Renal reserve filtration capacity in man
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SUMMARY

In man the glomerular filtration rate (GFR) rises during pregnancy. An increased GFR also can be found during the use of a high protein diet compared with a low protein diet. Both observations indicate that in man a reserve filtration capacity is available. An even more convincing evidence for this supposition is the fact that after kidney donation GFR roughly amounts to 70 per cent of the pre-donation GFR. The latter also indicates that a loss of glomeruli can be compensated for by hyperfiltration of the remnant glomeruli. However, in rats it has been found that compensatory hyperfiltration, for instance induced by subtotal nephrectomy, leads to a progressively downhill course of the renal function and the development of proteinuria, both of which can be ameliorated by a protein-restricted diet. Recently, we have demonstrated that protein restriction also slows down the progression towards end-stage renal failure in patients with moderate to severe renal insufficiency. This may indicate that "harmful glomerular hyperfiltration" can exist in man too. Therefore, we have investigated whether reserve filtration capacity (i.e. the absence of glomerular hyperfiltration) can be measured in patients with renal disease by manipulation of the GFR. For the latter purpose we have used the infusion of low-dose dopamine and the infusion of amino acids, separately or simultaneously administered.

Subpharmacological doses of dopamine (1-2 μg/kg/min), an endogenous catecholamine, cause renal vasodilatation mediated by specific dopaminergic receptors. This results in an increased renal blood flow and GFR. Thus, we have used the infusion of dopamine at a rate of 1.5-2.0 μg/kg/min in order to increase GFR. Firstly, this has been done in 32 patients with IgA glomerulonephritis (chapter 2). In these patients the infusion of low-dose dopamine does not affect effective renal plasma flow (ERPF) and GFR if baseline GFR fall below this level related to increase in effective filtration rate in a predominate arteriole. In other renal disease the dopamine-induced GFR falls below baseline ERPF and GFR. This is also true after uninfusion of dopamine. Thus baseline GFR is an index of renal disease reserve filtration capacity.

Urinary volume.

Both is known to increase as a result of an amino acid infusion (chapter 4). However, patients did not respond to dopamine infusion.
GFR if baseline GFR amounts to 73 ml/min/1.73 m² or less. Above this level the dopamine-induced increase in GFR is closely related to the baseline GFR, i.e. a larger rise in GFR occurs with increasing baseline GFR. Because of a substantial larger rise in effective renal plasma flow (ERPF) than in GFR, the filtration fraction (FF=GFR:ERPF) falls. This can be explained by a predominant dopamine-induced dilatation of the efferent arteriole. However, a dopamine-induced shift in renal blood flow to nephrons of the inner cortex with a low FF may attribute to this fall in FF also. It is concluded that in IgA glomerulopathy nephron loss is compensated for by a progressive utilization of reserve filtration capacity which seems to be exhausted when compensated GFR falls below 73 ml/min/1.73 m².

In chapter 3 those observations are extended to patients with other renal diseases, healthy individuals after uninephrectomy and healthy control subjects. Once again it is demonstrated that the dopamine-induced rise in GFR increases with increasing baseline GFR and that GFR cannot be increased if baseline GFR falls below 50 ml/min/1.73 m². The dopamine-induced changes in ERPF and GFR of healthy volunteers are significantly higher than dopamine-induced changes in ERPF and GFR of healthy individuals after uninephrectomy as well as of renal patients with a normal baseline GFR. Therefore, it is concluded that already early in renal disease there exists a diminished reserve filtration capacity. During the infusion of low-dose dopamine heart rate is unaffected whereas mean arterial pressure decreases slightly. Urine volume and natriuresis increase.

Both infusion of amino acids and a meal of meat are well-known to increase GFR. Therefore, we also have used the infusion of an amino acid solution (Vamin®N) in order to affect GFR (chapter 4). In healthy volunteers an increase in GFR is found. However, patients with moderate to severe renal insufficiency do not respond to the infusion of amino acids. Unlike during dopamine infusion, the FF tends to increase during amino acid infusion. This is in accord with the hypothesis of Alvestrand and Bergström that amino acids affect GFR by the induction of
afferent vasodilation thus increasing net ultrafiltration pressure.

Since dopamine infusion and amino acid infusion appear to affect GFR in different ways, we also have investigated the effect of the combined infusion of these agents on the GFR (chapter 5). Indeed we have been able to demonstrate that dopamine and amino acids were additive with respect to their effect on GFR. The highest values for GFR are found during the combined infusion in healthy volunteers. In patients with moderate to severe renal impairment no significant changes in GFR could be found which may point to the existence of glomerular hyperfiltration in these patients.

In patients with Type 1 (= insulin-dependent) diabetes mellitus a supernormal GFR can be found. This usually is attributed to an enlarged kidney size with increased glomerular surface area and/or a decreased renal vascular resistance. To investigate whether the supernormal GFR in Type 1 diabetic patients is based on a predominant dilatation of the efferent arteriole, we have investigated the effect of low-dose dopamine on renal haemodynamics of 12 well-regulated patients with this disease (chapter 6). The dopamine-induced changes in renal haemodynamics did not differ between these patients and healthy volunteers. Therefore, we have concluded that the supernormal GFR in Type 1 diabetic patients is not caused by a predominant efferent vasodilatation. This is in accord with a recent hypothesis which assumes that the increased GFR after protein ingestion as well as the supernormal GFR in Type 1 diabetic patients are based on afferent vasodilatation which is induced by a liver-derived substance. Thus, we also have investigated the effect of the administration of amino acids on GFR of satisfactory controlled Type 1 diabetic patients (chapter 7). It is concluded that diabetic patients may be subdivided in two groups. Firstly, a group of patients with a normal GFR who possess a normal renal reserve filtration capacity, i.e. an amino acid- and dopamine-induced increase in GFR not different from healthy volunteers. Secondly, a group of patients with a supernormal GFR which is caused by amino acid infusion. Furthermore, are provided with Type 1
ultrafiltration and amino acid infusion appear to studied the agents on the GFR demonstrate that changes in GFR who possess amino acid- and supernormal GFR which is caused by dilatation of the afferent arteriole since amino acid infusion does not affect GFR whereas dopamine infusion increases GFR to the same extent as healthy subjects.

In the general discussion it is suggested that it makes more sense to subdivide the so-called "glomerular hyperfiltration" in glomerular hyperperfusion and in glomerular hypertension, especially so, as the latter seems to be the harmful factor. Furthermore, studies warranted and possible treatment strategies are provided for both patients with renal disease and patients with Type 1 diabetes mellitus with or without nephropathy.