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Renovascular disease

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Chapter 7

Summary and conclusions

This thesis addresses two aspects of renovascular disease in more detail. Our long standing interest in the effects of ACE inhibitors on kidney function has been expanded to include its use in conjunction with radioisotope methods to study both the diagnostic potential and the changes in renal function *casu quo* handling of different tracer materials. Secondly, the effects of renovascular disease on renal function and the possible benefits of active intervention by surgery and in particular by PTRA have been studied.

The first part of this thesis (Chapters 2 & 3) describes observations on radioisotope investigations in human unilateral renal artery stenosis, before and after challenge with ACE inhibitors under controlled conditions. The case reported in chapter 2 is one of the first among the many studies in this field, and represents the first published case of reversible decreased uptake of the tracer ^{99m}Tc -DMSA (dimercapto succinic acid) in this situation. This study delineates the now familiar concept of angiotensin-II mediated vasoconstriction, essential to effectively maintain transmembrane filtration pressure and hence glomerular filtration in a kidney with high grade renal artery stenosis. Renal blood flow usually is maintained in this situation, but the handling of tracer materials, considered to be dependent upon renal perfusion and (peri)tubular uptake is clearly altered.

The diagnostic potential of different radioisotope investigations before and after ACE inhibition was subsequently studied prospectively in a larger group of patients with unilateral renal artery stenosis, as described in chapter 3. ^{123}I -hippurate and ^{99m}Tc -DTPA renography and ^{99m}Tc -DMSA scintigraphy, with their clearly different predominant mechanism of renal uptake and excretion, were studied concurrently to evaluate the usefulness of these different methods in diagnosing renal artery stenosis, and to gain insight in the altered renal hemodynamics and handling of the tracers. The results of these different radioisotope investigations were evaluated both visually and quantitatively. Furthermore (changes in) blood pressure and in particular renal function were studied. The sensitivity percentages for detection of renovascular disease, already high in this selected population, were further increased for all radioisotope methods after challenge with ACE inhibitors, confirming preliminary observations of other investigators. Despite the at times substantial drop in blood pressure, ACE-stimulated renography and scintigraphy proved to be rather simple and safe methods of investigations. Overall renal function usually is well maintained in this situation, except in some patients with more marked renal impairment. Tracer handling, however, can show striking changes, most typically "retention" curves in ^{123}I -hippurate renography and diminished or even absent uptake of ^{99m}Tc -DTPA and ^{99m}Tc -DMSA at the stenotic side. Quantitative evaluation objectivates asymmetry of kidney renography and scintigraphy and can be useful to compare results of these

methods in different centres. ^{123}I -hippurate renography and $^{99\text{m}}\text{Tc}$ -DMSA renal scintigraphy are methods of choice, in situations of marked overall renal impairment, or discrete segmental stenosis respectively.

Chapter 4 represents an extensive review of the literature on the effects of renal artery stenosis and in particular the effects of treatment by surgery or angioplasty on kidney function. It has become more generally accepted that preservation of renal function is an important factor and in selected cases the sole reason for active intervention in renovascular disease. Atherosclerosis and fibromuscular dysplasia, the two disorders responsible for all except a few patients with renovascular disease, have clinically clearly distinct characteristics, especially with regard to the risk of renal functional deterioration. In fibromuscular dysplasia type of stenosis renal function generally is not severely impaired and the risk of total vascular occlusion is relatively small, except in certain less frequent subtypes of this disorder. In atherosclerotic renovascular disease preservation of renal function is most important because of the risks of progression and renal failure.

A first preliminary overview is given of the effects of revascularization on renal function in the different clinical situations, characteristic of this heterogenous disorder. In short, active intervention can lead to improved or stabilized renal function in many cases but is unrewarding under some circumstances. The improvement in renal function usually is only modest, except in favourable cases of vascular occlusion or high grade stenosis to the entire renal mass (occlusive disease in a solitary functioning kidney or bilaterally). However, perhaps more importantly, the resulting kidney function after successful revascularization can be maintained over long-term follow up in most patients. Unfortunately results of revascularization are not universally beneficial, either because the intervention has not been (completely) successful, has met with complications, or because too far advanced structural renal damage already had been present. This latter situation is frequently present in particular in (unilateral) atherosclerotic renal artery stenosis with marked decreased overall renal function and in the case of total vascular occlusion.

Increased awareness of the risks to renal mass and function and the still improving methods of intervention make active revascularization a more attractive, but not clearly defined treatment option, also because of the lack of good comparative studies with medical treatment.

Chapter 5 describes results of accurate renal function measurements shortly before and after uncomplicated PTRAs in unilateral renal artery stenosis. For this purpose glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured by constant infusion methods, using ^{125}I -iothalamate and ^{131}I -hippurate, in 12 patients during standardized diet and either no or unchanged antihypertensive medication. ERPF increased in the majority (75%) of patients but GFR, at least when measured within two weeks after the procedure, increased simultaneously in only 33% of the patients. This modest improvement of GFR (of 15% at most) was only seen in patients with initially a relatively well maintained renal function. The anatomical severity of the stenosis and the extent of dilatation, at least as calculated from the angiograms were not predictive of the response obtained. Marked size differences and shrinkage of the kidney were prognostically unfavourable.

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avourable characteristics. As opposed to effects on blood pressure, response of (overall) renal function after successful PTRA is not positively correlated with PRA ratio. In fact, patients with the highest PRA ratio had unchanged or even somewhat decreased renal function after PTRA. These patients, however, were also characterised by a low initial renal function and a small kidney size at the stenotic side, most probably reflecting long standing structural ischemic and/or hypertensive damage.

In chapter 6, we describe the results of PTRA treatment during the first 5 years after introduction of this technique in our clinic in 1979. A total of 43 patients were treated in this period and in 33 of these complete reevaluation, including blood pressure response, effect on renal function and angiographic status of the dilated vessels could be performed. At that time, a relatively high percentage of restenosis was found in both atherosclerotic (42%) and fibromuscular dysplasia type of stenosis (22%). Blood pressure response was favourable after successful dilatation of uni- or bilateral disease. When contralateral stenosis or occlusion remained untreated, blood pressure, as expected, was not altered markedly in most cases. Renal function was studied, by both serum creatinine values and creatinine clearance estimations over long-term follow up up to 4 years after the procedure. Initial renal function was impaired to some extent in all patients. After successful dilatation, improvement or stabilization of renal function was seen in the majority of patients. Also in the patients of the more complicated subgroup, mentioned above, in whom blood pressure had not changed markedly after PTRA, improvement of renal function was observed in a more or less similar percentage of the patients. However, now the result was optimal only after a few months.

Human renovascular disease is a rather heterogeneous disorder, characterised by the triad of compromised renovascular hemodynamics, hypertension and ischaemia. As opposed to the situation in most animal experiments, its presentation can vary greatly, including for example the classical "therapy resistant" severely hypertensive patient with localised focal stenosis and patients with surreptitiously progressed bilateral disease, presenting acutely with left sided congestive heart failure or end stage renal disease. Even apart from the relatively low prevalence of renovascular disease in the general population, this heterogeneity and the incomplete understanding of the pathophysiology therefore augment the difficulties in screening for this disease.

Over the years many methods have been advocated for this purpose including two considered to be "gold standards": conventional angiography for anatomical diagnosis and adaptations of the Howard and Stamey tests for more physiological evaluation. Nowadays these two have been abandoned, largely because of their impracticality, but no other methods of choice have emerged, showing a sufficiently high sensitivity and specificity. Of the more contemporary methods under investigation, renography and renal scintigraphy have received (renewed) interest, in part because they are relatively simple, non-invasive and readily available methods, which also can be repeated easily. More importantly, the different radionuclids give dynamic information on "functional" characteristics of renal perfusion and glomerular filtration. Apart from technical improvements in this

field, intervention in the renin-angiotensin-aldosterone system (RAAS) can reveal or augment changes compatible with "critical" renal artery stenosis.

This demonstration of functional significance of the stenosis is important for several reasons. First, the presence of renal artery stenosis has been shown in healthy individuals and at autopsy, without evidence of hypertension or renal impairment. Secondly, angiographic "anatomical" renal arterial narrowing is an imperfect reflection of the severity and of the functional significance of the lesion, and therefore cannot be used to establish the causal relationship with the hypertension present. Unfortunately, the evaluation of "functional" characteristics of renal arterial disease has not lived up to expectation at present. Studies of ACE-stimulated renography in dogs have documented a 100% sensitivity in diagnosing unilateral renovascular disease. However, experiments in animals are usually done shortly after the induction of renovascular hypertension by clamping the renal artery. The importance of the RAAS has clearly been established in this situation. Subsequently, a transition period can be found, where removal of the clamp still restores blood pressure, even though Angiotensin II levels already had returned already to pre-stenosis levels, but ultimately no change in blood pressure is seen any longer after removal of the original stenosis. In the human situation, generally the severity and the duration of the stenosis are unknown and intrarenal abnormalities of various etiology can be present at the same time. Not surprisingly therefore ACE-stimulated renography and scintigraphy have not attained a similar high degree of sensitivity, when compared to experimental animal studies. Further studies therefore are clearly needed, both to study the exact indications, but even before that, to standardize the appropriate conditions of investigation in order to maximize the yield of these methods.

Thus, although radionuclide imaging with ACE inhibitor challenge clearly is a valuable addition to the diagnostic arsenal, both historical and scientific reasons should warn against its indiscriminative use as a new "ideal" screening method in hypertension. Future diagnostic methods, however, should be selected upon their ability to demonstrate this "functional" character of the lesion.

The concept of evaluating renal hemodynamics or altered handling of various tracers, before and after interference in different intrarenal regulatory mechanisms, is also very appealing in order to further elucidate the complex intrarenal changes secondary to renovascular disease. One of the major clinical problems in this disorder is our inability to prove beyond doubt the secondary nature of the hypertension in all cases before intervention. Also presumably somewhat different intrarenal factors come into play when causing hypertension or renal impairment. Contrasting effects therefore can be seen with regard to blood pressure and renal function after intervention, also depending on the etiology of the disease. ACE inhibitors can be helpful to more precisely indicate the limits of renal contraregulatory mechanisms, activated to preserve renal perfusion and function.

In fibromuscular dysplasia the main indication for treatment is the hypertension present. Revascularization is best done by PTRAs as results are more or less equal to those of surgery. Effects on blood pressure and, if renal function is impaired, on renal function generally are rewarding, obviating the need for life-long antihypertensive therapy.

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Ablative procedures should be avoided, if possible, in view of the propensity for (de novo) development of new lesions contralaterally. Improvement in PTRA and especially in surgical both in situ and extracorporeal techniques have made intervention more feasible, also in case of extensive or branch disease.

The value of intervention in atherosclerotic renovascular disease is much less easily summarized. Revascularization both confers the greatest benefit, but unfortunately also the highest risks in this situation. Although still reduced compared to the general population, long-term survival is better in successfully revascularized patients. The degree of blood pressure control achieved and the extent of extrarenal significant atherosclerotic lesions are major determinants in this regard. Adequate medical antihypertensive therapy is much more feasible nowadays and can be a good treatment option, in particular in high risk patients. Careful follow up of renal function and renal size, however, is warranted as progressive disease is noted, especially in patients with advanced atherosclerotic stenosis, whether or not blood pressure is controlled. Revascularization can arrest or reverse the decline of renal function in many cases, the best results obtained, when all renal mass is ischaemic. Timely intervention is mandatory as combined ischaemic and hypertensive damage can lead to progressive irreversible loss of renal function and renal size in a relatively short time. Prevention of total occlusion and the possible restoration of long-term vessel prognosis to that without stenosis are encouraging findings, but the lack of large systematic investigations and the still evolving methods of treatment in this relatively rare condition preclude a really definitive standpoint on intervention in renovascular disease at this moment.