Renin inhibition

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Summary

Section I of this thesis- Pharmacology- focuses on the systemic and renal effects of the specific renin inhibitor remikiren (Ro 42-5892) in hypertensive patients with different degrees of renal function impairment. It tests the hypothesis that remikiren is an effective antihypertensive agent with a favorable renal profile. This was the first study on the renal effects of an orally administered renin inhibitor in this target population. In section II- Pathophysiology- the renin inhibitor is used as a specific pharmacologic tool to study the role of the RAAS in the pathophysiology of renal sodium handling in primary hypertension. Since it is not feasible to measure local intrarenal RAAS-activity, the response to remikiren was used as a surrogate indicator for the state of activation of the RAAS. In these studies we tested the hypothesis that dysregulation of the (intrarenal) RAAS, leading to inappropriately elevated levels of the effector hormone angiotensin II, plays al role in the impaired renal sodium handling and abnormal renal hemodynamics, either or not in mutual interaction, in primary hypertension.

Chapter 1 provides a general introduction, reviewing data that shows primary hypertension to be a main mediator of target organ damage, such as congestive heart failure, cerebro- and peripheral vascular disease and chronic renal failure. The multifactorial pathogenesis of primary hypertension and its sequelae is incompletely understood. Possible clues to underlying mechanisms are discussed, particularly outlining the role of the kidney as the ultimate effector organ of sodium- and volume homeostasis and thus long term arterial pressure regulation. The pressure natriuresis relationship is assumed to reflect an intrinsic renal property capable of maintaining long term blood pressure within narrow limits by renal perfusion pressure induced modulation of sodium excretion. The rightward shift of the pressure natriuresis relationship in human hypertension as compared to normotension, implies impairment of renal sodium handling in hypertension. Its precise nature and pathophysiology is incompletely understood. Apparently hypertensive patients maintain sodium homeostasis at the cost of an elevated blood pressure. On top of that a heterogenous blood pressure response to shifts in dietary salt intake has been observed in these patients, indicating variable sodium-sensitivity of blood pressure. Sodium sensitivity has been associated with more severe target organ damage. Refining our understanding of the mechanism of renal sodium handling and sodium sensitivity in primary hypertension may thus have important implications for our therapeutical approach.

Our studies focused on the RAAS as this system plays an important role in the pathogenesis of hypertension, particularly by its impact on renal sodium handling. It is the principal hormonal system that modulates both renal hemodynamics, i.e glomerular filtration rate and renal blood flow, as well as tubular function and thus affects renal sodium handling in both a direct and indirect fashion. Moreover, increased RAAS-activity has been shown to induce a

rightward shift of the pressure natriuresis relationship, which subsequently appeared reversible during RAAS-blockade. An overview of the RAAS, including its biochemistry and the multiple actions of the effector hormone angiotensin II in human physiology and pathophysiology is given. Finally, we summarized the scope of the thesis and defined our specific study questions.

Chapter two addresses the different modes of intervention in the RAAS: renin inhibition, ACE inhibition and angiotensin II subtype 1 receptor blockade. Potential differences in the mode of action between these different classes of drugs are being discussed. The literature on renin inhibition is reviewed in more detail, particularly referring to the test compound remikiren. This compound induced blood pressure lowering and distinct renal effects in animal experiments, whereas the experience with orally active renin inhibitors in the target population, that is humans with hypertension, is to date still limited. No data is available on the renal effects of remikiren or any other orally administered renin inhibitor in man. Section I therefore further explores the pharmacological characteristics of the renin inhibitor remikiren.

Section I: Pharmacology

In chapter 3 we described the effects of a single oral administration of 600 mg remikiren in 16 patients with essential hypertension, who were on a moderately restricted dietary sodium intake. Remikiren induced a substantial fall in mean arterial pressure, albeit with a considerable interindividual variation, which was not explained by the variable drug levels, thus suggesting that remikiren exerts its effect mainly at the tissue level. Remikiren corrected the renal vasoconstriction that usually features primary hypertension. The glomerular filtration rate remained stable, whereas the effective renal plasma flow rose. As a consequence filtration fraction and renal vascular resistance fell, despite the fall in blood pressure, suggesting renal vasodilation both at the level of the efferent and afferent arteriole, consistent with reduced formation of angiotensin II. Both the systemic and renal hemodynamic effects were more pronounced in individuals with a higher initial immunoreactive renin, presumably related to the individual renin response to prevailing sodium status as well as the adaptation to the supine position during the study days. The hemodynamic response was also more pronounced in patients with a greater reactive rise in immunoreactive renin during renin inhibition, considered to be due to interruption of the short feedback loop with angiotensin II, and suggesting, at least in our short term study, that the rise in renin, which has by some been considered a drawback of renin inhibition, does not counteract the remikiren induced hemodynamic response, but instead indicates adequate net inhibition of the RAAS. The renal effects of remikiren furthermore consisted of a rise in the fractional excretion of sodium and lithium, suggesting a decreased reabsorption in the proximal tubule. Moreover, we observed a decrease in urinary albumin excretion.

In chapter 4 we described the systemic and renal effects of multiple dose remikiren in essential hypertensive patients with different degrees of renal

function impairment. The once-daily dose of 600 mg of remikiren elicited RAAS inhibition throughout the 24 hours. The observed dissociation between a sustained decrease in PRA and a transient fall in angiotensin II is in line with previous studies using renin inhibitors. The peak drug levels immediately after dosing and subsequent rapid clearance from the plasma confirms the pharmacokinetic profile of remikiren, as described earlier. Animal experimental data suggested that the kidney is the main target tissue for remikiren and may provide a reservoir of drug within the body, a possible explanation for the sustained pharmacodynamic effects despite undetectable plasma drug levels. Likely, in spite of the low oral bioavailability, enough drug is available at the target level. Renal function impairment did not cause plasma accumulation of the drug even in patients with a GFR as low as 20 ml/min. This is in accordance with rapid biliary elimination of the drug, but does not rule out the possibility of higher tissue concentrations in patients with impaired renal function. Continued treatment for eight days with remikiren induced a fall in blood pressure that was sustained throughout the day, without reflex tachycardia. The patients with renal function impairment showed a more pronounced blood pressure response than the essential hypertensives, despite similarity in the systemic hormonal response. Whether higher tissue levels of remikiren or a greater contribution of the RAAS to vasomotor tone in these patients underly this difference is unclear. Remikiren induced a rise in renal plasma flow and a fall in renal vascular resistance, thereby indicating renal vasodilatation. Glomerular filtration rate was unchanged, resulting in a fall in filtration fraction. Renal protein excretion decreased during remikiren, not only in patients with overt nephrotic range proteinuria, but also in the essential hypertensives in whom albuminuria fell significantly. Despite the lack of a control group or a recovery period, the antiproteinuric effect is likely to be genuine, considering the well-controlled study conditions, and well-established stabilization of proteinuria before the onset of treatment. Several factors may account for the antiproteinuric effect, such as the remikiren induced renal vasodilation, mainly located at the efferent arteriole, which despite the fall in blood pressure, causes a decrease in filtration pressure. Moreover, the inhibition of other angiotensin II related intrarenal effects, such as mesangial cell contraction and a decrease in filtration surface area may have contributed to the antiproteinuric effect of remikiren. Yet, our study design does not allow to conclude that the antiproteinuric effect is specifically due to RAAS-blockade, as the lower blood pressure may have played a role as well. Finally, a net negative sodium balance was observed, with considerable interindividual variation. No side effects were observed.

Implications of the pharmacology of remikiren

What are the implications of our pharmacological results? First, remikiren, at least during moderately restricted dietary sodium intake, is a potent and well tolerated antihypertensive drug in hypertensive patients with different degrees of renal function impairment, proving the principle of renin inhibition to be sound

and once again corroborating the crucial involvement of the RAAS in primary hypertension. The more pronounced effect on blood pressure in renal failure patients is of interest and deserves further study. Remikiren lowers blood pressure both by inducing vasodilation and by facilitating natriuresis, as indicated both by the induced negative sodium balance and the shift in the pressure natriuresis relationship. (see section two) Second, remikiren does not compromize renal function as glomerular filtration rate did not change. However, remikiren induced reduction in renal function may well occur in conditions with impairment of renal perfusion, such as hypovolemia, renal artery stenosis and heart failure, i.e clinical situations in which renal function critically depends on prevailing angiotensin II levels. Sodium depletion is well known to further enhance this dependency. Third, the obtained reduction of proteinuria and albuminuria suggests that remikiren has renoprotective properties. Reduction of proteinuria is a consistent predictor of long term renoprotection, both in diabetic and non-diabetic patients. Studies in diabetes suggest that reduction in albumiuria is also a marker of renoprotection, but for the moment this not established for non-diabetic populations. Fourth, measurement of pretreatment circulating components of the RAAS was of limited value, at least in predicting the long term hemodynamic and renal response to remikiren. Plasma renin activity, the initial immunoreactive renin and the renin response to renin inhibition, on the other hand, reflected most consistently the systemical state of activation of the RAAS, as well as the remikiren-induced acute hemodynamic response. Measurements of angiotensin II showed conflicting results, although we cannot exclude underlying methodological fallacies, as the determination of angiotensin II is notoriously difficult and subject to variability. However, there is also increasing evidence that tissue levels of angiotensin II, rather than plasma levels, are important for the pharmacological response to RAAS inhibition. Whether plasma values of the RAAS accurately reflect the state of activation at critical tissue target sites is only hypothetical. Fifth, measuring drug levels did not have explanatory power as there was no correlation whatsoever to the pharmacodynamic responses. No accumulation of remikiren occurred in patients with renal function impairment, but such could be the case if treatment is prolonged.

Renin inhibition versus other modes of RAAS inhibition

Could there be advantages of renin inhibition as compared to other modes of RAAS blockade, such as ACE inhibition or angiotensin II receptor antagonism? As we did not make a direct comparison, we can not deduce from our data whether remikiren is in any way superior to, or different from, these other modes of RAAS inhibition. Theoretically it might be advantageous to block the RAAS at its first and rate-limiting step. In contrast to the non-specific ACE-inhibitors, which also interfere in other systems such as the kinins and prostaglandins, renin inhibitors quite specifically inhibit the formation of angiotensin II. Moreover, they also prevent the formation of angiotensin II via non-ACE pathways. They inhibit the RAAS independently of the presence and distribution of angiotensin II receptor subtypes. Lastly, they lack the reciprocal

rise in angiotensin II that occurs in response to angiotensin II receptor blockers, of which the (patho)-physiological significance is still unclear, but may relate to its vasodilatory effect through its effect on the angiotensin II type 2 receptor.

To date, data from the literature is still too limited to draw final conclusions on the therapeutic potential of renin inhibitors in comparison to the alternative RAAS-blockers. Systemically administered renin inhibitors induced both a more and a less pronounced lowering of blood pressure as compared to ACE inhibitors, whereas the few orally available renin inhibitors appeared to exert a somewhat less pronounced blood pressure response, but the implications of these studies for therapeutics are limited due to the only brief duration of treatment and relatively small study samples.

The renal effects of renin inhibitors appear at least promising and deserve more study. Animal experiments demonstrated substantial renal vasodilation due to renin inhibition. The renin inhibitors zankiren and enalkiren in healthy humans induced significantly more pronounced renal vasodilation in direct comparison with ACE inhibitors, suggesting that prostaglandins or endothelial nitric oxide are not involved in the response. It has been postulated that intrarenal conversion of angiotensin I to angiotensin II occurs, at least in part, at a site which is inaccessible to ACE inhibition, or that there may be an alternative pathway for intrarenal conversion that is not blocked by ACE-inhibition. Greater lipophilicity and tissue penetration may also have contributed to the more pronounced renal hemodynamic response of renin inhibitors in these studies.

In our study, the fall in proteinuria with remikiren was somewhat less than usually observed with ACE inhibition or AT_1 receptor blockade. However, we only treated for eight days, whereas it takes approximately four weeks before the maximum antiproteinuric effect of ACEi and AT_1 blockade is reached. It would be of interest, therefore, to investigate whether more prolonged renin inhibition would further reduce proteinuria. Moreover, it might be of interest to investigate whether additive therapy with renin inhibition could provide a strategy to circumvent treatment resistance to ACE-inhibition or AT_1 blockade by precluding the reactive rise in renin activity with those modes of RAAS blockade.

In conclusion, whereas the clinical application of renin inhibitors has thus far been hampered by their poor bioavailability, and subsequently a less favorable marketing profile, the data presented here suggest that renin inhibition can be clinically useful and is moreover a specific tool to unravel the mechanisms of primary hypertension and the renoprotective action of RAAS blockade. In our opinion it has been too early to close renin inhibitor development programmes, at least from a pharmacological standpoint.

Section II: Pathophysiology

This section explores the role of the RAAS in the pathophysiology of renal sodium handling in established hypertension. Renal hemodynamic abnormalities, both due to structural and functional changes in the renal vasculature may play an important role in the blunted natriuresis of hypertensive

patients. Chapter 5 covers the issue of renal hemodynamics in human hypertension. Impairment of renal blood flow is common in primary hypertension. Renal blood flow is mostly decreased, whereas glomerular filtration rate remains normal until advanced hypertensive disease. As a result, renal vascular resistance and filtration fraction is increased. Findings in normotensive offspring suggest that renal hemodynamic abnormalities may precede hypertension and play a causal role. On the other hand, renal hemodynamic abnormalities may be a marker rather than a mediator of renal processes involved in the elevation of blood pressure. In established hypertension abnormal renal hemodynamics associated with impaired renal sodium handling, either due to a primary defect or due to hypertensive renal damage, are likely to play a role in the maintenance of high blood pressure. Drugs blocking the RAAS improve both renal blood flow and sodium handling, suggesting that RAAS-activity is functionally involved in the renal abnormalities. Hypertension is still a major cause of end-stage renal failure, and importantly, a treatable one. Pathophysiological and epidemiological findings suggest the presence of subgroups with an increased risk for renal function loss. As a lower target blood pressure may be needed for adequate renoprotection, it would be important to identify high risk patients, to warrant agressive blood pressure treatment in these susceptible individuals. Moreover, it would be important to know whether blockade of specific pathophysiological pathways, such as the RAAS, could exert protective effects in addition to reduction of blood pressure.

Unravelling of the role of the RAAS in renal hemodynamics and renal sodium handling and its impact on blood pressure in patients with primary hypertension is complex for several reasons. First, the state of activation of the RAAS at the target level, i.e within the kidney, cannot be directly measured. Second, several intrarenal hemodynamic parameters with established pathophysiological importance in experimental animals (i.e., intrarenal blood flow distribution, medullary blood flow, intraglomerular hemodynamics, and heterogeneity between nephron populations) cannot reliably be assessed in man either. Third, other intrarenal neurohormonal systems may act as confounding factors. Finally, it is difficult to discern cause and effect, as all involved parameters mutually interact. Specific blockade of the RAAS- as possible with renin inhibition- could be helpful to unravel these complex interactions.

In chapter 6 we studied the pressure natriuresis relationship by assessing the effect of spontaneous diurnal variations in blood pressure on sodium excretion in untreated primary hypertensive patients in balance on a fixed sodium intake, thereby testing the efferent part of the renal feedback loop. So far, studies on the relationship between sodium and blood pressure in man almost exclusively addressed blood pressure response to a change in sodium status, i.e sodium sensitivity of blood pressure. Our approach, by investigating spontaneous fluctuations in blood pressure, also circumvented the need for interventions in blood pressure. This is important as measures that modify blood pressure in man (i.e infusion of vaso-pressor or -depressor agents) usually exert direct pharmacological effects on sodium excretion as well. To test whether RAAS activity limits the efficacy of pressure natriuresis, we investigated whether RAAS blockade by remikiren could improve the pressure natriuresis relationship. Both

before and during remikren treatment a normal diurnal pattern of sodium excretion and blood pressure was observed. During remikiren treatment the diurnal variation in blood pressure correlated positively with the variations in sodium excretion in all patients, whereas without treatment such a correlation was present in only 3 out of 8 patients. The slope of the regression equation was steeper during remikiren in 7 out of 8 patients. Thus, the relationship between blood pressure and natriuresis was more readily apparent during RAAS blockade, suggesting that RAAS activity blunts pressure natriuresis in hypertensive patients. This pathogenetic role of the RAAS is also supported by the fact that- in the untreated condition- the correlation between blood pressure and sodium excretion was strongest in the patients with the lowest PRA level. Our data suggest that resetting of the pressure natriuresis mechanism by remikiren may contribute to its blood pressure lowering action. Whether the absence of a relationship between variations in blood pressure and sodium excretion in the untreated condition is specific for essential hypertension can not be ascertained from our data, as this would require a comparison with healthy controls.

Several mechanisms could account for the impact of remikiren on pressure natriuresis. Renal vasodilation can enhance the transmission of changes in renal perfusion pressure to the peritubular and the medullary microcirculation, thus transmitting blood pressure changes to renal interstitial pressure. The latter is presumed to mediate the natriuretic tubular responses to elevated renal perfusion pressure. Since we did not study other renal vasodilator agents, we cannot dissociate between the role of renal vasodilation and the role of reduced angiotensin II activity as such. Finally, we cannot exclude that remikiren synchronized the diurnal patterns of blood pressure and sodium excretion by an unidentified mechanism other than enhancement of the blood pressure dependency of natriuresis. Yet, combining our data with those from the litterature suggests that the alterations in pressure natriuresis in our study are likely to be due to RAAS blockade and consequently reduced angiotensin II effects.

Other lines of evidence confirmed the importance of renal hemodynamic alterations in sodium handling by the kidney. Campese et al demonstrated increased renal vascular resistance in salt-sensitive patients. Hollenberg et al observed a blunted renal vasodilation to an increased dietary sodium intake in a subpopulation of primary hypertensives with concomitant impairment of renal sodium handling, denoted as non-modulators. Apparently, high sodium intake unmasks a primary disturbance within the kidney, with an inappropriately high renal vascular tone during high sodium. The associated rise in blood pressure can be considered a compensatory response for the decreased capacity of the kidney to excrete sodium, in line with the principle of pressure natriuresis. Our data, as well as those of Hollenberg, suggest that inappropriate renal RAAS-activity is involved in this abnormal adaptation to sodium.

Chapter 7, therefore, further explored the role of the RAAS in the renal hemodynamic and systemic adaptation to high dietary sodium. Our premise was that a blunted renal vascular response to sodium, as an index of inadequate suppression of intrarenal angiotensin II by high sodium, would be accompanied by a rise in blood pressure. If so, one would expect a more

pronounced systemic and renal hemodynamic response to remikiren during high sodium in subjects with an abnormal adaptation to sodium. We tested this hypothesis in patients with uncomplicated established hypertension and in healthy controls.

In the healthy subjects high sodium intake had no effect on blood pressure or body weight, whereas effective renal plasma flow increased and immunoreactive renin decreased significantly. In hypertensive subjects, high sodium intake induced a heterogeneous response of both blood pressure and effective renal plasma flow. Body weight increased and immunoreactive renin decreased. Interestingly, an increase in body weight and a distinct rise in blood pressure occurred only in those patients with a blunted response of renal plasma flow to the high sodium intake, whereas the latter correlated well with a less pronounced fall in immunoreactive renin. The adaptation of glomerular filtration rate, and consequently the filtered load of sodium, was similar in subjects with a sodium-resistant or a sodium-sensitive blood pressure. Thus, in response to high sodium, renal vascular resistance and filtration fraction increased only in patients, in whom blood pressure rose as well. This probably indicates both an increased preglomerular and postglomerular vascular tone. The absence of a renal vasodilator response to high sodium may partly be due to structural abnormalities of the renal vascular bed, i.e hypertensive arteriolar nephrosclerosis. In accord with this assumption, effective renal plasma flow was lower in the hypertensive patients, already during low sodium. Moreover, effective renal plasma flow was lowest in the oldest hypertensive patients. The sodium-induced increase in flow, however, did not relate to age. The observed impairment of renal blood flow, therefore, at least to some extent, appears functional as also suggested by the association with filtration fraction.

Multiple regression demonstrated that race, sex, age, or body weight did not explain the observed differences in the blood pressure response to sodium. The fact that body weight increased only in patients with a rise in blood pressure, indicates that volume expansion, probably due to impaired sodium excretion, may have contributed to this rise.

During remikiren treatment we observed a heterogeneous response in renal plasma flow. Patients with a blunted renal plasma flow response to high sodium intake showed the largest rise in renal flow during remikiren. This shows the reversibility of the impaired renal hemodynamic response to sodium, and points towards greater renal RAAS activity. The remikiren-induced rise in renal plasma flow correlated well with the fall in blood pressure. Thus, the response to renin inhibition shows that insufficient suppression of the renal RAAS impedes an adequate renal vascular response to high sodium, which is associated with a sodium-induced rise in blood pressure. The correlation between the reduction in renin and renal vasodilation also existed in a subgroup of our hypertensive patients with renin levels that were similar to those in the control group. This refutes the assumption by others that renin is low and of no impact in salt sensitivity. In addition, multivariate analysis in the normotensive subjects demonstrated a correlation between the sodium-induced renin decrease and renal vasodilation when age was added to the model. The observed variation in renin response could not be explained by differences in adherence to the diet.

Remarkably, in both normotensive and hypertensive subjects, the renin response to sodium corresponded strikingly with the reactive rise in renin induced by remikiren. This strongly suggests that the responsiveness of the RAAS to several different stimuli is an individual characteristic.

Thus, adaptation of the normal kidney to a high sodium is characterized by a rise in glomerular filtration rate and effective renal plasma flow, with unchanged blood pressure. The RAAS is a modulator of these renal hemodynamic changes. In essential hypertension, a rise in blood pressure in response to high sodium intake appears to result partially from insufficient renal vasodilation. Insufficient suppression of (possibly intrarenal) RAAS-activity may be involved, but the precise level of disturbance remains to be determined. Our data primarily suggest dysregulation within the kidney. Differences in responsiveness of the renal vasculature to prevailing angiotensin II levels may also be involved. Further studies on the local state of activation of the intarenal RAAS are needed to clarify this issue.

In our next study we sought further evidence for our hypothesis that dysregulation of the intrarenal RAAS plays a role in the impairment of renal sodium handling in established hypertension, by assessing the natriuretic response to remikiren. We argued that increased renal vascular tone could be a marker of RAAS-mediated impairment of renal sodium excretion. If so, one would expect that RAAS blockade would induce natriuresis in proportion to pretreatment renal vascular tone. This hypothesis is tested in **chapter 8**, that describes the effects of remikiren on renal hemodynamics and sodium excretion in essential hypertensives, both acutely and after multiple dosing, which allows to establish the eventual effect on sodium balance. Pretreatment renal vascular tone, as estimated from filtration fraction and renal vascular resistance, showed considerable individual differences. Remikiren induced a fall in blood pressure, filtration fraction and renal vascular resistance, with a considerable interindividual variability in natriuretic response. The natriuretic response to remikiren during single as well as multiple dose correlated with pretreatment renal vascular tone, but not with remikiren-induced changes in renal hemodynamics or in hormonal parameters. Cumulative sodium loss was largest in patients with a higher pretreatment filtration fraction and renal vascular resistance. Our findings are the first to demonstrate such a relationship.

In the multiple dose study pre-treatment angiotensin II correlated with pretreatment renal vascular resistance and the remikiren-induced natriuresis. On the other hand, correlations between pretreatment PRA and immunoreactive renin and the renal responses to renin inhibition, or between the remikiren-induced changes in hormonal parameters and natriuresis were absent in both studies. Apparently our findings do not simply reflect greater RAAS-activity and consequently more pronounced effects of RAAS blockade at all parameters. However, we cannot exclude possible confounding effects of methodological factors in the assessment of RAAS-components.

The natriuretic response did not correlate with the observed renal vasodilation during remikiren, suggesting that natriuresis did not depend on renal hemodynamic responses. However, renal hemodynamics were assessed at a single time point, whereas cumulated sodium loss reflects a continuous

measurement. Thus, an all-too-straightforward conclusion cannot be drawn on this issue. Moreover, alterations in renal blood flow distribution can be present with an unchanged effective renal plasma flow: intrarenal infusion of a low dose angiotensin II can markedly reduce medullary blood flow and sodium excretion without altering whole-kidney blood flow. This raises the possibility that in patients with a higher pretreatment renal vascular tone, remikiren induced a relatively greater increase in medullary blood flow, resulting in larger natriuresis.

Whereas assumptions on the intrarenal mechanisms must remain speculative, nevertheless, the consistent predictive value of pretreatment renal hemodynamics for natriuresis during remikiren stands out as a main finding. The concordance between the single and multiple dose study supports its robustness. The multiple dose data, moreover, demonstrate that the predictive value not only applies to the acute pharmacological effects, but also to the final effect on sodium balance. As the latter reflects the net effect of pharmacological intervention and counterregulatory homeostatic responses, we consider this a better indicator of the pathophysiological significance of the observation.

These findings suggest that pretreatment renal vascular resistance and filtration fraction indeed reflect inappropriate intrarenal RAAS activity, resulting in impaired sodium handling, that is unmasked by RAAS blockade. Studies from Hollenbergs group support the association of elevated renal vascular resistance during high sodium with intrarenal RAAS activity in the subset of essential hypertensive patients denoted as non-modulators. Whereas we did not attempt to delineate subgroups, our data are consistent with inappropriately high intrarenal RAAS activity in part of the hypertensive population.

We have previously found an individual response pattern of natriuresis for ACE inhibition: our present findings are the first to link the individual natriuretic response to RAAS blockade to individual pre-treatment characteristics of renal vascular tone.

Impact of the pathophysiological studies

What could be the relevance of our pathophysiological studies? Our study of the pressure natriuresis curve shows, first, that analysis of spontaneous fluctuations can be succesfully applied in studies on renal pathophysiology in man. This approach is analogous to -for instance- the analyses of the spontaneous variability in heart rate, a well established parameter in cardiovascular research. It allows to study biological phenomena without the confounding effect of intervention, which allows a more unbiased appreciation of the biological phenomena of interest. This approach has not previously been applied in human renal physiology. Thus, our data not only provide new insights on the role of the RAAS in pressure natriuresis in human hypertension, but also open up a new angle for studies in renal (patho)-physiology in man.

The studies in chapters 7 and 8 both analyse differences between individual patients with respect to RAAS-mediated responses. These studies provide new insights as to the role of the RAAS-mediated impairment of renal sodium

handling in the pathogenesis of high blood pressure, showing that some individuals, characterized by a high, RAAS-mediated, renal vascular tone, have inappropriate sodium retention and consequently higher blood pressure during high sodium intake. Moreover, these data show that interindividual differences in responsiveness to RAAS blockade can be related to specific characteristics of the patients' physiology, i.e to differences in RAAS-physiology. Individual differences in therapeutic benefit of RAAS blockade have been noted to be considerable in recent studies in renal patients and in experimental renal disease. Rotation schedules with different interventions showed that responsiveness to RAAS blockade is determined by individual patient factors. Elucidation of the mechanisms underlying these individual differences in responsiveness to RAAS blockade would be of great importance to optimize the therapeeutic benefit. Genetic variability in the RAAS- i.e polymorphisms in the genes coding for ACE and for the AT1 receptor- as well as interaction with sodium as an environmental factor may be involved in the individual differences in responsiveness to RAAS blockade. Recent data suggest that these polymorphisms have functional consequences for the RAAS phenotype. The present studies underline the importance of phenotypic characteristics of the RAAS for the individual differences in the response to RAAS blockade, and prompt for studies integrating genotype-phenotype relationships as factors underlying individual differences in therapy response.