascular causes or hospitalization for cardiovascular events among patients whose acute myocardial infarction was complicated by left ventricular dysfunction and heart failure.

One-year mortality among patients assigned to placebo, the majority of whom received an ACE inhibitor or angiotensin-receptor blocker and a betablocker, was 13.6 %. It was lower and the magnitude of the effect of aldosterone blockade was smaller than in the Randomized Aldactone Evaluation Study (RALES). These differences may be attributable to several factors, including the greater use of beta-blockers and a higher base-line left ventricular ejection fraction in the EPHESUS study. In RALES, the mean left ventricular ejection fraction at base line was 25 %, and patients had New York Heart Association class III or IV heart failure, whereas in the EPHESUS study in patients with acute myocardial infarction, the mean left ventricular ejection fraction was 33 % at base line and may have improved after reperfusion, recovery of ventricular stunning, or both. The severity of left ventricular dysfunction, the degree of heart failure and the intensity of background therapy are most likely important factors determining the absolute mortality as well as the effectiveness of therapeutic agents. The reduction in cardiovascular mortality was in large part due to a 21 % reduction in the rate of sudden death from cardiac causes. The reduction in the rate of hospitalization for cardiovascular events was largely due to a 15 % reduction in the risk of hospitalization for heart failure and a 23 % reduction in the number of episodes of hospitalization for heart failure. The mechanisms by which eplerenone provides myocardial protection in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure are in blocking harmful effects of aldosterone.

The rate of discontinuation of blinded treatment due to adverse events other than hyperkalemia and a variety of minor gastrointestinal complications in patients receiving eplerenone were low. The incidence of gynecomastia and impotence among men in the eplerenone group was no greater than that in the placebo group. This finding differs from the findings in RALES1 and can be attributed to the fact that eplerenone has greater selectivity for the mineralocorticoid receptor than does spironolactone, which also binds to androgen and progesterone receptors.

Spironolactone reduced ventricular arrhythmias in patients with congestive heart failure treated with spironolactone in ad-

dition to standard therapy compared with patients receiving standard therapy only (129).

These salutary effects of spironolactone therapy in congestive heart failure are summarized in (Fig. 2).

A small clinical study (46 patients, mean age 60+11 ys, 34 males, with a first episode of anterior transmural thrombolized myocardial infarction) evaluated wheter the suppression of aldosterone may be helpful in reducing postinfarction collagen synthesis and progressive left ventricular dilation in patients treated with an ACE inhibitor for a recent myocardial infarction. At hospital discharge patients were randomized to receive potassium canrenoate (an oral aldosterone inhibitor, 50 mg once daily) (group 1:24 patients) or placebo (group 2:22 patients). The serum concentration of the amino-terminal propeptide of type III procollagen was used to measure the collagen synthesis rate and was obtained before enrollment, at hospital discharge and after 3, 6 and 12 months of follow-up. After 3, 6 and 12 months of treatment the amino-terminal propeptide of type III procollagen serum levels was significantly higher in the placebo group compared with the aldosterone inhibitor group. After 6 and 12 months there were significantly smaller left ventricular volumes in the active treatment group (130). Authors concluded that aldosterone antagonist combined with ACE inhibitor may reduce postinfarction collagen synthesis and progressive left ventricular dilation.

Aldosterone antagonists

Spironolactone, a competitive aldosterone receptor antagonist (ARA) is partially absorbed, is extensively metabolized mainly by the liver and its therapeutic properties are attributable to active metabolite canrenone. At therapeutic doses of 25 to 400 mg per day, spironolactone effectively controls blood pressure and hypokalaemia in the majority of cases. Endocrine side effects are often associated and mainly consist of gynecomastia, decreased libido and impotence in man and menstrual irregularities in women.

Spironolactone is an extremely versatile drug. It has been proven useful in essential hypertension, oedematous conditions for patients with congestive heart failure, cirrhosis of the liver accompanied by oedema and/or ascites, the nephrotic syndrome, hypokaliaemia and primary hyperaldosteronism.

The optimal dose is 100 mg a day, although lower doses may suffice. Oral spironolactone is converted to active hepatic metabolites, the principal ones being the sulphur – containing metabolites 7alfa-(thiomethyl)-spironolactone and 6 beta-hydroxy-7alfa-(thiomethyl)-spironolactone. Spironolactone bioavailability is enhanced with meals, due to the increased hepatic portal blood flow and synthesis of active metabolites (131).

Diuretic effect: spironolactone is a very effective diuretic. In patients with congestive heart failure its action could merely be by improving natriuresis so that cardiac preload and afterload are reduced. Spironolactone could influence preload and afterload without producing the neuroendocrine activation (that for example an equivalent dose of furosemide would produce). So spironolactone could uniquely also make a neuroendocrine inhibition. In that way its profile of action is very similar to the profile of action of natriuretic peptides – diuresis plus neuroendocrine inhibition.

Antialdosterone effect: as spironolactone is an aldosterone's receptor blocker it prevents the action of aldosterone through activation of its receptors. In that way spironolactone prevents harmful effects of aldosterone. Spironolactone and its metabolites also inhibit adrenal aldosterone biosynthesis by inhibition of aldosterone synthetase. Spironolactone effects on aldosterone is therefore biphasic: (a) first, an acute increase in renin and aldosterone production occurs for the first few days. (b) This is followed by a decrease in aldosterone levels, with rise in aldosterone precursors, DOC and 18-hydroxy-corticosterone. Although spironolactone accumulates in the adrenal gland, the inhibition of aldosterone biosynthesis is reversible and no long-term effects occur (131).

Canrenone and the K^+ salt of canrenoate are also in clinical use: they avoid the formation of intermediate products with antiandrogenic and progestational actions, resulting in a decreased incidence of side effects.

Furthermore, a relatively new selective ARA compound "eplerenone" with reduced affinity for androgen and progesterone receptors, has currently passed useful and important clinical trials.

At present ARAs are indicated in the management of primary hyperaldosteronism, in oedematous conditions in patients with congestive heart failure, in cirrhosis of the liver accompanied by oedema and ascites, in essential hypertension and in hypokalaemic states (132). Its indication as adjunctive therapy of heart failure is currently under investigation.

References

1. Lombes M, Oblin ME, Gasc JM et al. Immunohistochemical and biochemical evidence for a cardiovascular mineralocorticoid receptor. Circulat Res 1992; 71: 503—510.

2. Mueller J. Regulation of aldosterone biosynthesis: physiological and clinical aspects. Monogr Endocrinol 1988; 29: 1—364.

3. Anand IS, Ferrari R, Kalra GS et al. Edema of cardiac origin. Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. Circulation 1980; 80: 299—305.

4. Lainchburry JG, Nicholls MG, Espiner EA et al. Bioactivity and interactions of adrenomedullin and brain natriuretic peptide in patients with heart failure. Hypertension 1999; 34: 70—75.

5. Ferrari R. The harmful effects of aldosterone in heart failure. Europ Heart J 2000; 2 (Suppl A): A6—A12.

6. Hatakeyama H, Miyamori I, Fujita T et al. Vascular aldosterone. Biosynthesis and a link to angiotensin II-induced hypertrophy of vascular smooth muscle cells. J Biol Chem 1994; 269: 24316—24320.

7. Silvestre JS, Heymes C, Oubenaissa A et al. Activation of cardiac aldosterone production in rat myocardial infarction. Effect of angiotensin II receptor blockade and role in cardiac fibrosis. Circulation 1999; 99: 2694—2701.

8. Cleland JGF, Dargie HJ, Hodsman GP et al. Captopril in heart failure: a double-blind controlled trial. Brit Heart J 1984; 52: 530—535.

9. Rossier B. Mechanisms of action of mineralocorticoid hormones. Endocr Res 1989; 15: 203—226.

10. Wehling M, Spes C, Win N et al. Rapid cardiovascular action of aldosterone in man. J Clin Endocr Metab 1998; 83: 3517—3522.

11. Lombés M, Alfaidy N, Eugene E et al. Prerequisite for cardiac aldosterone action: mineralocorticoid receptor and 11beta-hydroxysteroid dehydrogenase in human heart. Circulation 1995; 92: 175—182.

12. Bonvalet JP, Alfaidy N, Farman N et al. Aldosterone: intracellular receptors in human heart. Europ Heart J 1995; 16: 92—97.

13. Korichneva J, Pucéat M, Vassort G. Aldosterone modulates pH regulatory systems in neonatal rat cardiomyocytes abstract. Presented at Biologie et Pathologie du Coeur et des Vaisseaux. XIIéme Congrés, European Joint Session Marseille, April 25—26, 1995.

14. Robert V, Heymes C, Silvestre JS et al. Angiotensin AT1 receptor subtype as a cardiac target of aldosterone: role in aldosterone-salt-induced fibrosis. Hypertension 1999; 33: 981—986.

15. Struthers AD. Aldosterone escape during ACE inhibitor therapy in chronic heart failure. J Cardiac Failure 1996; 2: 47—54.

16. Pacher R, Globits S, Bergler-Klein J et al. Clinical and neurohumoral response of patients with severe congestive heart failure treated with two different captopril dosages. Europ Heart J 1993; 14: 273—278.

17. Pitt B. "Escape" of aldosterone production in patients with left ventricular dysfunction treated with an angiotensin converting enzyme inhibitor: implications for therapy. Cardiovasc Drugs Ther 1995; 9: 145—149.

18. McKelvie RS, Yusuf S, Pericak D et al. Comparison of candesartan, enalapril and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction RESOLVD. Pilot study: The RESOLVD Pilot Study Investigators. Circulation 1999; 100: 1056—1064.

19. Dahlstrom U, Karlsson E. Captopril and spironolactone therapy in patients with refractory congestive heart failure. Curr Ther Res 1992; 51: 235—248.

20. van Vliet AA, Donker AJM, Nauta JJP et al. Spironolactone in congestive heart failure refractory to high-dose loop diuretic and low-dose angiotensin-converting enzyme inhibitor. Amer J Cardiol 1993; 71: 21A—28A.

21. Lombés M, Ferman N, Bonvalot J et al. Identification and role of aldosterone receptors in the cardiovascular system. Ann Endocrinol 2000; 61: 41—46.

22. Rudolph A, Blasi E, Delyani J. Tissue-specific corticoidogenesis in the rat. J Mol Cell Endocrinol 2000; 165: 221—224.

23. Takeda Y, Yoneda T, Demura M et al. Cardiac aldosterone production in genetically hypertensive rats. Hypertension 2000; 36: 495—500.

24. MacKenzie SM, Clark CJ, Fraser R et al. Expression of 11-beta-hydroxylase and aldosterone synthase genes in the rat brain. J Mol Endocrinol 2000; 24: 321—328.

25. Barr CS, Lang CC, Hanson J et al. Effects of adding spironolactone to an ACE inhibitor in chronic congestive heart failure secondary to coronary artery disease. Amer J Cardiol 1995; 76: 1259—1265.

26. Benitah J, Vassort G. Aldosterone upregulates Ca^{2+} current in adult rat cardiomyocytes. Circulat Res 1999; 85: 1139—1145.

27. Wang W, Mc Clain JM, Zucker IH. Aldosterone reduces baroreceptor discharge in the dog. Hypertension 1992; 19: 270—277.

28. Wang W. Chronic administration of aldosterone depresses baroreceptor reflex in the dog. Hypertension 1994; 24: 571—575.

29. Yee KM, Struthers AD. Aldosterone blunts the baroreflex response in man. Clin Sci 1998; 95: 687—692.

30. Weber KT, Brilla CG. Myocardial fibrosis, aldosterone and antialdosterone therapy: evolving concepts in the management of congestive heart failure. Wilson, CT, USA: Medical Education program Ltd, 1991.

31. Brilla CG, Matsubara LS, Weber KT. Anti-aldosterone treatment and the prevention of myocardial fibrosis in primary and secondary hyperaldosteronism. J Mol Cell Cardiol 1993; 25: 563—575.

32. Rocha R, Stier C, Kifor J et al. Aldosterone: a mediator of myocardial necrosis and renal arteriopathy. Endocrinology 2000; 141: 3871—3878.

33. Klappacher G, Franzen P, Haab D et al. Measuring extracellular matrix turnover in the serum of patients with idiopathic or ischaemic dilated cardiomyopathy and impact on diagnosis and prognosis. Amer J Cardiol 1995; 75: 913—918.

34. Diez J, Laviades C, Mayor G et al. Increased serum concentrations of procollagen peptides in essential hypertension. Circulation 1995; 91: 1450—1456.

35. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. Circulation 1991; 83: 1849—1865.

36. Duprez DA, De Buyzere ML, Rietzschel ER et al. Inverse relationship between aldosterone and large artery compliance in chronically treated heart failure patients. Europ Heart J 1998; 19: 1371—1376.

37. Benetos A, Lacolley P, Safar ME. Prevention of aortic fibrosis by spironolactone in spontaneously hypertensive rats.Arterioscler Thromb Vasc Biol 1997; 17: 1152—1156.

38. Swan JW, Anker SD, Walton C et al. Insulin resistance in congestive heart failure: relation to severity and aetiology of heart failure. J Amer Coll Cardiol 1997; 30: 527—532.

39. Farquharson CAJ, Struthers AD. Spironolactone increases nitric oxide bioactivity, improves endothelial vasodilator dysfunction and suppresses vascular angiotensin I/angiotensin II conversion in patients with chronic heart failure. Circulation 2000; 101: 594—597.

40. Taddei S, Virdis A, Mattei P et al. Vasodilation to acetylcholine in primary and secondary forms of human hypertension. Hypertension 1993; 21: 929—933.

41. Brown NJ, Agirbasli MA, Williams GA et al. Effects of activation and inhibition of the renin-angiotensin system on plasma PAI-1. Hypertension 1998; 32: 965—971.

42. Brown NJ, Nakamura S, Ma L et al. Aldosterone modulates plasminogen activator inhibitor-1 and glomerulosclerosis in vivo. Kidney Int 2000; 58: 1219—1227.

43. Arora RB, Somari P. Ectopic arrhythmia provoking action of aldosterone. Life Sci 1962; 5: 215—218.

44. Wester PO, Dyckner T. Intracellular electrolytes in cardiac failure. Acta Med Scand 1986; 707: 33—36.

45. Lisenberg MJ. Magnesium deficiency and sudden death. Amer Heart J 1992, 124: 544—549.

46. Barr CS, Hanson K, Kennedy N et al. The effect of a mineralocorticoid antagonist on myocardial MIBG uptake in congestive heart failure. Circulation 1993; 88: I—256.

47. Mihailidou A, Buhagiar K, Rasmussen H. Na^+ influx and Na^+-K^+ pump activation during short-term exposure of cardiac myocytes to aldosterone. Amer J Physiol 1998; 274: C175—C181.

48. Cardiac Arrhythmia Suppression Trial CAST. Investigators. Preliminary report: effect of encainide and flecainide on mortality in randomized trial of arrhythmia suppression after myocardial infarction. New Engl J Med 1989; 321: 406—412.

49. Pitt B, Zannad F, Remme WJ et al for the RALES Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. New Engl J Med 1999; 341: 709—717.

50. Fu GS, Meissner A, Simon R. Repolarisation dispersion and sudden cardiac death in patients with left ventricular dysfunction. Europ Heart J 1997; 18: 281—289.

51. Barr CS, Naas A, Freeman M et al. QT dispersion and sudden unexpected death in congestive heart failure. Lancet 1994; 343: 327—329.

52. Naas AAO, Davidson NC, Thompson C et al. QT and QTc dispersion are accurate predictors of cardiac death in newly diagnosed NIDDM patients: cohort study. Brit Med J 1998; 316: 745—746.

53. Choy AM, Lang CC, Chomsky DM et al. Normalisation of acquired QT prolongation in humans by intravenous potassium. Circulation 1997; 96: 2149—2154.

54. Darbar D, Luck J, Davidson NC et al. Sensitivity and specificity of QTc dispersion for identification of risk of cardiac death in patients with peripheral vascular disease. Brit Med J 1996; 312: 874—878.

55. Aldigier JC, Huang H, Dalmay F et al. Angiotensin-converting enzyme inhibition does not suppress plasma angiotensin II increase during exercise in humans. J Cardiovasc Pharmacol 1993; 21: 289—295.

56. Rocha R, Chander PN, Zuckerman A et al. Role of aldosterone in renal vascular injury in stroke-prone hypertensive rats. Hypertension 1999; 33 (Part 2): 232—237.

57. Rocha R, Stier CT Jr, Kifor I et al. Aldosterone: a mediator of myocardial necrosis and renal arteriopathy. Endocrinology 2000; 141: 3871—3878.

58. Gomez-Sanchez EP, Venkataraman MT, Thwaites D et al. Intracerebroventricular ICV. Infusion of corticosterone antagonizes ICV-aldosterone hypertension. Amer J Physiol 1990; 258: E649—E653.

59. Gomez-Sanchez EP, Fort C, Thwaites D. Central mineralocorticoid receptor antagonism blocks hypertension in Dahl S/JR rats. Amer J Physiol 1992; 262: E96—E99.

60. Armbruster H, Vetter W, Beckerhoff R et al. Diurnal variations of plasma aldosterone in supine man: relationship to plasma renin activity and plasma cortisol. Acta Endocrinol 1975; 80: 95—103.

61. Muller JE, Stone PH, Turi ZG et al. Circadian variation in the frequency of onset of acute myocardial infarction. New Engl J Med 1985; 313: 1315—1322.

62. MacFadyen RJ, Barr CS, Struthers AD. Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. Cardiovasc Res 1997; 35: 30—34.

63. Yee KM, Pringle SD, Struthers AD. Aldosterone blockade improves QT dispersion in CHF. Europ Heart J 1998; 19 (Suppl): 601.

64. American Heart Association: 2000 Heart and Stroke Statistical Update. American Heart Association, 1999.

65. Joint National Committee on Prevention, Detection, Evaluation and Treatment of Blood Pressure: The sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of Blood Pressure. Arch Intern Med 1997; 157: 2413—2446.

66. Brunner HR, Laragh JH, Baer L et al. Essential hypertension: renin and aldosterone, heart attack and stroke. New Engl J Med 1972; 286: 441—449.

67. Alderman MH, Madhavan S, Ooi WL et al. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. New Engl J Med 1991; 324: 1098—1104.

68. Pfeffer MA, Braunwald E, Moye LA et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. New Engl J Med 1992; 327: 669—677.

69. The Acute Infarction Ramipril Efficacy AIRE. Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993; 342: 821—828.

70. Pitt B, Segal R, Martinez FA et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure Evaluation of Losartan in the Elderly Study, ELITE, Lancet 1997; 349: 747—752.

71. Thuermann PA, Kenedi P, Schmidt A et al. Influence of the angiotensin II antagonist valsartan on left ventricular hypertrophy in patients with essential hypertension. Circulation 1998; 98: 2037—2042.

72. Laragh JH, Sealy JE. The renin-angiotensin-aldosterone system in hypertensive disorders: a key to two forms of arteriolar constriction and a possible clue to risk of vascular injury heart attack and stroke and prognosis. 1329—1348. In: Laragh JH, Brenner BM (Eds). Hypertension: Pathophysiology, Diagnosis, and Management. Raven Press, 1990.

73. Ferrario CM, Flack JM. Pathologic consequences of increased angiotensin II activity. Cardiovasc Drugs Ther 1996; 10: 511—518.

74. Mangelsdorf DJ, Thummel C, Beato M et al. The nuclear receptor superfamily: the second decade. Cell 1995; 83: 835—839.

75. Pratt WB. The role of heat shock proteins in regulating the function, folding and trafficking of the glucocorticoid receptor. J Biol Chem 1993; 268: 21455—21458.

76. Bhargava A, Fullerton MJ, Mylas K et al. The serum — and glucocorticoid-induced kinase is a physiological mediator of aldosterone action. Endocrinology 2001; 142: 1587—1594.

77. Granger JP, Kassab S, Novak J et al. Role of nitric oxide in modulating renal function and arterial pressure during chronic aldosterone excess. Amer J Physiol 1999; 276: R197—R202.

78. Gómez-Sánchez EP, Fort CM, Gómez-Sánchez CE. Intracerebroventricular infusion of RU 283 18 blocks aldosterone—salt hypertension. Amer J Physiol 1990; 258: E482—E484.

79. Young M, Head G, Funder J. Determinants of cardiac fibrosis in experimental hypermineralocorticoid states. Amer J Physiol 1995; 269: E657—E662.

80. Gavras H, Brunner HR, Laragh JH et al. Malignant hypertension resulting from deoxycorticosterone acetate and salt excess. Role of renin and sodium in vascular changes. Circulat Res 1975; 36: 300—309.

81. Mistry M, Muirhead EE, Yamaguchi Y et al. Renal function in rats with angiotensin II-salt-induced hypertension: effect of thrombo-

xane synthesis inhibition and receptor blockade. J Hypertens 1990; 8: 77—83.

82. Stier CT Jr, Chander P, Gutstein WH et al. Therapeutic benefit of captopril in salt-loaded stroke-prone spontaneously hypertensive rats in independent of hypotensive effect. Amer J Hypertens 1991; 4: 680—687.

83. Stier CT Jr, Benter IF, Ahmad S et al. Enalapril prevents stroke and kidney dysfunction in salt-loaded stroke-prone spontaneously hypertensive rats. Hypertension 1989; 13: 115—121.

84. Rocha R, Chander PN, Khanna K et al. Mineralocorticoid blockade reduces vascular injury in stroke-prone hypertensive rats. Hypertension 1998; 31: 451—458.

85. Rocha R, Chander PN, Zuckerman A et al. Role of mineralocorticoids in renal injury in stroke prone spontaneously hypertensive rats. Hypertension 1998; 32: 598A.

86. Rocha R, Zuckerman A, Chander P et al. Adrenalectomy prevents renal vascular injury in stroke prone SHR. J Amer Soc Nephrol 1998; 9: A2065.

87. Greene EL, Kren S, Hostetter TH. Role of aldosterone in the remnant kidney model in the rat. J Clin Invest 1996; 98: 1063—1068.

88. Rocha R, Stier ChT Jr. Pathophysiological effects of aldosterone in cardiovascular tissues. Trends in Endocrinol and Metabolism 2001; 12: 308—314.

89. Nicoletti A, Heudes D, Hinglais New et al. Left ventricular fibrosis in renovascular hypertensive rats. Effect of losartan and spironolactone. Hypertension 1995; 26: 101—111.

90. Robert V, Silvestre JS, Charlemagne D et al. Biological determinants of aldosterone-induced cardiac fibrosis in rats. Hypertension 1995; 26: 971—978.

91. Brilla CG, Pick R, Tan LB et al. Remodeling of the rat right and left ventricles in experimental hypertension. Circulat Res 1990; 67: 1355—1364.

92. Brilla CG, Matsubara LS, Weber KT. Antifibrotic effects of spironolactone in preventing myocardial fibrosis in systemic arterial hyprtension. Amer J Cardiol 1993; 71: 12A—16A.

93. Hené RJ, Boer P, Koomans HA et al. Plasma aldosterone concentrations in chronic renal disease. Kidney Int 1982; 21: 98—101.

94. Duprez DA, Bauwens FR, De Buyzere ML et al. Influence of arterial blood pressure and aldosterone on left ventricular hypertrophy in moderate essential hypertension. Amer J Cardiol 1993; 71: 17A—20A.

95. Schunkert H, Hense HW, Muscholl M et al. Associations between circulating components of the renin-angiotensin-aldosterone-system and left ventricular mass. Heart 1997; 77: 24—31.

96. Blacher J, Amah G, Girerd X et al. Association betweeen increased plasma levels of aldosterone and decreased systemic arterial compliance in subjects with essential hypertension. Amer J Hypertens 1997; 10: 1326—1334.

97. Epstein M, Buckalew V, Altamirano J et al. Eplerenone reduces proteinuria in type 2 diabetes mellitus: implications for aldosterone involvement in the pathogenesis of renal dysfunction. J Amer Coll Cardiol 2002; 39 (Suppl A): 249A.

98. Gómez-Sánchez CE. Primary aldosteronism and its variants. Cardiovasc Res 1998; 37: 8—13.

99. Nishimura M, Uzu T, Fuji T et al. Cardiovascular complications in patients with primary aldosteronism. Amer J Kidney Dis 1999; 33: 261—266.

100. Grady RW, Kaylor WM, Lee JC et al. Renal pathology in patients with primary hyperaldosteronism secondary to an adrenal cortical adenoma. Urology 1996; 48: 369—372.

101. Halimi JM, Mimram A. Albuminuria in untreated patients with primary aldsoteronism or essential hypertension. J Hypertens 1995; 13: 1801—1802.

102. Takeda R, Matsubara T, Miyamori I and the Research Committee of Disorders of Adrenal Hormones in Japan. Vascular complications in patients with aldosterone producing adenoma in Japan: comparative study with essential hypertension. J Endocrinol Invest 1995; 18: 370—373.

103. Rossi GP, Sacchetto A, Visentin P et al. Changes in left ventricular anatomy and function in hypertension and primary aldosteronism. Hypertension 1996; 27: 1039—1045.

104. Denolle T, Chatellier G, Julien J et al. Left ventricluar mass and geometry before and after etiologic treatment in renovascular hypertension, aldosterone-producing adenoma, and pheochromocytoma. Amer J Hypertens 1993; 6: 907—913.

105. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction. Circulation 1998; 97: 2202—2212.

106. Latini R, Maggioni AP, Flather M et al. ACE inhibitor use in patients with myocardial infarction: summary of evidence from clinical trials. Circulation 1995; 92: 3132—3137.

107. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure New Engl J Med 1991; 325: 293—302.

108. Staessen J, Lijnen P, Fagard R et al. Rise in plasma concentration of aldosterone during long-term angiotensin II suppression. J Endocrinol 1981; 91: 457—465.

109. Ayers CR, Davis JO, Lieberman F et al. The effects of chronic hepatic venous congestion on the metabolism of d,l-aldosterone and d-aldosterone. J Clin Invest 1962; 41: 884—895.

110. Tait JF, Bougas J, Little B et al. Splanchnic extraction and clearance of aldosterone in subjects with minimal and marked cardiac dysfunction. J Clin Endocrinol Metab 1965; 25: 219—228.

111. Francis GS, Benedict C, Johnstone DE et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with a without congestive heart failure: a substudy of the Studies of Left Ventricular Dysfuction SOLVD. Circulation 1990; 82: 724—729.

112. Schrier RW, Abraham WT. Hormones and haemodynamics in heart failure. New Engl J Med 1999; 341: 577—585.

113. Robert V, Thiem N, Cheav L et al. Increased cardiac type I and III collagen mRNAs in aldosterone salt hypertension. Hypertension 1994; 24: 30—36.

114. Bashir Y, Sneddon JF, Straunton HA et al. Effects of long-term oral magnesium chloride replacement in congestive heart failure secondary to coronary artery disease. Amer J Cardiol 1993; 72: 1156—1162.

115. Stergiou GS, Mayopoulou-Symvoulidou D, Mountokalakis TD. Attenuation by spironolactone of the magnesiuric effect of acute furosemide administration in patients with liver cirrhosis and ascites. Miner Electrolyte Metab 1993; 19: 86—90.

116. Ascherio A, Rimm EB, Hernan MA et al. Intake of potassium, magnesium, calcium and fiber and risk of stroke among US men. Circulation 1998; 98: 1198—1204.

117. Zuanetti C, Ferrari GM, Priori SG et al. Protective effect of vagal stimulation on reperfusion arrhythmias in cats. Circulat Res 1987; 61: 429—435.

118. Nolan J, Batin PD, Andrews R et al. Prospective Study of heart rate variability and mortality in chronic heart failure. Reults of the UK Heart Failure Evaluation and Assessment of Risk Trial UK Heart. Circulation 1998; 98: 1510—1516.

119. Zannad F. Aldosterone and heart failure. Europ Heart J 1995; 16 (Suppl N): 98—102.

120. Swedberg K, Eneroth P, Kjekshus J et al for the CONSENSUS Trial Study Group. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. Circulation 1990; 82: 1730—1736.

121. Swedberg K, Eneroth P, Kjekshus J et al. for the CONSENSUS Trial Study Group. Effects of enalapril and neuroendocrine activation on prognosis in severe congestive heart failure follow-up of the CONSENSUS trial. Amer J Cardiol 1990; 66: 40D—45D.

122. Vaughan DE, Lamas GA, Pfeffer MA. Role of left ventricular dysfunction in selective neurohumoral activation in the recovery phase of anterior wall acute myocardial infarction. Amer J Cardiol 1990; 66: 529—532.

123. Benedict CR, Johnstone DE, Weiner DH et al. Relation of neurohumoral activation to clinical variables and degree of ventricular dysfunction: a report from the registry of SOLVD. J Amer Coll Cardiol 1994; 23: 1410—1420.

124. The RALES Investigators. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure the Randomized ALdactone Evaluation Study, RALES. Amer J Cardiol 1996; 78: 902—907.

125. CIBIS-II Investigators and Committees. The Cardiac Insufficiency BIsoprolol Study II CIBIS II: a randomised trial. Lancet 1999; 353: 9—13.

126. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: MEtoprolol CR/XL Randomised Intervention Trial in congestive Heart Failure MERIT-HF. Lancet 1999; 353: 2001—2007.

127. Delyani JA. Anti-aldosterone therapy in the treatment of heart failure: new thoughts on an old hormone. Exp Opin Invest Drugs 1998; 7: 753—759.

128. Zannad F, Alla F, Dousset B et al for RALES Investigators. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study RALES. Circulation 2000; 102: 2700—2706.

129. Ramires FJA, Mansur A, Coelho O et al. Effect of spironolactone on ventricular arrhythmias in congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. Amer J Cardiol 2000; 85: 1207—1211.

130. Modena MG, Aveta P, Menozzi A et al. Aldosterone inhibition limits collagen synthesis and progressive left ventricular enlargement after anterior myocardial infarction. Amer Heart J 2001; 141: 41—46.

131. Weber KT, Villarreal D, Griffing GT. Heart Failure: pathophysiology, aldosterone and anti-aldosterone therapy. In: Wilton J, Conn J (Eds). Medical Education Programs, Ltd, 1993.

132. Mantero F, Lucarelli G. Aldosterone antagonists in hypertension and heart failure. Annales d'Endocrinologie 2000; 61: 52—60.

133. Pitt B, Remme W, Zannad F et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. New Engl J Med 2003; 348: 1309—1321.

Received February 12, 2004.
Accepted January 3, 2005.