Renal reserve filtration capacity in man

Wee, Pieter Marten ter

RENAL RESERVE FILTRATION CAPACITY IN MAN

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Stellingen
behorende bij het proefschrift van
P.M. ter Wee

Groningen
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1 Het begrip "glomerulaire hyperfiltratie" dient gerelateerd te worden aan het onderliggende hemodynamische moment.

2 Bij een verlies van nefronen wordt het door middel van dopamine stimuleerbare deel van de reserve filtratiecapaciteit van de nier aangesproken.

3 Het ontstaan van diabetische nefropathie bij patienten met type I diabetes mellitus wordt mede bepaald door de kans op het krijgen van essentiële hypertensie.

4 Bij de behandeling van diabetische nefropathie dient een eiwitbeperkt dieet overwogen te worden.

5 Hyperalimentatie kan de farmacokinetiek van renaal geklaarde medicamenten beïnvloeden. Dosisaanpassing op geleide van serumconcentraties is dan noodzakelijk.

6 Het instellen van een eiwitbeperkt dieet heeft vooral zin bij patienten met proteinurie.

7 Campylobacter pyloridis speelt waarschijnlijk een pathogenetische rol bij gastritis en duodenitis.

8 Als om obduktie wordt gevraagd, dient ook de mogelijkheid van orgaandonatie ter sprake te komen.

9 Binnen de opleiding tot internist dient meer aandacht te worden besteed aan statistiek.

10 Promoveren is een diep(t)e investering.

11 Milieuverontreiniging vertoont overeenkomsten met hypertensie. Beiden zijn "silent killers".

12 Arbeidsduurverkorting voor een arts-assistent is gelijk een fata morgana voor een dorstende in de woestijn.

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Prof. Dr. A.J.M. Donker

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Voor Marieke
en Martijn

CONTENTS

Voorwoord

Ook ik wil niet van de goede gewoonte afwijken om door middel van een voorwoord een aantal personen te bedanken, zonder wie de voltooiing van dit proefschrift nog lang op zich had laten wachten. Prof. dr. A.J.M. Donker is de initiator van dit onderzoek geweest. Met zijn aanstekelijke enthousiasme stuurde en stimuleerde hij dit onderzoek. Daarbij bleek hij een uitstekende mentor te zijn met wie op vrijwel elk ogenblik overleg kon plaatsvinden. Dit alles waardeer ik ten zeerste. Prof. dr. G.K. van der Hem (hoofd van de afdeling Nefrologie van de Interne Kliniek van het Academisch Ziekenhuis Groningen, waarbinnen dit onderzoek werd verricht) ben ik zeer erkentelijk voor de mij geboden mogelijkheden om met dit onderzoek te participeren in de werkgroep Nefrologie. Het deelnemen aan de refereeravonden werd en wordt door mij als zeer stimulerend ervaren.

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Chapter 1

INTRODUCTION

The human body normally contains two kidneys which each contain roughly one million functional units called "nephrons". Such a nephron consists of a ball of very thin blood vessels, the glomerulus, which is attached to an unbranched tubule. The latter drains via a collecting duct, the renal pelvis and the ureter into the bladder. In former times, it was thought that the basic process in urine production consisted of secretion of fluid by the glomerulus [1-3]. Later on, however, it became clear that the basic process was based on a difference in pressure between the glomerulus and the tubule (Bowman's space) resulting in ultrafiltration of fluid through the glomerular capillary wall [4,5]. More recently, the insights in the factors which govern glomerular filtration have been widely deepened.

The determinants of glomerular ultrafiltration

Four main factors determine glomerular ultrafiltration [6-15]. Firstly, the glomerular plasma flow (Q_A). Secondly, the ultrafiltration coefficient (K_f) which is the product of the glomerular surface area and the hydraulic permeability of the glomerular wall. Thirdly, the transcapillary hydrostatic pressure difference (ΔP) which is the difference between the hydrostatic pressure in the glomerular capillary ($\bar{P}_{GC}$) and the hydrostatic pressure at the start-point of the tubule called Bowman's space ($\bar{P}_T$). Fourthly, the oncotic pressure (Π) in the glomerular capillary which counteracts the transcapillary hydrostatic pressure difference. As in Bowman's space the protein concentra-

tion is extremely small [16], the oncotic pressure of the ultrafiltrate can be neglected. With those four factors single nefron glomerular filtration rate (SNGFR) can be calculated using the following equation:

$$SNGFR = K_f \times (\Delta P - \bar{\Pi}) \quad [3]$$

From this equation can be seen that Q_A can affect SNGFR only indirectly by changing $\bar{\Pi}$.

Studies in Munich-Wistar rats, a strain of rats which possesses superficial glomeruli easily accessible for micropunction, have revealed that before the glomerular blood stream reaches the efferent arteriole the oncotic pressure in the glomerular capillary counterforces the transcapillary hydrostatic pressure difference completely and thus, prevents further filtration [6]. This condition is called filtration equilibrium. Further studies have demonstrated that in case of filtration equilibrium the glomerular plasma flow is the main determinant of glomerular ultrafiltration. There even appeared to exist a linear relationship between these variables as long as filtration equilibrium is reached and the oncotic value of arterial plasma does not change [8,9]. It is, however, doubtful whether filtration equilibrium does exist in all species including man since, for instance, it has been demonstrated that in the dog glomerular haemodynamics are characterized by filtration disequilibrium [17]. Nevertheless, other investigators have shown that in case of filtration disequilibrium glomerular plasma flow still remains the most important determinant of the glomerular filtration process [18,19]. Concerning the ultrafiltration coefficient, it was found that this determinant remained constant in a wide range of glomerular plasma flows [10] but will be reduced in case of a fall in glomerular protein concentration (i.e. oncotic pressure) [20,21]. The glomerular hydrostatic pressure declines only slightly along the glomerular capillary [6,7].

Glomerular hyperfiltration

In healthy rats the values for single nephron glomerular filtration rate (SNGFR) are within a narrow range [21]. Interestingly, however, when renal mass is reduced, for instance in chronic pyelonephritis [22], ischaemic injury [11] or renal ablation [12,23,24], the range of values for SNGFR increases and SNGFR may amount to more than twice the value of its upper normal limit [22]. This mainly is achieved by rises in glomerular plasma flow and hydrostatic pressure in the glomerular capillaries due to decreased resistances of afferent and efferent arterioles [12,23]. Thus, a loss of glomeruli is partially compensated for by hyperfiltration of the remnant glomeruli.

One of the most striking events, however, is the fact that if single nephron hyperfiltration is induced by a 5/6 reduction of renal mass, rats progressively develop end-stage renal failure. This course is characterized by massive proteinuria and diffuse glomerulosclerosis [25-28], and made Brenner and co-workers develop the so-called "hyperfiltration theory": once a certain degree of reduction in renal mass has occurred, the compensatory increased glomerular plasma flow and filtration pressure in the remaining glomeruli are harmful to those glomeruli and ultimately cause glomerulosclerosis. Thus, a vicious circle originates which results in a progressively downhill course of renal function and might be a final common pathway for all renal diseases to end-stage renal failure [29-33].

Factors influencing "harmful" hyperfiltration

A reduction in renal mass is often accompanied by hypertension [34,35]. After uninephrectomy an accelerated decrease in renal function has been demonstrated in spontaneously hypertensive rats compared with normotensive animals [36,37]. In rats with 5/6 reduction in renal mass, however, deterioration of renal function occurs even when they are kept normotensive whereas rats with partial infarction of one kidney develop hypertension but show only transient glomerular lesions [26]. These findings are

in accordance with the hypothesis that renal function deteriorates autonomically once a critical amount of renal mass has vanished. In the latter situation glomerular hyperfiltration exists on which a superimposed hypertension will cause an accelerated decrease in renal function, whereas optimal blood pressure control doesnot prevent a further loss in renal function.

A factor which appears to be successful in slowing down the deterioration of renal function is dietary protein restriction. It is well known that high protein intake can cause glomerulosclerosis [38-40]. Likewise, in case of reduced renal mass (e.g. after uninephrectomy), a high protein intake accelerates the loss in renal function [41-46]. On the other hand protein-restricted healthy rats live longer than rats fed a high protein diet [47,48]. In case of reduced renal mass, protein restriction attenuates the loss of renal function [28,49-52]. Initially, Farr and Smadell postulated that a high protein load was harmful, because of a concomitant increased acid load [43,44]. Later on the beneficial effect of protein restriction was attributed to a reduced workload of the kidney because of a reduced necessity to excrete urea [53]. Nowadays explanation yields in a beneficial effect of protein restriction on renal haemodynamics, i.e. in reducing glomerular hyperfiltration. As outlined before, Deen et al. [12] demonstrated that ablation of renal mass resulted in an increased SNGFR based on elevated glomerular pressure and flow. Hostetter et al. [28] showed that in case of subtotal nephrectomy values for SNGFR and glomerular plasma flow after restriction of protein intake were not significantly elevated when compared with control rats whereas the glomerular hydrostatic pressure tended to be lower. Moreover, the glomerular lesions in these rats were considerably less severe when compared with non-protein-restricted animals. These findings support the assumption that protein restriction is protective against deterioration of renal function by preventing glomerular hyperfiltration (or glomerular hypertension) [28].

Does glomerular hyperfiltration exist in man ?

Early protein restriction has been proven to have a favourable effect on the course of chronic renal disease in man [54-59] since an attenuated decline in renal function is observed after protein restriction, although a slight decrease in glomerular filtration rate (GFR) often occurs immediately after the institution of the protein-restricted diet (Table 1). A reduction in dietary protein does reduce proteinuria also in patients with moderate to severe renal insufficiency withhout or with nephrotic syndrome [59-61]. Analogous to observations in animal studies, these observations might indicate that also in man hyperfiltration in remnant glomeruli occurs.

Table 1

		GFR		ERPF	
		LP	HP	LP	HP
PR	mean	42.2	46.9**	181	209*
	SD (±)	20.6	22.3	77	94
C	mean	37.0	35.4	154	146
	SD (±)	25.0	24.4	103	97

*p<0.005; **p<0.001

Effects of low protein diet (LP=30g daily) and high protein diet (HP=90g daily) on GFR and effective renal plasma flow (ERPF; ml/min/1.73 m^2 both) in patients with moderate to severe renal insufficiency. PR = protein-restricted patients (n=18) and C = control patients (n=5). Published with permission of the investigators (Schaap et al. [62]).

However, there are more indications that glomerular hyperfiltration can occur in man. In obese individuals it has been demonstrated that GFR is increased when compared with the GFR of non-obese control subjects [63-65]. Likewise, in patients with acromegaly [66,67] or insulin-dependent diabetes mellitus [68-70] an increased GFR can be found. Most convincing indications that human glomeruli can hyperfiltrate, however, are provided by

studies on renal haemodynamics in pregnant women and kidney donors. During pregnancy an increased GFR exists when compared with the GFR after delivery [71-74]. This rise in GFR during gestation is attributed to renal vasodilatation induced by circulating prostaglandines [75], resulting in an increased effective renal plasma flow (ERPF). ERPF increases even more than GFR and, therefore, causes a fall in the filtration fraction (FF = GFR:ERPF) [73,74]. In kidney donors values for GFR and ERPF amount to roughly 70 per cent of the values prior to kidney donation [76-81]. After a few months values for GFR and ERPF in the recipients may amount to more then 50 per cent of the donor values for GFR and ERPF before kidney donation [79]. These observations indicate that the remnant kidney compensates for the loss of glomeruli by hyperfiltration. As it is unlikely that during pregnancy and after kidney donation the number of glomeruli increases, the observed rise in GFR must be attributed to an increased glomerular ultrafiltration. These observations also indicate that in healthy subjects a reserve in glomerular filtration capacity must be present.

Basic aims of this thesis

Based on the idea of a reserve in glomerular filtration capacity, two basic questions have risen which we shall try to answer in this thesis. Firstly, is it possible to demonstrate a reserve in glomerular filtration capacity in healthy subjects and if so, is it possible to measure the maximal GFR? Secondly, is this reserve in glomerular filtration capacity consumed in case of renal disease before renal function starts to decline and does the absence of reserve in glomerular filtration capacity point to the existence of glomerular hyperfiltration in moderate to severe renal insufficiency? In order to provide answers for these questions, changes of the GFR have been pursued by the infusion of dopamine and/or amino acids.

Dopamine

Dopamine is an endogenous catecholamine which acts on α-adrenergic receptors (vasoconstriction), β-adrenergic receptors (vasodilatation) and specific dopaminergic receptors [82]. The latter receptors are amongst others located in cardiac, coeliac and renal vascular beds. Especially the dopaminergic receptors in the kidney are considered to have an important physiological function in the control of the renal blood flow [83]. Infusion of dopamine at a dose of 1-3 μg/kg/min causes renal vasodilatation [84-86]. The maximal increases in GFR and ERPF are observed at a dopamine infusion rate of 4 μg/kg/min (A.J. Smit; personal communication). At higher doses, β-receptors located in the cardiac tissue also are stimulated, which results in an increased cardiac output. At doses exceeding 20 μg/kg/min, systemic and renal vasoconstriction occurs because of stimulation of α-receptors [84]. Administration of low-dose dopamine causes an increase in cortical blood flow together with a relative shift of flow from outer medulla to cortex [87]. The rise in renal blood flow is accompanied by an increase in GFR and sodium excretion [88,89]. FF falls during dopamine infusion [89,90]. This might be explained by an increased renal blood flow through nephrons with a low FF [91] and/or by a relatively larger increase in ERPF than GFR because of a fall in renal vascular resistance due to vasodilatation of afferent and efferent arterioles [92]. Thus, dopamine is an agent capable to increase GFR and, therefore, might be used to demonstrate the existence or absence of reserve glomerular filtration capacity.

The effects of a low dose dopamine (1.5-2.0 μg/kg/min) on renal haemodynamics of 32 patients with IgA nephropathy, a fairly well defined renal disease, have been investigated. The results of this particular study are discussed in chapter II. In patients with IgA glomerulopathy the above-mentioned effects of dopamine on renal haemodynamics could be demonstrated. Furthermore, it was concluded that GFR could not be improved if baseline GFR amounted to 72 ml/min/1.73 m^2 or less and, therefore, that the infusion of

a low dose of dopamine could be used to demonstrate the existence or absence of renal reserve filtration capacity.

To compare the effects of low-dose dopamine between patients with IgA glomerulopathy and patients with other renal diseases, the investigations have been extended to other renal patients. Furthermore, the effects of dopamine on renal haemodynamics of healthy subjects and healthy individuals after uninephrectomy (due to trauma, kidney donation etc.) have been investigated and compared with the observations in patients with renal diseases. These patients were subdivided in three groups. The first group consisted of patients with an apparently normal GFR, that is a baseline GFR comparable with the baseline GFR of healthy subjects. The second group consisted of patients with moderate renal failure, that is a GFR between 30 and 90 ml/min/1.73 m^2. The third group consisted of patients with a severe impairment of renal function, defined as a baseline GFR <30 ml/min/1.73 m^2. The results of this study are discussed in chapter III.

Protein intake and administration of amino acids

It is well-known that protein intake as well as infusion of amino acids have a marked effect on GFR [93-106]. It seems that this effect on GFR can be subdivided into an effect due to long-term protein intake and into an effect due to acute protein loading. A high daily protein intake is accompanied by a higher value for GFR when compared with the value obtained during a low daily protein intake as, for instance, was demonstrated by Pullman et al. [96]. These investigators found an average difference between high dietary protein intake and low dietary protein intake of 22 ml/min. It has been demonstrated that the increase in GFR during a high protein intake is merely based on an increase in the ultrafiltration coefficient [100,106], which probably can be attributed to an increased glomerular filtration surface area [100], and a decrease in renal vascular resistance. The latter results in a rise in glomerular plasma flow and possibly in an increase in the transcapillary hydrostatic

pressure difference [100,106]. As the ERPF increases proportional to or even less than the GFR, the FF is unaffected or rises slightly during protein loading.

The short-term effect of protein intake on normal glomerular filtration is demonstrated by a diurnal variation in GFR which is related to the food intake [95,102] and can be induced by a meat meal or by infusion of amino acids [97-104]. Several authors have found that the increase in GFR thus obtained is probably independent of baseline GFR [94,105,107] although Bosch et al. [102] showed that after a protein load GFR increases more during a low protein diet than during a high protein diet. It is likely that the factors mentioned above also contribute to the rise in GFR during short-term protein loading. However, it might be that changes in glomerular plasma flow are less important since Zager et al. [108] demonstrated in rats that renal blood flow, measured with flow probes, did not alter significantly after the infusion of amino acids. The latter indicates that changes in GFR after short-term protein loading or amino acid infusion mainly seem to be based on an increased ultrafiltration coefficient and/or a rise in glomerular hydrostatic pressure difference.

Until now it is not clear what induces the rise in GFR during protein loading. A very interesting hypothesis was postulated by Alvestrand and Bergström [109]. They proposed the theory that the increase in GFR observed after a protein gift or infusion of amino acids is induced by a factor (hormone) called "glomerulopressin", synthesized in the liver. This factor was first found in the toad by Uranga [110-112]. and, later on, could be demonstrated in the rat, the rabbit and the dog [113-115]. It has been excluded that this factor is glucagon since infusion of glucagon into the renal artery of dogs does not change GFR whereas plasma derived from the hepatic vein after infusion of glucagon into the portal vein, results in a significant increase in GFR [116,117]. This also indicates that glucagon might be a mediator to release glomerulopressin. It is thought that glomerulopressin induces afferent vasodilatation and thus increases the transcapillary pressure difference [118], although

effects on the ultrafiltration coefficient are not excluded. So far, only indirect evidence has been provided that glomerulopressin also may exist in man: in patients with liver cirrhosis a protein gift does not increase GFR [119].

Bosch et al. [102] and Hostetter [120] have demonstrated that a meat meal can be used to test renal reserve filtration capacity. Infusion of amino acids and a meat meal do increase GFR to the same extent [121]. In this thesis we have used the infusion of an amino acid solution (Vamin^{R}N; KabiVitrum, Limoges, France) to demonstrate the existence or absence of reserve filtration capacity. Investigations were performed in healthy subjects, in healthy individuals after uninephrectomy and in patients with renal disease, who were subdivided as outlined above. The results of this study are discussed in chapter IV.

As mentioned before, dopamine infusion results in a fall in FF. However, infusion of amino acids does not affect or even increases FF. These observations indicate that dopamine and amino acids exert their effect on GFR in different ways. Therefore, the effects of a combined infusion of dopamine and amino acids on renal haemodynamics were studied to investigate in what way these agents interact. The results of this particular study are discussed in chapter V.

Diabetes mellitus

Approximately 40 per cent of all patients with Type I (insulin-dependent) diabetes mellitus develop renal failure due to diabetic nephropathy [122-127]. Proteinuria and hypertension frequently are the first signs of an existing diabetic nephropathy. Once clinical proteinuria occurs, the average period until end-stage renal failure has developed amounts to five years [128]. Optimal blood glucose control cannot prevent this [129]. Prolonged hyperfiltration and microalbuminuria, the latter probably partially the result of hyperfiltration, usually are considered to be provoking factors in the development of diabetic nephropathy [130,131], whereas inadequate blood pressure control

will accelerate the progression of diabetic nephropathy to end-stage renal failure [132].

An increased GFR can be found in Type I diabetic patients despite good metabolic control [70,133-135]. Poor metabolic control even results in a further increase in GFR [68,69] in which hyperglycaemia [136,137], elevated glucagon levels [138], the postulated "glomerulopressin" [109] and other factors may be involved. In rat studies it has been demonstrated that the increased GFR during moderate hyperglycaemia is mainly based on a rise in glomerular hydrostatic pressure and plasma flow because of a predominantly afferent vasodilatation [106,139]. As the glomerular filtration rate increases more than the glomerular plasma flow, FF rises. In diabetic patients an increase in GFR and FF can be found also [68,135]. Furthermore, it has been demonstrated that in diabetes mellitus an increased glomerular surface area can exist [140,141] which possibly affects GFR by means of an increased ultrafiltration coefficient. However, this observation cannot completely account for the elevated GFR since optimal metabolic control decreases GFR, while the glomerular surface area remains the same [141]. Another factor which might be involved in the supernormal GFR is a general fall in renal vascular resistance. The latter has proven to occur when kidney size increases [142] and results in a rise in glomerular plasma flow. A change in extracellular volume has been excluded by Brøchner-Mortensen et al. [143]. These investigators have found that in diabetes mellitus the extracellular volume is not elevated and, therefore, that the supernormal GFR reflects a real hyperfiltration. Thus, several factors have been implicated to explain the rise in GFR in Type I diabetic patients, which is thought to initiate diabetic nephropathy [144].

To investigate whether the supernormal GFR in well-controlled Type I diabetic patients leads to a loss of reserve filtration capacity, we firstly have studied the effect of low-dose dopamine on renal haemodynamics of patients with well-regulated short-term diabetes mellitus. The results are given in chapter VI. However, as in diabetes mellitus the FF is unaffected or increased, a

phenomenon that also can be found after protein or amino acid loading, it might be that mechanisms through which amino acids or protein affect GFR are involved in the supernormal GFR of Type I diabetic patients. Therefore, the effects of amino acids on renal haemodynamics in Type I diabetic patients were studied and compared with the effects of dopamine, infused separately as well as combined with amino acids, on renal haemodynamics of diabetic patients. The results of the latter study are discussed in chapter VII.

Methods

A standard procedure which consists of a combination of the standard method and the constant infusion method was used to determine GFR and ERPF simultaneously [145]. The GFR was measured with ^{125}I-iothalamate which has proven to be a satisfactory substitute for inulin [134]. ^{131}I-hippurate was used to measure the ERPF. The clearances of ^{131}I-hippurate and p-aminohippurate are both representative of the ERPF as long as the difference in extraction is taken into account [146]. The radiopharmaceuticals were infused at a constant rate after a priming dose was given. After an equilibration period of one and a half hour, two 2-hour clearances were determined, each calculated from the 2-hour urinary tracers excretion and the mean serum tracer values of three blood samples drawn at the beginning, midway and the end of each period using the formula UxV/120xP (U=urine counts, V=urine volume, P=plasma counts). The coefficient of variation of the day to day determinations for the GFR amounts to $\leq$2.2 per cent and for the ERPF to $\leq$5.0 per cent [145]. The measurements were carried out in supine position, but the subjects were allowed to void in upright position, if necessary. A diuresis of at least 100 ml per hour was procured by oral administration of fluids.

If the effects of low-dose dopamine on renal haemodynamics had to be investigated, the standard procedure was prolonged for another 2-hour period during which dopamine was infused at a dose

of 1.5-2.0 μg/kg/min. The values for GFR and ERPF thus obtained were compared with the values for GFR and ERPF of the preceding 2-hour period.

The effects of amino acids were studied as follows. On day one, a standard procedure was carried out to determine baseline GFR and ERPF. On day two, the infusion of a 7 per cent amino acid solution (Vamin^{R}N) was started at 6.00 p.m. at a rate of 83 ml/hr. This is equal to the amount used by von Graf et al. who infused a 10 per cent amino acid solution at a rate of 60 ml/hr [101]. On day three, the above-mentioned procedure including the dopamine infusion was repeated while the amino acid infusion was continued.

As outlined before, FF is defined as the ratio GFR:ERPF. The normal values for FF in our laboratory vary between 0.22 and 0.28.

A common mercury sphygmomanometer was used to measure blood pressure. Mean arterial pressure was calculated by adding one third of the pulse pressure to the diastolic pressure. Blood pressure and heart rate were measured every 15 minutes during the last two hours of the standard procedure and during dopamine infusion.

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Chapter 2

EFFECT OF LOW-DOSE DOPAMINE ON EFFECTIVE RENAL PLASMA FLOW AND GLOMERULAR FILTRATION RATE IN 32 PATIENTS WITH IGA GLOMERULOPATHY

Abstract

Low doses of dopamine are known to increase renal blood flow without influencing heart rate or systemic blood pressure. Indeed this effect was observed in 32 patients with IgA glomerulopathy. A concomitant increase in glomerular filtration rate (GFR), however, was only observed in patients with a baseline GFR ≥73 ml/min/1.73 m^2. Moreover, the change in GFR during dopamine infusion increased with increasing baseline GFR. We conclude that in IgA glomerulopathy nephron loss is compensated for by a progressive utilization of the kidney's functional reserve capacity which seems to be exhausted when compensated GFR falls below 73 ml/min/1.73 m^2.

Introduction

After uninephrectomy in healthy individuals, the glomerular filtration rate (GFR) amounts to roughly 70% of the original value [1,2]. The increase in GFR in the remaining kidney is a result of vasodilatation in the spared organ [1,3]. One can wonder whether in renal diseases with affected and/or hyalinized glomeruli such an adaptation is present before GFR falls.

One of the agents that can increase renal blood flow is dopamine [4,5]. At a low dose, dopamine does not influence heart rate and/or systemic blood pressure [6].

In this study we infused a low dose of dopamine in patients with primary IgA glomerulopathy with or without impaired GFR during a simultaneous measurement of the effective renal plasma flow (ERPF) and GFR. The results support the idea that if GFR in

renal disease is substantially impaired, normally no significant reserve in GFR is present anymore.

Patients and methods

32 Patients (24 men and 8 women; median age 35, range 19-70 years) with primary IgA glomerulopathy have been investigated. The diagnosis was based on a renal biopsy specimen on which immunofluorescence studies had been performed. Patients with Henoch-Schonlein purpura, systemic lupus erythematosus, and cirrhosis of the liver were excluded [7]. Patients used neither diuretics nor antihypertensive drugs.

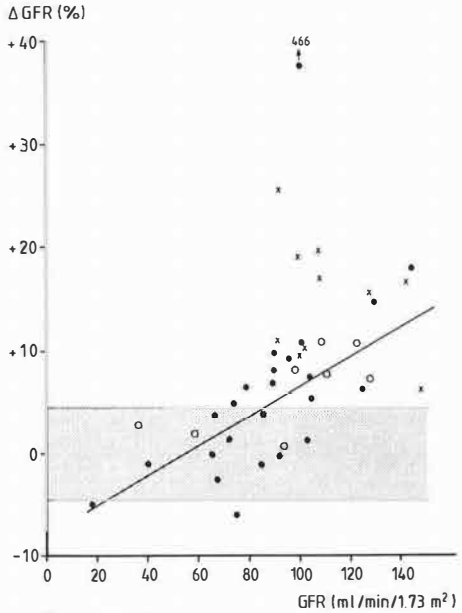
All patients gave verbal consent to the infusion of dopamine during a routine measurement of the GFR and ERPF. The study had been approved by the medical ethics committee.

Supine GFR and ERPF were measured simultaneously with ^{125}I-iothalamate and ^{131}I-hippurate, respectively, according to a method previously described [8]. During the procedure a diuresis >100 ml/hr is maintained by oral administration of fluids. The coefficients of variation are ≤2.2% and ≤5.0%, respectively.

At the end of the standard procedure, dopamine was infused at a dose of 1.5-2.0 μg/kg/min for two hour (Braun Unita II pump). GFR and ERPF during these two hour were compared with the GFR and ERPF just before the infusion (also measured over a 2-hour period). Before and during the administration of dopamine, heart rate and blood pressure were recorded at intervals of 15 min during four hour.

The mean arterial pressure was calculated by adding one third of the pulse pressure to the diastolic pressure. Filtration fraction (FF) was defined as the ratio GFR:ERPF. The normal value of the FF in our laboratory varies between 0.22 and 0.28.

For statistical analysis Wilcoxon's tests on paired and unpaired samples were used. Deming's method was used to evaluate linear regressions [9].



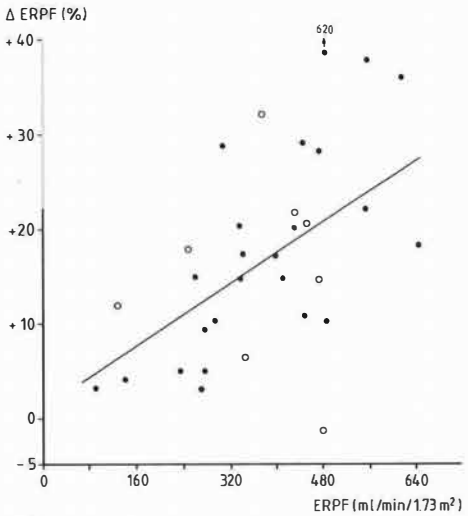


Figure 1 Figure 2

The relation between percentage increase (Δ) in GFR during dopamine infusion and baseline GFR is depicted in figure 1. The shadowed area depicts the 95% confidence limits of the GFR determination. o = women and ● = men with IgA glomerulopathy. x = healthy subjects. Figure 2 shows the relation between percentage increase in ERPF during dopamine infusion and baseline ERPF.

Results

During infusion of the low dose of dopamine, median heart rate (72 versus 78 beats/min) and median mean arterial pressure (101 versus 100 mmHg) did not change significantly. Diuresis before dopamine ranged from 155 to 729 ml/2hr (median 347 ml/2hr) and during dopamine infusion from 129 to 690 ml/2hr (median 389 ml/2hr). The difference was not significant.

Dopamine caused a change in natriuresis of -40 up to +140% of the preceding values. Although the median sodium excretion only increased from 30.1 to 34.6 mmol/2hr, the increase for all patients was statistically significant ($0.01<2\alpha<0.02$).

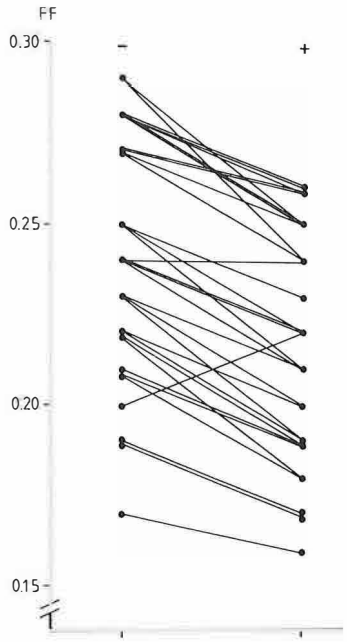


Figure 3
FF before (-) and during (+) dopamine infusion.

During dopamine infusion GFR increased from -6.0 to 47%, and ERPF from -1 to +62%. After elimination of one patient on Chauvenet's criterion, the change in GFR ranged from -6 to +18%, and the change in ERPF from -1 to +39%. The relative changes in GFR and ERPF tended to increase with increasing baseline values ($r = 0.74$ and 0.55, respectively; figures 1 and 2). FF fell in 30 patients (figure 3). When looking at individual patients, GFR did only increase beyond the 95% confidence limits of the baseline value if GFR exceeded 72 ml/min/1.73 m^2. Significant increases in GFR occurred in 18 out of 24 patients with a baseline GFR $\geq$73 ml/min/1.73 m^2, and in 0 out of 8 patients with a baseline GFR <73 ml/min/1.73 m^2 (Fischer exact, $p=0.0003$, one tailed).

The absolute change in GFR (ΔGFR) appeared to be positively related to the absolute change (Δ) in ERPF ($\Delta GFR = 2.763 + 0.127 \times \Delta ERPF$ ml/min; $r = 0.89$, $p<0.001$).

Finally, 10 out of 12 patients with a ΔGFR 8 ml/min did not have proteinuria. However, 13 patients with a ΔGFR <8 ml/min

revealed a urinary protein loss of ≥1.0 g/24hr ($p<0.02$). No relationship could be established between the degree of baseline proteinuria and ΔGFR.

Discussion

It has been postulated, on the basis of micropuncture studies in the rat, that single-nephron GFR only depends on pressure ($\bar{P}_{GC}$) in and flow (Q_A) through the glomerular capillaries, provided that oncotic pressure of the peripheral plasma, hydraulic permeability of the glomerular basement membrane, and hydrostatic pressure in Bowman's space (P_T) remain constant [10]. As long as filtration pressure equilibrium is attained, single-nephron GFR is directly proportional to Q_A and single-nephron FF is constant [11]. However, if Q_A is disproportionally increased and filtration equilibrium is not reached, single-nephron FF falls [12].

Dopamine receptors are among others located in cardiac, coeliac, mesenteric and renal vascular beds. The latter site is considered to have particular physiological importance in the control of renal blood flow [13]. In the dog it has been shown that dopamine administration is associated with an increase in both outer and inner cortical blood flow. Moreover, a relative shift in blood flow from the outer two thirds to the inner one third of the cortex was established. This change in fractional distribution of blood flow occurred in dogs receiving intravenously administered dopamine and in kidneys of dogs receiving the agent directly into the renal artery [14].

We observed in patients with IgA glomerulopathy and a GFR ≥73 ml/min/1.73 m^2 that GFR increased and that FF fell during the infusion of a low dose of dopamine. The higher the baseline GFR, the greater the increase in GFR (and ERPF) on dopamine. This can be explained by an increase in blood flow to deeper nephrons with a low FF [15] or by a disproportional increase in Q_A. Only a substantial increase in Q_A will be associated by both a rise in single-nephron GFR and a fall in single-nephron FF, although a

concomitant, dopamine-induced change in $\bar{P}_{GC}$, P_T, and/or ultrafiltration coefficient cannot be excluded and even seems likely if in human glomeruli normally a filtration pressure equilibrium is not reached. Interestingly, patients with a baseline GFR <73 ml/min/1.73 m^2 did not show a substantial change in GFR during dopamine infusion, although their FF also fell. Regression analysis revealed that ΔGFR was strongly correlated with ΔERPF ($r=0.89$; $p<0.001$) and that an increase in ERPF up to 22 ml/min was not associated with a positive change in GFR. This implies that in IgA patients with a severely impaired renal function ERPF can increase during dopamine without a change in GFR.

From our findings one can speculate that in patients with IgA glomerulopathy and an apparently normal GFR, to some extent an adaptation is present. It might be that in these patients blood flow to (outer and inner) nephrons already is increased with consequently a lesser effect of dopamine on ERPF and especially on GFR. IgA patients with an impaired GFR have once more lesser possibilities to increase their ERPF, while their GFR already is maximal.

Our results show parallels with the physiological increase in GFR during pregnancy, a phenomenon also explained by renal vasodilatation [16]. It is especially observed if renal function is within normal ranges [17]. In women with a renal homograft, only half of the individuals show an increase in creatinine clearance during gestation [18].

Recently, comparable observations have been made by Bosch et al. [19]. Normal subjects showed an increase in GFR 2.5 hr after a protein load. In patients with a reduced number of nephrons, the renal functional reserve appeared to be diminished or absent. Another recent and supplemental study of Hostetter [20] describes an increase of both GFR and ERPF in normal individuals after a meat meal. The increase in GFR was only observed if the baseline GFR amounted to 80 ml/min or more!

Renal adaptations to the loss of nephrons include hypertrophy, hyperplasia, and a resetting of tubular and regulatory functions [21-23]. An additional mechanism seems to be

an utilization of the reserve filtration capacity as suggested by our results in IgA glomerulopathy. In normal man (n=9) we found a mean relative increase in GFR of 12 ± 1.1% during infusion of 1.5-2.0 μg/kg/min dopamine. In normal individuals after uninephrectomy and in patients with other kidney diseases, a lesser or no effect of the drug was observed (chapter 3).

In conclusion, our results with dopamine in patients with primary IgA glomerulopathy are well in accordance with the view that a decline in GFR implies a progressive use of the reserve filtration capacity which ultimately might result in a constant state of glomerular hyperfiltration [24,25] and proteinuria [26]. Thus, an impaired GFR usually means more than a partial decrease of "normal" GFR.

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Chapter 3

THE EFFECT OF INTRAVENOUS INFUSION OF A LOW-DOSE DOPAMINE ON RENAL FUNCTION IN NORMAL INDIVIDUALS AND IN PATIENTS WITH RENAL DISEASE

Abstract

A low-dose dopamine was infused in 28 normal volunteers and in 137 patients with varying degrees of renal insufficiency during a routine measurement of the effective renal plasma flow (ERPF) and the glomerular filtration rate (GFR). Dopamine infusion led to an increase in the ERPF and the GFR, and to a fall in the filtration fraction. The effect of dopamine on renal function was most pronounced if baseline GFR was normal. However, healthy individuals showed greater increases in both ERPF and GFR than renal patients with a comparable baseline GFR. In renal patients no effect of dopamine was observed if baseline GFR was below 50 ml/min/1.73 m^2. It is concluded that early in renal disease a loss of nephrons is compensated for. If GFR is less than 50 ml/min/1.73 m^2, renal reserve filtration capacity seems to be exhausted.

Introduction

Recently it was shown in patients with IgA glomerulopathy that intravenous infusion of low-dose dopamine (1.5-2.0 μg/kg/min) increases GFR significantly, provided that baseline GFR is $\geq$73 ml/min/1.73 m^2 [1]. A comparable finding has been reported by Hostetter, who showed that after a meat meal GFR increases unless baseline GFR is <80 ml/min [2]. A meat meal even has been recommended to measure the "renal reserve filtration capacity" or alternatively, the existence of so-called hyperfiltration [3].

The precise effect of a fixed low-dose dopamine on renal function of normal individuals and patients with various renal

diseases has not been established. For this reason we undertook such a study and analyzed the results obtained in healthy volunteers, in healthy individuals after uninephrectomy, and in patients with renal diseases and varying degrees of renal insufficiency. The results in healthy individuals moreover, were compared with the results in patients with IgA glomerulopathy and an apparently normal renal function.

Patients and methods

One hundred and sixty five persons, subdivided in five groups, have been investigated. Group I consisted of 28 healthy volunteers with a baseline GFR ≥90 ml/min/1.73 m^2. Group II consisted of 40 renal patients (including 19 patients with IgA glomerulopathy) with a GFR ≥90 ml/min/1.73 m^2. Group III consisted of 14 healthy individuals who had lost one kidney (kidney donation; trauma). Groups IV and V finally, consisted of renal patients with a baseline GFR between 30 and 90 (n=58; 17 with IgA glomerulopathy) and <30 ml/min/1.73 m^2 (n=25; one with IgA glomerulopathy), respectively.

All individuals gave verbal consent to the study that included an infusion of a low dose of dopamine. The study protocol had been approved by the local medical ethics committee.

Supine GFR and ERPF were measured simultaneously with ^{125}I-thalamate and ^{131}I-hippurate, respectively. The radiopharmaceuticals were infused at a constant rate after a priming dose was given. Three hours after the priming dose, 2-hour clearances were determined using for each clearance calculation the 2-hour urinary excretion of the involved tracer and the mean serum value of this tracer in three blood samples drawn at the start, midway and end of the two hours. At the end of this standard procedure, dopamine was infused at a dose of 1.5-2.0 μg/kg/min for two hours. GFR and ERPF during these two hours were compared with the preceding GFR and ERPF just before infusion. The coefficients of variation of the GFR and ERPF determinations amount to ≤2.2 and

≤5.0 per cent, respectively [4]. Filtration fraction was defined as the ratio GFR:ERPF (normal value in our laboratory 0.22-0.28).

Before and during the administration of dopamine, heart rate (HR) and blood pressure were recorded at intervals of 15 minutes during four hours. Mean arterial presure (MAP) was calculated by adding one third of the pulse pressure to the diastolic blood pressure.

Statistical analysis was performed on median values since most of the results were not normally distributed. Wilcoxon's tests on paired and unpaired samples were used. Linear regression analysis was performed to study correlations [5]. A probability level of 5% was chosen as level of significance.

Table 1

Group	n	BL GFR	ΔGFR ml/min	ΔGFR %	BL ERPF	ΔERPF ml/min	ΔERPF %	ΔFF %
I	28	109	11**	12.5	443	161**	35.0	-16.5**
II	40	108	8**	7.5	450	96**	20.5	-11.3**
III	14	76	6*	8.0	308	68*	21.5	-10.0*
IV	58	67	2**	4.1	281	32**	13.0	-6.9**
V	25	15	0	0	66	2	4.0	0

*p<0.01; **p<0.0001

The effect of dopamine on baseline (BL) GFR (ml/min/1.73 m²), baseline ERPF (ml/min/1.73 m²) and change in (Δ) FF. For group explanation see text.

Results

Median baseline GFR in group I (109 ml/min/1.73 m²; range 90-145) was not statistically different from median baseline GFR in group II (108 ml/min/1.73 m²; range 90-143), but differed from median baseline GFR in group III (76 ml/min/1.73 m²; range 38-96), group IV (67 ml/min/1.73 m²; range 30-89) and group V (15 ml/min/1.73 m²; range 1-28) p<0.001 each). Median baseline GFR in group III was lower than median baseline GFR in group II (p<0.001), not different from that in group IV and higher than that in group V (p<0.001). Similar comparisons hold true for

median baseline ERPF, values being 443 (range 327-679), 450 (range 299-873), 308 (range 178-437), 281 (range 128-690) and 66 (range 1-261) ml/min/1.73 m^2, respectively (Table 1). FF in group I was 0.25 and in group II 0.23 (n.s.).

Infusion of low-dose dopamine caused statistically significant increases of both GFR and ERPF in groups I, II, III and IV, while no changes were observed in group V (see Table 1). The rise in GFR was highest in group I and trivial in group IV. The percentage increases of GFR and ERPF were significantly higher in group I when compared with group II (see Table 2 and 3). The difference in percentage increase in GFR of groups I and III did not reach statistical significance, whereas the difference in percentage increase in ERPF did. FF decreased significantly in groups I-IV, while no change was seen in group V (Table 1).

Table 2

Group	I	II	III	IV	V
I	-	p<0.03	ns	p<0.0001	p<0.0001
II	p<0.03	-	ns	ns	p<0.02
III	ns	ns	-	ns	p<0.03
IV	p<0.0001	ns	ns	-	ns
V	p<0.0001	p<0.02	p<0.03	ns	-

Cross table of significance levels of differences in percentage change in GFR (see also Table 1).

Table 3

Group	I	II	III	IV	V
I	-	p<0.001	p<0.01	$p<10^{-7}$	$p<10^{-8}$
II	p<0.001	-	ns	p<0.01	$p<10^{-5}$
III	p<0.01	ns	-	p<0.05	p<0.002
IV	$p<10^{-7}$	p<0.01	p<0.05	-	p<0.01
V	$p<10^{-8}$	$p<10^{-5}$	p<0.002	p<0.01	-

Cross table of significance levels of differences in percentage change in ERPF (see also Table 1).

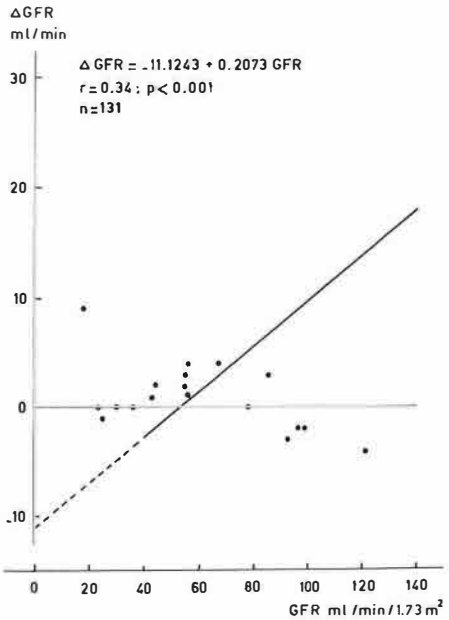

Figure 1
The relation between baseline GFR and the dopamine-induced change (Δ) in GFR (n=131). Dots depict the dopamine-induced changes in GFR of the 18 persons with full-blown nephrotic syndrome.

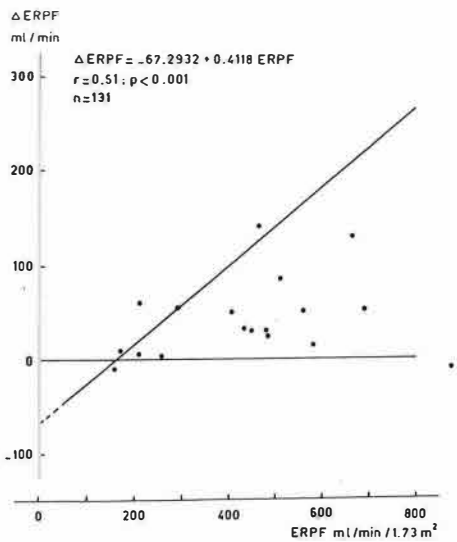

Figure 2
The relation between baseline ERPF and the dopamine-induced change (Δ) in ERPF. Dots depict the dopamine-induced changes in ERPF of the 18 persons with full-blown nephrotic syndrome.

After subdividing group II (n=40) in patients with IgA glomerulopathy (n=19) and patients with other kidney diseases (chronic glomerulonephritis n=6, interstitial nephritis n=4, nephrosclerosis n=4, polycystic kidney disease n=3, diabetic glomerulopathy n=2, and kidney graft n=2), dopamine-induced changes in renal hemodynamics were compared again with the control group (=I). Neither in the patients with IgA glomerulopathy nor in the patients with other renal diseases, median baseline GFR, ERPF or FF differed significantly from group I (healthy volunteers). The percentage increase in ERPF of group I (35.0%) was higher when compared with the percentage rise in ERPF of both the subgroup with IgA glomerulopathy (22.0%; $p<0.02$) and the subgroup with other renal diseases (18%; $p<0.01$). The percentage increase in GFR was also higher in group I (12.5%) when compared with both the subgroup with IgA glomerulopathy (8.4%) and the subgroup with other renal diseases (2.6%; $p<0.02$ each). Finally no differences between the subgroup with IgA glomerulopathy and the subgroup with other renal diseases could be established in respect to their reaction on exogenous dopamine.

To investigate if there existed a relationship between the dopamine-induced change in GFR and the baseline GFR, all subjects were arranged in eleven groups based on their baseline GFR. The results are shown in Table 4 from which it can be seen that a persistent increase in GFR was present if baseline GFR was 71 ml/min/1.73 m^2 or more, that a persistent increase in ERPF was present if baseline GFR mounted to 51 ml/min/1.73 m^2 or more and lastly, that the (percentage) rise in GFR (and ERPF) during dopamine infusion increased with rising baseline GFR.

Regression analysis, after excluding 34 patients with a baseline GFR $\leq$40 ml/min/1.73 m^2, revealed a relation between the absolute change in GFR and baseline GFR ($\Delta GFR = -11.1243 + 0.2073 \times GFR$ ml/min; $r = 0.34$; $p<0.001$; figure 1). The absolute change in ERPF was related to baseline ERPF ($\Delta ERPF = -67.2932 + 0.4118 \times ERPF$ ml/min; $r = 0.51$; $p<0.001$; figure 2). Finally, there

Table 4

GFR ml/min/1.73 m^2	n	Baseline GFR ml/min/1.73 m^2	ΔGFR ml/min	ΔGFR%	Baseline ERPF ml/min/1.73 m^2	ΔERPF ml/min	ΔERPF%	ΔFF%
1-10	10	7	0	0	22	0	0	0
11-20	10	18	1	5.5	122	6	6.5	-2.5
21-30	7	25	0	0	143	6	3.0	-6.8*
31-40	7	37	1	2.8	153	5	4.0	-3.8
41-50	8	46	2	3.0	206	25	6.5	-2.5
51-60	11	56	3**	5.0	263	39**	16.8	-8.7*
61-70	11	67	2	3.0	276	36*	11.0	-5.0*
71-80	15	75	5*	5.8	300	76***	22.0	-11.0***
81-90	21	87	6***	7.0	355	75****	19.8	-9.0***
91-100	18	97	10**	9.5	415	102***	23.0	-12.5***
101-145	47	116	10****	8.0	487	135****	27.9	-14.4****

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$

Effect of dopamine on baseline GFR, baseline ERPF, and FF after subdividing all investigated persons (n=165) according to their baseline GFR (median values)

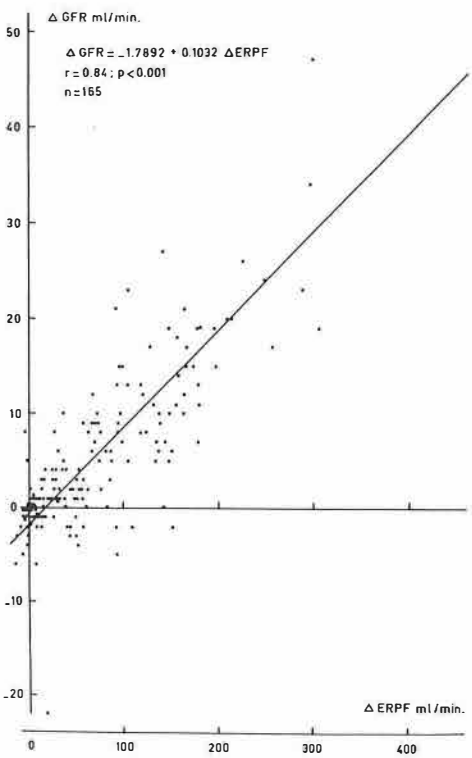

Figure 3
The relation between the dopamine-induced changes (Δ) in GFR and ERPF.

appeared to exist a strong relation between the absolute change in GFR and the absolute changes in ERPF ($\Delta GFR = -1.7892 + 0.1032 \times \Delta ERPF$ ml/min; $r = 0.84$; $n = 165$; $p<0.001$; figure 3).

The effects of low-dose dopamine on median HR, MAP, urine volume and sodium excretion are given in Table 5.

After excluding patients with the diagnosis of "nephrotic syndrome" (protein excretion ≥3.5 g/24hr; n=18), the median protein excretion in groups IV (1.7 g/24hr) and V (1.3 g/24hr) appeared to be significantly higher ($p<0.001$) when compared with the median protein excretions in groups I (0 g/24hr), II (0.05 g/24hr) and III (0 g/24hr).

Discussion

Subpharmacological doses (1-3 μg/kg/min) of dopamine, an endogenous catecholamine, interact with specific dopaminergic

Table 5

	HR	MAP	U vol	Na
	beats/min	mm Hg	ml/2hr	mmol/2hr
Baseline	72	100	309	18.4
Plus dopamine	76	97	340	19.0
Significance	n.s.	p<0.01	p<0.001	p<0.001

Influence of dopamine on HR, MAP, urine volume (U vol), and sodium excretion (Na) in the combined group (n=165; medians).

intrarenal receptors to reduce renal vascular resistance and improve renal cortical vasculature [6]. The dopamine-induced increase in renal blood flow can be accompanied by a rise in GFR and urinary output [7]. At higher doses the agent also stimulates β-adrenergic cardiac receptors, which increase the cardiac output. At doses in excess of 20 μg/kg/min however, α-receptors are stimulated, causing systemic vasoconstriction and a reversal of the vasodilatation of the renal vessels achieved at low levels [8].

In a recent study on the effect of low-dose dopamine (1.5-2.0 μg/kg/min) on renal function of patients with IgA glomerulopathy, we found that GFR only increased significantly if baseline GFR exceeded 72 ml/min/1.73 m^2 [1]. The present study extends those previous observations. The dopamine-induced increases in GFR and ERPF depended on the baseline values of these variables also in patients with other renal diseases. The largest increases were found in healthy volunteers. Their increases in renal function during dopamine infusion were significantly higher when compared with IgA patients and a comparable baseline GFR or patients with other renal diseases and a baseline GFR $\geq$90 ml/min/1.73 m^2. Thus, already early in renal disease (for instance IgA glomerulopathy), a loss of nephrons seems to be compensated for, maintaining GFR in the normal range. The significantly higher proteinuria established in the groups IV and V might fit in with the progress

of such compensation when renal function deteriorates and thus fit in with the so-called hyperfiltration hypothesis [9].

The correlation coefficients between ΔGFR and baseline GFR, and ΔERPF and baseline ERPF, although significant, are not high. This might be due to the fact that the patients with renal disease made up a very inhomogeneous group which contained among others 18 persons with a full-blown nephrotic syndrome (median protein loss 11.5 g/24 h). The latter patients in general are characterized by an increased ERPF and a strikingly low FF [10]. In our patients with a full-blown nephrotic syndrome (median baseline FF 0.13), ERPF still could be increased a little with dopamine but despite this, GFR did not change (see dots in figures 1 and 2). So, in most nephrotic patients GFR seems to be maximal already.

As shown in figure 3, ΔGFR was strongly correlated with ΔERPF suggesting that also in man filtration dynamics are plasma flow dependent. However, concomitant dopamine-induced changes in glomerular capillary pressure and/or ultrafiltration coefficient are not excluded [1].

From the data of Hostetter [2], it can be noticed that a meat meal increases GFR more than ERPF. This implies that after a meat meal FF rises, which contrasts with the fall in FF (together with an increase in GFR) during infusion of a low dose of dopamine. We recently found that infusion of amino acids increased GFR, whereas FF rose or was not affected [11]. These findings strongly suggest that a meat meal (or infusion of amino acids) and the administration of a low dose of dopamine increase filtration in different ways, for instance by predominantly an increase in net ultrafiltration pressure and an increase in glomerular plasma flow, respectively. Thus, neither dopamine infusion nor a meat meal (or amino acid infusion) seem to be the measure to determine maximal renal function, casu quo the reserve filtration capacity. A study on the effect of a combined infusion of amino acids and dopamine on baseline renal function therefore, is warranted.

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Chapter 4

TESTING RENAL RESERVE FILTRATION CAPACITY WITH AN AMINO ACID SOLUTION

Abstract

In healthy individuals and in patients with varying degrees of impaired renal function, glomerular filtration rate and effective renal plasma flow were measured before and during the infusion of an amino acid solution (Vamin^{R}N). Glomerular filtration rate increased during amino acid infusion in healhty individuals while the filtration fraction remained constant. However, in patients with an impaired renal function no significant changes in glomerular filtration rate were observed. The filtration fraction increased slightly. We conclude that amino acid infusion can increase glomerular filtration rate, possibly by utilization of "dormant cortical nephrons" together with a rise in net ultrafiltration pressure of other filtrating glomeruli, both due to afferent vasodilatation. Thus, amino acid administration can be used to test the presence of reserve filtration capacity.

Introduction

After kidney donation healthy donors appear to have a glomerular filtration rate (GFR) that amounts to roughly 70% of the value before uninephrectomy [1,2]. This indicates a "dormant filtration capacity" in healthy individuals. Recently, a meat meal was recommended to measure this so-called "functional renal reserve" [3].

Unless renal function is substantially impaired [3,4], an increase in GFR can be achieved by both a protein-rich diet [5-7] and intravenous infusion of amino acids [8-10]. In this study we have measured both the GFR and the effective renal plasma flow

(ERPF) during the infusion of the amino acid solution Vamin^{R}N. In order to elucidate the mechanism by which amino acids influence the GFR, studies were performed before and during Vamin^{R}N infusion in healthy volunteers, in healthy individuals after uninephrectomy and in patients with varying degrees of impaired renal function. The presented results will show that GFR indeed increased, provided that renal function was not severely impaired. We suggest that in moderate to severe renal insufficiency no significant reserve in filtration capacity is present.

Patients and methods

Three groups of individuals were investigated. Group I consisted of 20 healthy individuals subdivided in 10 healthy volunteers (Ia) and 10 healthy uninephrectomized persons (Ib). Group II consisted of 31 patients with renal disease without or with impaired renal function. This group was subdivided into 9 patients with a baseline GFR ≥90 ml/min/1.73 m^2 (IIa), 14 patients with a baseline GFR between 90 and 30 ml/min/1.73 m^2 (IIb), and 8 patients with a baseline GFR <30 ml/min/1.73 m^2. Finally, group III consisted of 5 healthy volunteers in whom the short-term effect of mannitol on renal haemodynamics was studied.

All patients gave verbal consent to the study including the infusion of Vamin^{R}N. The study protocol had been approved by the local medical ethics committee.

Supine GFR and ERPF were measured simultaneously with ^{125}I-iothalamate and ^{131}I-hippurate, respectively, according to a method previously described [11]. After a priming dose, the radiopharmaceuticals were infused simultaneously at a constant rate (Braun Unita II pump). After an equilibration period of 1.5 hr, two 2-hour clearances were determined using the formula UxV/120xP. During the procedure a diuresis of at least 100 ml/hr is maintained by oral administration of fluids (150 ml/hr). The coefficients of variation of the day to day determinations are ≤2.2% for the GFR and ≤5.0% for the ERPF [11].

On two separate days GFR and ERPF were measured in groups I and II. On day one, baseline values were achieved. At 6.00 p.m. on day two, the infusion of Vamin^{R}N was started (500 ml/6hr). GFR and ERPF were measured again on day three while Vamin^{R}N infusion was maintained at a rate of 500 ml/6hr. The supplemental sodium load by Vamin^{R}N was 85 mmol.

In five healthy volunteers (group III) 250 ml mannitol 20% was infused in approximately 5 min immediately after the determination of baseline GFR and ERPF on day one. GFR and ERPF after mannitol infusion were measured for two 1-hour periods and compared with the baseline values. This part of the study was performed to exclude effects of Vamin^{R}N on GFR and ERPF due to its hyperosmolality (700 mosm/kg H_2O).

Blood pressure and heart rate (HR) were measured four times during the determination of the baseline values for GFR and ERPF, and four times during Vamin^{R}N infusion. Mean arterial pressure (MAP) was calculated by adding one third of the pulse pressure to the diastolic blood pressure. Filtration fraction (FF) was defined as the ration GFR:ERPF. The normal value of the FF in our laboratory varies between 0.22 and 0.28. This range is higher than the range found if PAH is used for the determination of the ERPF. The difference is explained by a lower extraction of ^{131}I-hippurate. The latter most likely is due to contamination of ^{131}I-hippurate with free ^{131}I [11].

For statistical analysis paired and unpaired Wilcoxon rank sum tests were used.

Results

Median body weight in group Ia was 77 kg (range 53-84), in group Ib 75 kg (range 56-92), in group IIa 71 kg (range 58-84), in group IIb 78 kg (range 51-89) and in group IIc 68 kg (range 56-86). No significant differences between the various groups could be established.

Vamin^{R}N infusion did not change HR or MAP significantly in each group separately. Median HR of the combined groups I and II

Table 1. Effect of Vamin^{R}N (VN) on GFR, ERPF and FF.

No.	Sex	Age	Diagnosis	GFR ml/min/1.73 m²		ERPF ml/min/1.73 m²		FF	
				BL	VN	BL	VN	BL	VN
Group Ia: healthy volunteers									
1	F	22		92	125	405	557	0.23	0.22
2	M	25		90	94	403	382	0.22	0.24
3	M	19		141	153	679	580	0.21	0.26
4	M	22		145	141	586	561	0.25	0.24
5	F	24		105	135	400	531	0.26	0.26
6	F	23		127	138	534	571	0.24	0.24
7	M	26		115	126	543	662	0.21	0.19
8	M	27		98	107	435	440	0.22	0.24
9	M	42		125	124	427	420	0.29	0.30
10	F	43		99	110	376	383	0.26	0.29
Median				110	126*	431	543	0.24	0.24
Mean (± SEM)				114 (±6)	125 (±5)	479 (±30)	509 (±29)	0.24	0.25
Group Ib: healthy individuals after uninephrectomy									
1	M	28		63	66	235	232	0.27	0.28
2	M	63		78	76	292	289	0.27	0.26
3	M	37		80	87	314	313	0.25	0.28
4	M	25		44	50	221	225	0.20	0.22
5	M	31		72	89	318	373	0.23	0.24
6	M	25		47	57	178	211	0.26	0.24
7	M	70		54	66	218	218	0.25	0.30
8	F	29		86	94	335	382	0.26	0.25
9	M	22		81	77	321	342	0.25	0.23
10	F	54		38	45	179	194	0.23	0.25
Median				68	71*	264	261	0.25	0.25
Mean (± SEM)				64 (±5)	71 (±5)	261 (±18)	278 (±21)	0.25	0.26
Group IIa: renal patients with GFR ≥ 90 ml/min/1.73 m²									
1	F	40	DG	116	133	407	484	0.29	0.27
2	M	46	U	117	115	402	403	0.29	0.29
3	F	27	EH	119	109	418	396	0.28	0.28
4	M	23	EH	122	119	583	577	0.21	0.21
5	F	44	FG	113	148	408	476	0.28	0.31
6	M	26	IgA	103	119	551	563	0.19	0.21
7	F	43	PD	95	120	371	456	0.25	0.26
8	M	38	EH	122	140	493	577	0.25	0.24
9	M	47	IgA	124	122	644	648	0.19	0.18
Median				117	120	418	484	0.25	0.26
Mean (± SEM)				115 (±3)	125 (±4)	475 (±30)	509 (±27)	0.25	0.25
Group IIb: renal patients with GFR between 30 and 90 ml/min/1.73 m²									
1	F	29	RA	57	68	210	240	0.27	0.28
2	M	31	MGP	30	32	213	229	0.14	0.14
3	M	25	IgA	83	81	355	367	0.23	0.21
4	M	38	MGP	59	75	259	265	0.23	0.25
5	M	46	FG	58	69	254	309	0.23	0.22
6	F	44	EH	69	74	276	295	0.25	0.25
7	F	28	IN	65	53	318	241	0.20	0.22
8	M	60	FG	55	51	297	282	0.19	0.18
9	M	55	EH	87	84	333	291	0.26	0.29
10	F	55	FG	30	35	143	153	0.21	0.23
11	M	28	IgA	81	86	384	419	0.21	0.20
12	M	61	FG	42	44	190	218	0.22	0.20
13	M	60	EH	61	72	179	231	0.31	0.32
14	F	61	EH	37	39	146	145	0.25	0.26
Median				59	69	257	253	0.23	0.23
Mean (± SEM)				58 (±5)	62 (±5)	254 (±20)	263 (±19)	0.23	0.23
Group IIc: renal patients with GFR < 30 ml/min/1.73 m²									
1	M	60	MGP	19	20	140	147	0.14	0.13
2	F	67	IN	5	6	12	15	0.38	0.42
3	F	73	IN	9	10	45	46	0.19	0.22
4	F	70	V	5	4	20	16	0.23	0.24
5	M	31	FG	11	11	57	54	0.19	0.20
6	M	44	EH	17	18	128	135	0.13	0.13
7	F	72	FG	23	26	261	212	0.09	0.12
8	M	60	W	18	16	146	105	0.13	0.16
Median				14	14	93	80	0.17	0.18*
Mean (± SEM)				13 (±2)	14 (±2)	101 (±28)	91 (±23)	0.19	0.20

* significant versus baseline (BL). DG=diabetic glomerulopathy; U=urolithiasis; EH=essential hypertension; FG=focal glomerulosclerosis; IgA=IgA glomerulopathy; PD=polycystic kidney disease; MGP=membranous glomerulopathy; IN=interstitial nephritis; V=vasculitis; W=morbus Wegener; RA=renal amyloidosis.

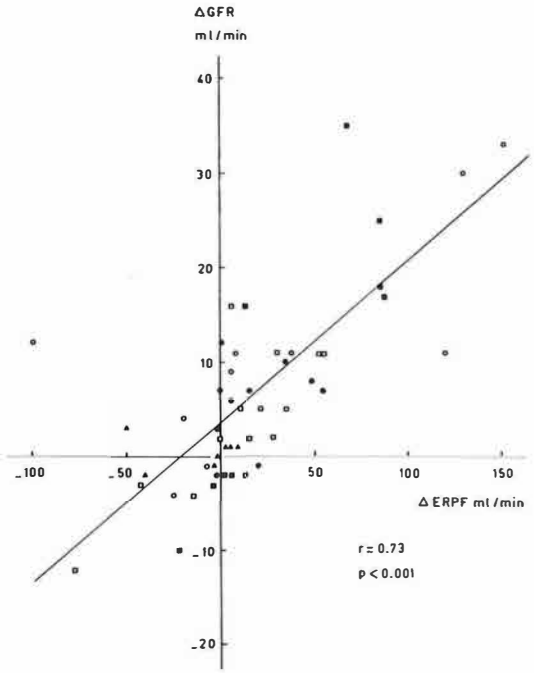

Figure 1
Absolute change (Δ) in GFR versus ERPF of all subjects during infusion of the amino acid solution Vamin N. o = healthy volunteers; ● = healthy individuals after uninephrectomy; ■ = renal patients with a GFR ≥90 ml/min/1.73 m²; □ = renal patients with a GFR ≥30 ml/min/1.73 m²; Δ = renal patients with a GFR <30 ml/min/1.73 m².

was 76 beats per minute (bpm; range 56-96) baseline and 76 bpm (range 58-92) during Vamin^{R}N (n.s.). MAP of groups I and II together showed a small rise from a median value of 98 (73-143) to 102 (72-147) mmHg ($p<0.01$).

In group I median GFR increased significantly during Vamin^{R}N infusion in both healthy volunteers and healthy uninephrectomized individuals (Table 1). In group Ia median GFR was 110 ml/min/1.73 m² baseline versus 126 ml/min/1.73 m² during Vamin^{R}N ($p<0.01$). In group Ib median GFR increased from 68 to 71 ml/min/1.73 m² ($p<0.02$). Some patients with renal disease and a normal to moderately impaired GFR showed an increase in GFR during Vamin^{R}N. The median rises in GFR in these subgroups, however, did not prove to be significant (Table 1). Patients with severely impaired renal function showed no significant change in GFR during Vamin^{R}N. Median ERPF did not change significantly in any

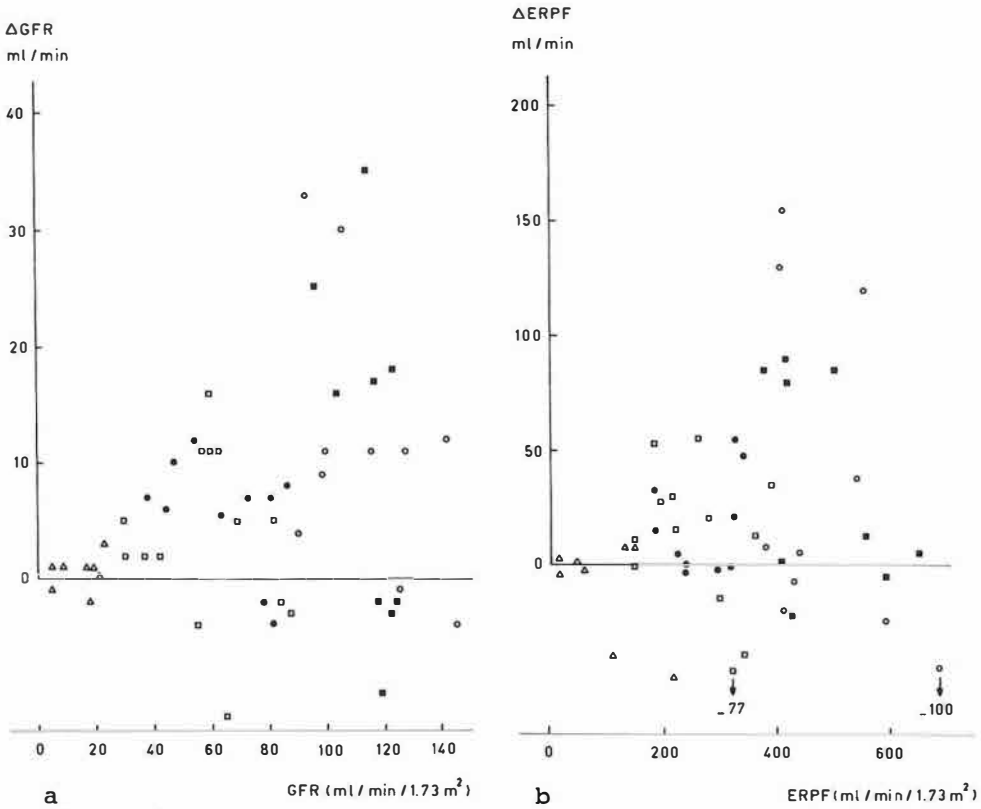

Figure 2.
Absolute change (Δ) in GFR versus baseline GFR (a) and ΔERPF versus baseline ERPF (b) of all subjects. For symbols, see figure 1.

group during Vamin$^{R}_{N}$ infusion (Table 1).

The median FF only increased in patients with severely impaired renal function (0.18 versus 0.17; $p<0.05$). In the combined group II, FF also increased ($p<0.05$), as did FF of the combined groups I and II ($p<0.05$). Median baseline FF in patients with moderately to severely impaired renal function was significantly lower when compared with FF of renal patients with normal GFR and healthy individuals (0.21 versus 0.25; $p<0.01$).

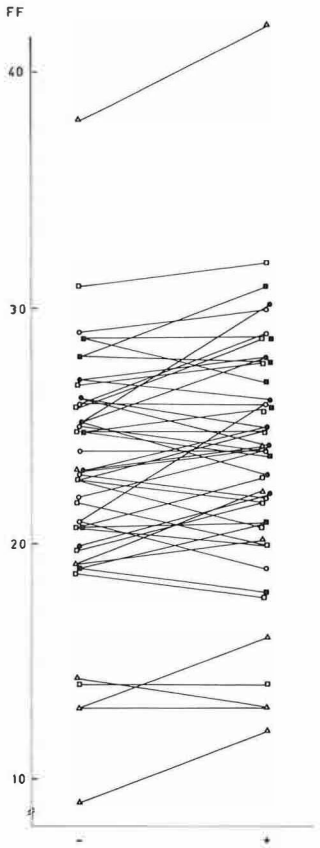

Figure 3
Filtration fraction (%) before (-) and during (+) Vamin N infusion. For symbols, see figure 1.

There appeared to exist a positive relation between the absolute change in GFR (ΔGFR) and the absolute change in ERPF (ΔERPF; ΔGFR = 0.1731xΔERPF + 3.6607 ml/min; r=0.73; p<0.001; figure 1). The absolute changes in GFR and ERPF in relation to the baseline GFR and ERPF are shown in figure 2. In figure 3 the effect of Vamin^{R}N on the FF of all individuals is shown.

Vamin^{R}N infusion led to a rise in urine volume of the combined groups I and II [median urine volume 321 ml/2hr (range 94-820) baseline versus 388 ml/2hr (22-1135) during Vamin^{R}N; p<0.01], although in each group separately no significant change in urine volume was apperent. Sodium excretion also increased only in the

Table 2

No	Age	Sex		GFR ml/min	ERPF ml/min	FF	U vol ml/hr	Na mmol/hr
1	26	F	1	111	457	0.24	138	6
			2	110	463	0.24	340	27
			3	113	463	0.24	182	12
2	23	F	1	117	541	0.22	300	15
			2	109	518	0.21	480	31
			3	115	485	0.24	208	19
3	27	M	1	134	592	0.23	290	27
			2	135	604	0.22	415	31
			3	137	643	0.21	475	32
4	24	F	1	99	356	0.28	289	12
			2	96	363	0.27	520	26
			3	101	358	0.28	295	19
5	23	M	1	135	631	0.21	488	22
			2	139	634	0.22	778	44
			3	125	624	0.20	612	32

Effect of mannitol infusion (250 ml 20%) on GFR, ERPF, FF, urine volume (U vol) and sodium excretion (Na) of 5 healthy volunteers. 1=before infusion; 2=1st hr after infusion; 3=2nd hr after infusion.

combined groups I and II [18.6 mmol/2hr (range 0.8-49.1) versus 24.5 mmol/2hr (0.1-62.5); $p<0.05$].

The results of mannitol infusion on GFR and ERPF in the five healthy volunteers are listed in Table 2. Urine volume and sodium excretion increased significantly, whereas there was no consistent effect on GFR or ERPF.

Discussion

Micropuncture studies in rats have led to the conclusion that pressure ($\bar{P}_{GC}$) in, and flow (Q_A) through the glomerular capillaries are the two factors which govern single nephron GFR (SNGFR) as long as oncotic pressure of peripheral plasma, hydraulic

permeability of the glomerular basement membrane (K_f) and hydrostatic pressure in Bowman's space (P_T) remain constant [12]. A rise in SNGFR can be achieved by an increase in net ultrafiltration pressure ($\bar{P}_{UF}$) and occurs if afferent arterioles dilatate. This rise will slightly elevate single nephron FF (SNFF). An increase in glomerular plasma flow (due to afferent and efferent vasodilatation) will be accompanied by a proportional rise in SNGFR unless Q_A is substantially increased and a filtration equilibrium cannot be reached anymore. In the latter case SNFF will fall [13].

Our results show that GFR in healthy individuals can be increased significantly by the infusion of amino acids, interestingly without any effect on FF. In renal patients with moderately to severely impaired function such a rise in GFR could not be established whereas FF increased sligthly. The observed increase in GFR can be caused by a rise in transcapillary hydrostatic pressure difference (i.e. afferent vasodilatation), although concomitant changes in Q_A and/or the ultrafiltration coefficient (K_f) are not excluded. The increase in GFR together with a constant FF can also be explained by utilization of "dormant cortical nephrons" as postulated by Brenner et al. [7] in analogy to observations in desert quails, in which a water load led to employment of superficial nephrons [14]. Our observation that there exists a strong correlation between the change in GFR and the change in ERPF during amino acid infusion, while FF remained unchanged or increased, supports our hypothesis that during the infusion of amino acids GFR rises by utilization of "dormant cortical nephrons" together with an increase in net ultrafiltration pressure due to afferent vasodilatation. As shown in figure 1, GFR can rise during administration of amino acids without any change in ERPF. In rats, amino acid infusion increases the ratio GFR to renal blood flow (measured with a flow probe), as can be calculated from the data recently presented by Zager and Venkatachalam [15]. The latter excludes an amino acid-induced lower extraction of hippurate which could explain the observed effect of Vamin^{R}N on FF. Finally, in humans, a meat meal

also increases GFR more than ERPF, the latter being measured with PAH [4].

In a recent study we found that a rise in GFR can also be achieved by infusion of a low dose dopamine, provided that renal function is not severely impaired [16]. However, this rise was accompanied by a marked increase in ERPF and a substantial fall in FF. The finding has been explained by a rise of the cortical blood flow in combination with a relative shift of this flow to the inner cortex and/or an increase in Q_A both due to dopamine-induced decrease in renal vascular resistance (i.e. afferent and efferent vasodilatation).

The question remains how amino acids can influence net ultrafiltration pressure of functioning and/or dormant nephrons. Amino acids may have a slight direct effect on renal haemodynamics [17,18]. However, an effect of the postulated liver hormone "glomerulopressin" on renal haemodynamics could be more important as shown in the toad, rabbit and dog [19,20]. The recent observation that in severe liver cirrhosis a protein load does not change GFR in man might indicate that glomerulopressin exists in human beings, too [21]. Whether the release of glomerulopressin is induced by amino acids per se or indirectly by glucagon is at the moment an open question. Serum glucagon levels increase after infusion of amino acids [22,23]. Glucagon, however, does not have a direct effect on renal haemodynamics [24,25], but is very effective in releasing glomerulopressin [24]. Glomerulopressin is thought to induce afferent vasodilatation [20,26] and this will increase ultrafiltration pressure. Whether glomerulopressin also induces an empolyment of "dormant nephrons" is not clear yet.

Interestingly, the amino acid-induced percentage rise in GFR in healthy volunteers did not differ from the percentage rise in GFR in individuals after uninephrectomy (median 10 versus 12%, respectively, n.s.). Perhaps such a difference can be found if the latter persons are studied in a paired way before and after uninephrectomy. It is possible that factors leading to an increase in GFR after amino acid administration are not involved

in the mechanisms that lead to the rise in GFR after uninephrectomy. In this respect it is noteworthy that we found a significant difference in the percentage changes in GFR and ERPF between normal volunteers and healthy individuals after kidney donation during the infusion of low dose dopamine (chapter 3).

From Table 1 and figure 2a it can be seen that there were healthy individuals in whom GFR did not change after amino acid infusion. Factors which might be responsible for this could be ageing and/or already existing high protein intake, as simultaneous measurement of GFR and ERPF during amino acid infusion was not preceded by standardization of dietary protein intake. Patients with renal disease and a "normal" GFR might similarly have failed during amino acid infusion, but the nature of the disease, for instance essential hypertension, can also have been responsible for this.

Infusion of Vamin^{R}N did not influence GFR in renal patients with a substantially impaired kidney function. In patients with IgA glomerulopathy we found earlier that dopamine cannot increase GFR if baseline GFR is 72 ml/min/1.73 m^2 or less, despite the fact that ERPF still increased and, therefore, FF fell. Thus, one can speculate that patients with moderately to severely impaired renal function have exhausted their physiological reserve filtration capacity or, alternatively, are already hyperfiltering. As amino acids and dopamine differ in their effect on renal haemodynamics, a study on the combined infusion of GFR and ERPF is warranted. It might be that infusion of amino acids (afferent vasodilatation) together with a low dose dopamine (afferent and efferent vasodilatation) results in the highest GFR and will measure best so-called renal reserve filtration capacity.

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Appendix

Vamin^{R}N (KabiVitrum, Limoges, France) contains per 1000 ml: l-asparaginic acid 4.1 g; l-glutaminic acid 9.0 g; l-alanin 3.0 g; l-arginine 3.3 g; l-cysteine/cystine 1.4 g; glycine 2.1 g; l-histidine 2.4 g; l-isoleucine 3.9 g; l-leucine 5.3 g; l-lysine 3.9 g; l-methionine 1.9 g; l-phenylalanine 5.5 g; l-proline 8.1 g; l-serine 7.5 g; l-threonine 3.0 g; l-tryptophan 1.0 g; l-tyrosine 0.5 g and l-valine 4.3 g.

Chapter 5

RENAL HAEMODYNAMICS DURING SEPARATE AND COMBINED INFUSION OF AMINO ACIDS AND DOPAMINE

Abstract

Healthy volunteers (n=9) and patients with varying degrees of renal insufficiency (n=36) were given a low dose of dopamine and/or amino acids intravenously during a simultaneous measurement of the glomerular filtration rate and the effective renal plasma flow. Dopamine infusion led to a rise in the glomerular filtration rate and a fall in the filtration fraction. Infusion of amino acids was accompanied by an increase in the glomerular filtration rate while the filtration fraction remained unchanged or increased slightly. The highest values for the glomerular filtration were obtained during the combined infusion of amino acids and dopamine. A reserve in filtration capacity was not or hardly present in patients with moderate (GFR 30 to 90 ml/min/1.73 m^2) to severe (GFR <30 ml/min/1.73 m^2) renal insufficiency. We conclude that dopamine decreases total renal vascular resistance while amino acids mainly reduce the tone of afferent arterioles. As amino acids and dopamine seem to be additive in their effects on the glomerular filtration rate, we recommend the combined infusion of these two stimuli to measure renal reserve filtration capacity.

Introduction

Both a diet rich in protein [1-3] and an intravenous infusion of amino acids [4-6] cause an increase in glomerular filtration rate (GFR), provided that renal function is not severely impaired [7,8]. A meat meal has been recommended to measure the so-called

"renal functional reserve" [8], that is, the absence of glomerular hyperfiltration.

Recently, we found in patients with IgA glomerulopathy that a low dose of dopamine increased GFR if the baseline GFR amounted to 73 ml/min/1.73 m^2 or more [9]. The relative changes in GFR increased with increasing baseline values ($r=0.74$, $p<0.001$). Thus, a low dose of dopamine administered during simultaneous measurement of GFR and effective renal plasma flow (ERPF) could be an alternative for a meat meal or an amino acid infusion if the presence (or absence) of hyperfiltration has to be determined. However, in a study on the effect of an amino acid solution on GFR and ERPF, we observed that amino acids, in contrast with dopamine, barely affected the filtration fraction, that is, the renal vascular resistance [10].

The aim of this study, therefore, was to compare the effects of amino acids and a low dose of dopamine, separately or simultaneously infused, on the GFR and ERPF in healthy volunteers, in healthy individuals after nephrectomy, and in patients with renal disease with or without impaired function.

Patients and methods

Five groups were studied consisting of nine healthy volunteers (group I), nine healthy kidney donors (group II), nine renal patients with a GFR ≥90 m/min/1.73 m^2 (group III), 11 patients with moderate renal insufficiency, i.e. a GFR between 30 and 90 ml/min/1.73 m^2 (group IV), and seven patients with severely impaired renal function, i.e. a GFR <30 ml/min/1.73 m^2 (group V). Renal diseases included essential hypertension (n=6), focal glomerulosclerosis (n=6), IgA glomerulopathy (n=4), membranous glomerulopathy (n=3), interstitial nephritis (n=3), polycystic kidney disease (n=1), and miscellaneous (n=4).

The medical ethics committee approved to the study protocol and all the individuals verbally consented to an infusion of amino acids and/or dopamine.

The measurements were performed on two separate days. With the standard procedure baseline GFR and ERPF were measured simultaneously on day one, using ^{125}I-iothalamate and ^{131}I-hippurate according to a method previously descibed, with coefficients of variation of the day to day determination of ≤2.2 and ≤5.0%, respectively [11]. After a priming dose was given, the radiopharmaceuticals were infused at a constant rate (Braun Unita II pump). After an equilibration period of 1.5 hour, two 2-hour clearances were determined, each calculated from the 2-hour urinary tracers excretion and the mean serum tracer value from three samples drawn at the start, midway and at the end of each 2-hr period. During the procedure a diuresis of at least 100 ml/hr was maintained by orally administering fluids. At the end of this standard procedure, dopamine was infused at a rate of 1.5-2.0 μg/kg/min for two hour. GFR and ERPF during these two hour were compared with the GFR and ERPF just before the infusion of this agent.

At 6.00 p.m. on day two, the infusion of Vamin^{R}N (a 7% amino acid solution) was started at a rate of 500 ml/6hr (=83 ml/hr), analogous to the study of von Graf et al. who infused a 10% amino acid solution at a rate of 60 ml/hr [6]. On day three, GFR and ERPF were measured a second time as outlined above while the amino acid infusion was continued, including the infusion of low-dose dopamine at the end of the procedure.

Filtration fraction (FF) was defined as the ratio GFR:ERPF. The normal value of the FF in our laboratory varies between 0.22 and 0.28.

Before and during the administration of dopamine, heart rate (HR) and blood pressure were recorded at 15-min intervals for four hour. Mean arterial pressure (MAP) was calculated by adding one third of the pulse pressure to the diastolic pressure.

Paired and unpaired Wilcoxon rank sum tests were used for the statistical analysis of the data. This was performed on median values as we considered our data (especially dopamine- and amino acid-induced changes in GFR and ERPF) not normally distributed. To study correlations, linear regression analysis [12] or

Spearman's rank correlation test were used. A $p<0.05$ was chosen as level of significance.

Results

Neither the dopamine infusion, nor the amino acid infusion nor the combined infusion caused significant changes in HR or MAP. In the combined groups I to V, median HR values were 72 beats per minute (bpm) baseline, 76 bpm during dopamine infusion, 78 bpm during amino acid infusion and 76 bpm during the combined infusion. Median MAP values were 97 mmHg baseline, 97 mmHg during dopamine infusion, 102 mmHg during amino acid infusion and 103 mmHg during combined infusion.

In the healthy volunteers (group I) both the dopamine infusion and the amino acid infusion caused significant increases in GFR ($p<0.05$) which were of comparable magnitude (Table 1). The largest rise in GFR, however, was observed during the combined infusion. In healthy individuals after uninephrectomy (group II), the increase in GFR did not reach significance during the dopamine infusion but did during the amino acid infusion ($p<0.05$). Here as well, combined infusion increased GFR most (Table 1).

In Table 2, the effects of dopamine, amino acids and combined infusion on GFR in patients with renal disease are listed. In group III no significant changes in GFR could be obtained. In group IV only the dopamine infusion increased GFR significantly. In patients with severely impaired renal function (group V) neither the dopamine infusion, nor the amino acid infusion nor the combined infusion changed GFR.

As can be seen in Tables 1 and 2, dopamine infusion caused a fall in the FF in all groups except group V. Infusion of amino acids, however, either did not change the FF or slightly increased it. This indicates that dopamine and amino acids affect renal haemodynamics in different ways. Figure 1 shows the effects of the dopamine infusion, the amino acid infusion and the

Table 1

Group		GFR BL	GFR Do	GFR AA	GFR A+D	FF BL	FF Do	FF AA	FF A+D
I	median	115	125*	126*	143*#	0.23	0.19*	0.24	0.21*#
	mean	115	129	127	140	0.24	0.20	0.24	0.21
	SEM (±)	7	8	7	8				
II	median	72	76	76*	80*#	0.25	0.23*	0.26	0.22*#
	mean	67	72	74	79	0.25	0.22	0.26	0.22
	SEM (±)	5	7	5	6				

* significant versus baseline (BL); # significant versus Do

The effects of dopamine infusion (Do), amino acid infusion (AA), and combined infusion (A+D) on the GFR (ml/min/1.73 m^2) and FF in healthy subjects.

Table 2

Group		GFR BL	GFR Do	GFR AA	GFR A+D	FF BL	FF Do	FF AA	FF A+D
III	median	117	116	120	131	0.25	0.22*	0.26	0.23*#
	mean	115	124	125	132	0.25	0.21	0.25	0.21
	SEM (±)	1	6	4	7				
IV	median	59	66*	69	77	0.23	0.21*	0.22	0.21
	mean	61	64	64	72	0.22	0.20	0.23	0.21
	SEM (±)	6	6	6	6				
V	median	11	10	11	11	0.19	0.19	0.20	0.21*
	mean	13	13	14	12	0.19	0.19	0.21	0.22
	SEM (±)	2	2	2	3				

* significant versus baseline (BL); # significant versus Do

The effects of dopamine infusion (Do), amino acid infusion (AA), and combined infusion (A+D) on the GFR (ml/min/1.73 m^2) and FF in patients with renal disease.

combined infusion on the ERPF. This figure also shows that the dopamine infusion increased ERPF, whereas the amino acid infusion barely affected ERPF. Furthermore, in severe renal insufficiency no changes in ERPF could be observed.

Spearman's rank test revealed a positive relation between the baseline ERPF and the change in ERPF during dopamine infusion.

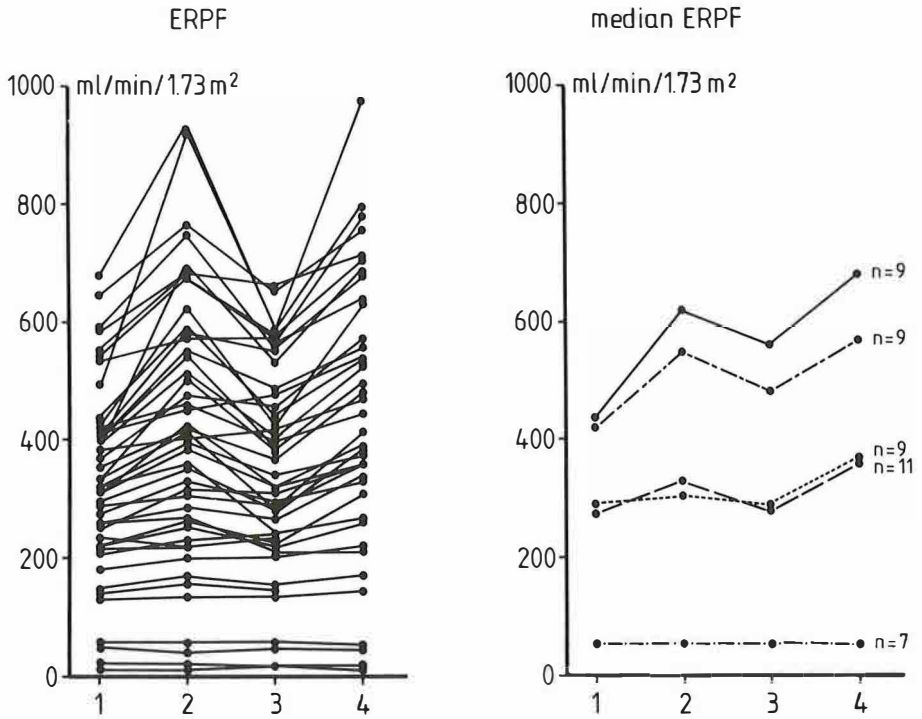

Figure 1
The effects of dopamine (2), amino acids (3) and the combined infusion (4) on the ERPF of the 45 subjects, plotted individually (left panel) and on the median ERPF (right panel) of the control group (——), the subjects with one kidney (····), and the patients with renal disease (·-·-· normal function; — — — moderate renal failure; ·—·—·; severe renal failure). 1 = baseline.

During amino acid infusion no such relationship could be found (figure 2). Figure 3 shows that similar findings were obtained for the baseline GFR and the absolute changes in GFR, that is, a positive relation during dopamine infusion and no significant relation during amino acid infusion ($p<0.1$). The absolute change (Δ) in GFR appeared to be strongly related to the absolute change in ERPF during dopamine infusion as well as the amino acid infusion and the combined infusion (figure 4). Using linear regression analysis we found during the dopamine infusion that the $\Delta GFR = -1.8164 + 0.0989 \times \Delta ERPF$ ml/min ($r=0.87$; $p<0.001$) during

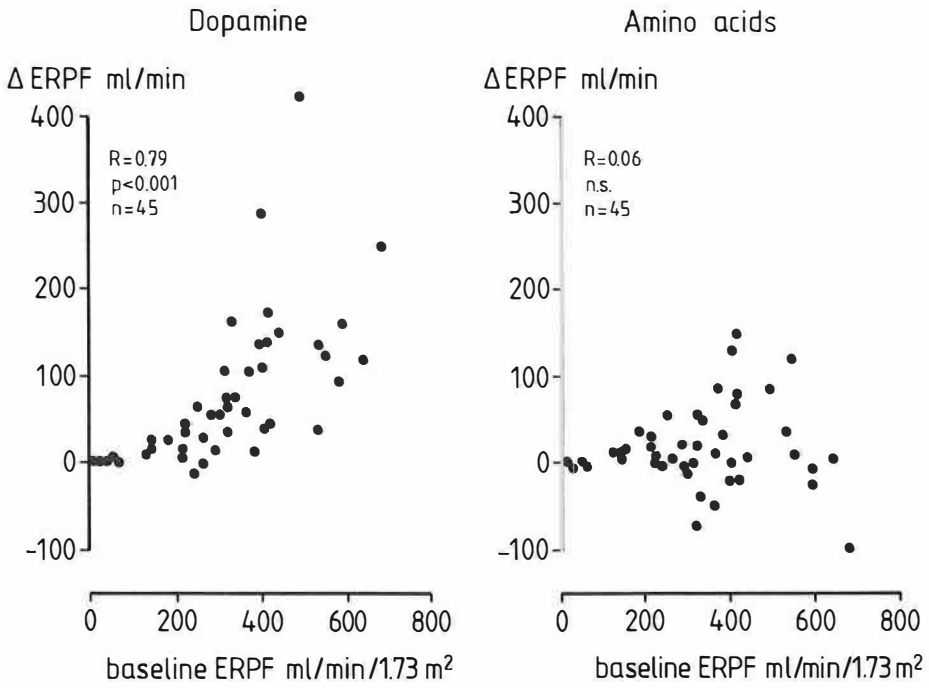

Figure 2
The relation between the absolute change in ERPF (ΔERPF) and baseline ERPF during infusion of dopamine and amino acids.

amino acid infusion ΔGFR = 3.644 + 0.1737xΔERPF ml/min ($r=0.73$; $p<0.001$), and during the combined infusion ΔGFR = -1.2910 + 0.1270xΔERPF ml/min ($r=0.81$; $p<0.001$). The relation between ΔGFR and ΔERPF during the dopamine infusion proved to be different from the relation between ΔGFR and ΔERPF during the amino acid infusion.

In the combined groups I to V, administration of amino acids appeared to increase urine volume ($p<0.05$) compared with both urine volume during baseline measurement and urine volume during dopamine infusion. Median values for urine volume (ml/2hr) were 340 (baseline), 302 (dopamine infusion), 390 (amino acid infusion) and 431 (combined infusion). The addition of dopamine

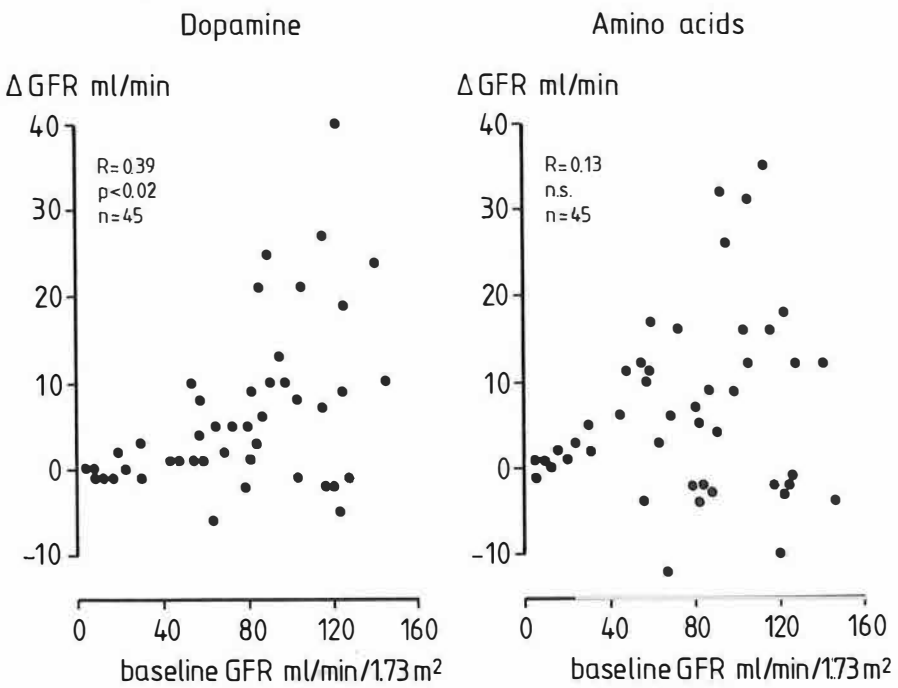

Figure 3
The relation between the absolut change in GFR (ΔGFR) and baseline GFR during infusion of dopamine and amino acids.

to amino acids did not change urine volume significantly.

Sodium excretion in groups I to V combined was only increased ($p<0.05$) during the combined infusion of amino acids and dopamine compared with baseline sodium excretion. Median values for sodium excretion (mmol/2hr) were 20.7 (baseline), 26.6 (dopamine), 31.4 (amino acids) and 31.9 (combined infusion).

Discussion

Renal plasma flow, net ultrafiltration pressure, colloid osmotic pressure of plasma and the ultrafiltration coefficient are the determinants of glomerular ultrafiltration [13]. In both filtration equilibrium and filtration disequilibrium, an increase in renal blood flow, for instance induced by a decreased renal

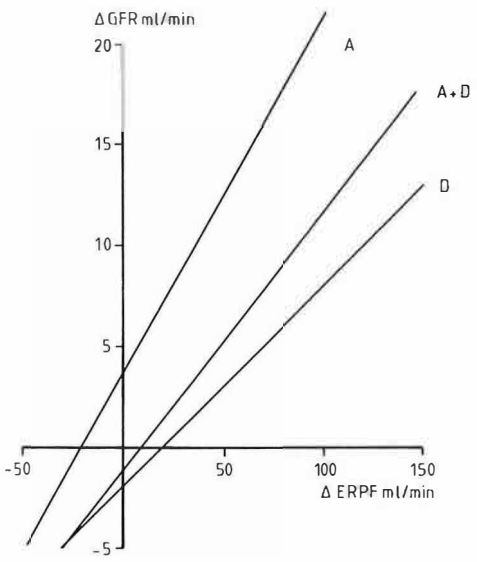

Figure 4
ΔGFR versus ΔERPF during infusion of dopamine (D), infusion of amino acids (A) and during the combined infusion (A+D).

vascular resistance, will result in an increase in glomerular ultrafiltration [13,14].

A general decrease in renal vascular resistance can be obtained by infusing a low dose of dopamine. This agent causes efferent and afferent vasodilatation by binding to specific dopaminergic receptors [15]. The decreased vascular resistance results in an increased renal plasma flow, a rise in glomerular filtration rate and a fall in filtration fraction. Indeed these effects of dopamine were observed in the present study unless renal function was severely impaired. In renal patients with a normal GFR, no significant rise in GFR could be obtained, a phenomenon probably due to the small number of patients and/or the variety of renal diseases. After eliminating three patients with essential hypertension the GFR values were parallel to the control group.

Glomerular filtration rate can also be increased by infusing amino acids [5,6,10]. Although this may occur partially because

of a direct effect of amino acids on renal haemodynamics [16,17], the effect of an amino acid-induced release of the postulated liver hormone glomerulopressin seems more important [18,19]. Recently, it has been demonstrated that no rise in GFR can be obtained after a meat meal in patients with severe liver disease [20]. Glomerulopressin causes afferent vasodilatation [21] and therefore increases GFR by a rise in net ultrafiltration pressure without affecting or only slightly elevating FF. Our observations that amino acids can increase GFR without affecting FF are in accord with the above mentioned hypothesis. In severe renal disease, infusion of amino acids also cannot increase GFR.

As dopamine and amino acids influence GFR in different ways, it is understandable why the highest values of GFR were observed during combined infusion: an amino acid-induced increase in the net ultrafiltration pressure and a dopamine-induced rise in renal plasma flow are additive. It may be that infusing amino acids in larger amounts than used in this study combined with a low dose of dopamine will result even in higher values of GFR than those observed in the present study and measures best so-called renal reserve filtration capacity.

Changes in GFR induced by infusion of amino acids are not likely caused by the hyperosmolality of the amino acid solution. In a recent study we demonstrated that infusion of mannitol 20% did not change GFR or ERPF [10].

Interestingly, the relative effect of dopamine on baseline ERPF and baseline GFR was greater in the normal volunteers when compared to the subjects after uninephrectomy (median increase in ERPF 34 versus 21%, $p<0.05$; median increase in GFR 11 versus 6%, respectively). However, the relative effect of amino acids on baseline GFR was the same in both groups (9 versus 10%, respectively). The combined infusion increased ERPF 23 versus 24%, and GFR 13 versus 22% (n.s.). It might be that we only found a difference with dopamine between the two groups because of the small number of subjects studied. Perhaps a difference with amino acid infusion and the combined infusion can be found if the subjects in group II are studied in a paired way before and

after nephrectomy. Another explanation may be that after uninephrectomy total vascular resistance is decreased without substantially affecting afferent tone.

In conclusion, amino acids and dopamine increase filtration by different mechanisms as expressed by the filtration fraction. The combination leads to the highest values for the GFR without an influence on systemic blood pressure or heart rate. The results support the hypothesis that if in renal disease GFR is severely impaired, a significant reserve in renal function is no longer present

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Chapter 6

THE EFFECT OF LOW-DOSE DOPAMINE ON RENAL HAEMODYNAMICS IN PATIENTS WITH TYPE 1 (INSULIN-DEPENDENT) DIABETES DOES NOT DIFFER FROM NORMAL INDIVIDUALS

Abstract

It is well-known that patients with Type 1 (insulin-dependent) diabetes exhibit both an increased glomerular filtration rate and an increased effective renal plasma flow which can be found even when these patients are well-controlled. Usually this is attributed to a decrease in renal vascular resistance and/or to an enlarged kidney size and glomerular volume.

Among the factors which govern glomerular filtration rate, renal plasma flow is most important. Renal plasma flow increases if renal vascular resistance decreases. The latter might exist in insulin-dependent diabetes mellitus because of either a predominantly afferent or a predominantly efferent vasodilatation. Dopamine is an agent which causes predominantly efferent vasodilatation. Therefore, the effects of infusing a low dose of dopamine on glomerular filtration rate and effective renal plasma flow in 12 well-controlled patients with insulin-dependent diabetes and 28 healthy volunteers were compared to investigate whether the increased glomerular filtration rate in insulin-dependent diabetes is induced by efferent vasodilatation.

The median increase in glomerular filtration rate during dopamine infusion amounted 13.0% in the diabetic patients and 12.5% in the healthy control subjects (n.s.). It is concluded that the elevated glomerular filtration rate in well-controlled insulin-dependent diabetes is not caused by a predominantly efferent vasodilatation.

Introduction

In Type 1 (insulin-dependent) diabetes, a supernormal glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) have been well-established, especially during poor metabolic control [1-3]. In obesity and acromegaly, conditions also characterized by a supernormal renal function [4,5], the high GFR has been attributed to an expanded extracellular fluid volume [6,7]. In Type 1 diabetes, however, it has been found that the relation between extracellular fluid volume and body weight (or body surface area) is normal [8]. This indicates that the high GFR in Type 1 diabetes reflects a real hyperfiltration. Recently, it has been suggested that such a hyperfiltration initiates the process of glomerulosclerosis [9,10].

A low dose of dopamine can be used to increase ERPF and GFR [11-13]. As the ERPF increases more than the GFR during dopamine infusion, the filtration fraction (FF) falls. Therefore, it has been concluded that the dopamine-induced decrease in renal vascular resistance [14] is obtained by predominantly efferent vasodilatation [13]. To investigate whether efferent vasodilatation is an important factor in the elevated GFR in Type 1 diabetes, the effects of dopamine infusion on GFR, ERPF and FF in 12 patients with this disorder were compared with the effects of low-dose dopamine on those parameters in 28 healthy control subjects.

Patients and methods

In 12 non-obese Type 1 diabetic patients (four male and eight female), renal function was measured before and during dopamine infusion. The median age was 25.5 years and the median duration of diabetes was 7.5 years (Table 1). All had developed diabetes before age 30. C-peptide levels were below 0.1 nmol/l after stimulation with glucagon. None had hypertension or signs of clinical nephropathy (i.e., proteinuria <0.5 g/24hr and creatinine clearance ≥80 ml/min), and there existed no or only mild background retinopathy. All were treated with intensified

insulin therapy, i.e., multiple insulin injections, frequent home blood glucose monitoring with reagent strips, and adjustment of the insulin dose accordingly. (Near) normoglycaemia (3-10 mmol/l) was the goal for all patients.

In supine position GFR was measured with ^{125}I-iothalamate and ERPF with ^{131}I-hippurate, which were simultaneously infused. Iothalamate is a satisfactory substitute for inulin [15]. The clearances of p-aminohippurate and ^{131}I-hippurate are both representative of the renal plasma flow when the difference in extraction is taken into account [15,16]. The radiopharmaceuticals were infused at a constant rate after a priming dose was given. After an equilibration period of 1.5 hour, two 2-hour clearances were determined using the formula UxV/120xP [16]. At the end of this standard procedure, dopamine was infused at a dose of 1.5-2.0 μg/kg/min for 2 hour (Braun Unita II pump, Melsungen, Germany). GFR and ERPF during these 2 hour were compared with the GFR and ERPF just before dopamine infusion (also measured over a 2-hour period). The coefficients of variation of the determinations are $\geq$2.2% for the GFR, and $\geq$5.0% for the ERPF [16]. The FF was defined as the ratio GFR:ERPF (normal value in our laboratory amounts to 0.22-0.28). During the procedure a diuresis of at least 100 ml/hr was pursued by oral administration of fluids.

To exclude effects of poor metabolic regulation, the renal functioning studies, including the effect of low-dose dopamine, were repeated after one year of careful glycaemic control. The latter consisted of obtaining 24-hour blood glucose profiles every 2-4 weeks by measuring blood glucose in finger prick samples which were taken at 03.00, 07.00 (fasting), 09.00, 11.00, 14.00, 17.00, 19.00 and 24.00 h. The samples were stored in small plastic cups for measurement in the laboratory (Auto-analyzer II, Technikon, Tarrytown N.Y., U.S.A.). All the curves obtained in this way during the control year were used to calculate an individual mean 24-hour blood glucose value during the control year. Furthermore, glycosylated haemoglobin (HbA_1) was measured every two months by the colorimetric method of Flückiger and

Table 1

sex	age	duration	mean HbA_1 (± SEM)	mean glucose (± SEM)
F	29	12	7.0 (0.3)	5.4 (0.3)
F	28	13	7.0 (0.2)	6.4 (0.3)
F	23	9	6.4 (0.2)	6.0 (0.7)
F	21	4	7.8 (0.2)	8.7 (0.4)
F	27	2	7.4 (0.3)	8.1 (0.9)
F	23	3	8.0 (0.3)	7.7 (0.9)
F	32	4	7.9 (0.3)	9.2 (0.5)
F	24	9	7.9 (0.3)	8.8 (0.4)
M	32	6	8.0 (0.4)	7.5 (0.6)
M	23	4	7.7 (0.4)	7.0 (0.6)
M	43	13	7.9 (0.4)	8.2 (0.3)
M	24	10	6.9 (0.3)	7.3 (0.5)
median	25.5	7.5	7.8	7.6
mean	27.4	7.4	7.5	7.5
		SEM (±)	0.2	0.4

Sex, age, (years), duration of diabetes (years), mean HbA (normal range 6.0-8.5%) (%) during the control year, and mean 24-hr blood glucose (mmol/l) during the control year in 12 patients with Type 1 (insulin-dependent) diabetes.

Winterhalter [17]. Thus, individual mean HbA_1 during the control year was calculated. Finally, all patients were seen at the diabetes outpatient clinic every four weeks.

The control group consisted of 22 male and 6 female volunteers, with a median age not significantly different from the median age of the patient group (31.5 years, range 19-48).

The study was approved by the medical ethics committee of the University Hospital Groningen. All individuals gave verbal consent to the infusion of dopamine.

Heart rate (HR) and blood pressure were recorded at intervals of 15 min during dopamine infusion and the preceding 2-hour

period. Mean arterial pressure (MAP) was calculated by adding one third of the pulse pressure to the diastolic blood pressure.

Statistical analysis was performed on median values, since we considered our data not normally distributed. Wilcoxon rank sum tests on paired and unpaired samples were used. A probability level of $p<0.05$ was chosen as level of significance. Though the control group contained significantly more males than females ($p<0.05$), no subdivision between males and females was made; neither in the control group nor in the patient group baseline GFR, baseline ERPF, baseline FF, and dopamine-induced changes in GFR, ERPF and FF in males did differ from those in females.

Table 2

		GFR	ERPF	FF
B	median	134.5	561.5	0.24
	mean	130.9	551.6	0.24
	SEM (±)	4.9	18.8	0.006
Do	median	142.5*	684.0*	0.22*
	mean	146.7	697.5	0.21
	SEM (±)	6.3	23.9	0.007

* $p<0.01$

GFR (ml/min/1.73 m^2), ERPF (ml/min/1.73 m^2) and FF before (B) and during dopamine infusion (Do) in 12 Type 1 diabetic patients at the beginning of the study.

Results

In Table 1 the individual data on sex, age, duration of diabetes, mean HbA_1 and mean 24-hour blood glucose of the 12 diabetic patients are listed. The median value of the individual mean HbA_1 during the control year was 7.8% (range 6.4-8.0; normal range 6.0-8.5%). The median value of the individual mean 24-hr blood glucose value during the control year was 7.6 mmol/l (range 5.4-9.2). From these two findings it was concluded that metabolic control during the control year was rather good. None of the

Table 3

		BL	Do	ΔGFR ml/min	ΔGFR %
I	median	109.0	124.5*	11.0	12.5
	mean	111.6	125.2	13.6	12.2
	SEM (±)	3.3	3.5	2.0	1.9
II	median	131.0	147.5*	14.0	13.0
	mean	128.6	142.7	14.1	11.0
	SEM (±)	5.9	5.4	2.4	1.9

* $p<0.01$

The effect of low-dose dopamine (Do) on baseline (BL) GFR (ml/min/1.73 m^2) in 28 control subjects (I) and in 12 Type 1 diabetic patients (II).

patients developed signs of clinical nephropathy or hypertension during the control year.

At the beginning of the control year, median GFR was 134.5 ml/min/1.73 m^2 (range 95-161), median ERPF 561.5 ml/min/1.73 m^2 (range 383-635) and median FF 0.24 (range 0.20-0.27), as can be seen in Table 2.

After the control year, median GFR in Type 1 diabetic patients had not significantly changed and was 131.0 ml/min/1.73 m^2 (range 86-170). This was significantly higher when compared with the median GFR of the healthy control subjects (109 ml/min/1.73 m^2; range 90-145; $p<0.02$). The median ERPF was 538 ml/min/1.73 m^2 (range 317-613) in the diabetic patients and 443 ml/min/1.73 m^2 (range 327-679) in the control sujects ($p<0.02$). In both the diabetic patients and the control subjects GFR increased significantly during the infusion of low-dose dopamine (Table 3). Interestingly, however, there was no significant difference in dopamine-induced increase in GFR between the two groups. Similar comparisons held true for the ERPF (Table 4). FF fell in both diabetic patients and control subjects during dopamine infusion (Table 4).

Dopamine infusion did not affect HR or MAP significantly. Median HR was 72 beats per minute (bpm) in control subjects

versus 76 bpm during dopamine infusion. In Type 1 diabetic patients, median HR was 74 bpm versus 80 bpm during dopamine. Median values for MAP were 94 versus 92 mmHg in control subjects, and 87 versus 87 mmHg in diabetic patients.

Table 4

		ERPF		FF	
		BL	Do	BL	Do
I	median	443.0	622.5*	0.25	0.20*
	mean	461.3	628.8	0.24	0.20
	SEM (±)	15.3	20.1	0.006	0.004
II	median	538.0	694.0*	0.24	0.21*
	mean	530.8	669.8	0.24	0.21
	SEM (±)	22.1	30.4	0.006	0.006

* $p<0.01$

The effect of low-dose dopamine (Do) on baseline (BL) ERPF (ml/min/1.73 m^2) and FF in 28 control subjects (I) and in 12 Type 1 diabetic patients (II).

Discussion

Increased kidney size with increased filtration surface area, high plasma levels of glucagon, growth hormone and non-specified other mediators, and poor metabolic control itself are the factors which have been implicated in the supernormal GFR and ERPF of Type 1 diabetic patients [18]. Especially during poor metabolic control, a very high GFR can be observed. The latter is most likely caused by a hyperglycaemia-induced change in renal haemodynamics [19]. The literature on the effect of long-term normoglycaemia on GFR and ERPF in Type 1 diabetic patients is contradictory. Recently, it was concluded that good metabolic control for one year normalizes GFR [20]. In a recent study, we also demonstrated that good metabolic control for a longer period decreases GFR [21]. In the present study, however, we found that GFR in the patient group was still increased when compared with the control group after one year of careful glycaemic control.

This might indicate that our patients still were not well-controlled enough or that in Type 1 diabetes even during careful glycaemic control for a long time renal vascular resistance is basically decreased [22]. Such a decrease in renal vascular resistance will exist in case of efferent vasodilatation, afferent vasodilatation or a generalized vasodilatation.

Infusion of a low dose of dopamine causes a predominantly efferent vasodilatation which is mediated by specific renal dopamine receptors and results in an increase in renal blood flow and GFR [13,14,23]. Administration of dopamine at a dose of 2.0 μg/kg/min results in the highest increase in ERPF and GFR, although in some individuals ERPF and GFR can be increased slightly more by infusing dopamine at a rate of 4.0 μg/kg/min (A.J. Smit, personal communication). The effect of dopamine on renal haemodynamics is most pronounced in healthy individuals [14]. In patients with IgA-glomerulopathy, GFR could not be improved if baseline GFR amounted to 73 ml/min/1.73 m^2 or less [12].

In the present study we found that the dopamine-induced changes in ERPF and GFR of normoglycaemic insulin-dependent diabetic patients did not differ from those observed in control subjects. This finding militates against a fall in renal vascular resistance caused by a predominantly efferent vasodilatation in Type 1 diabetes since a lesser effect of dopamine is expected in already existing efferent vasodilatation. The normal FF in our well-controlled diabetic patients is in accord with this also.

Recently, it was suggested that there exists an enhanced release of the liver hormone "glomerulopressin" in Type 1 diabetes which causes only afferent vasodilatation and, therefore, an increase in glomerular plasma flow and a rise in ultrafiltration pressure [24-26]. This results in an increased GFR with an unchanged or slightly elevated FF. An increased glomerular ultrafiltration pressure has been so demonstrated in diabetic rats [27].

The increase in GFR that can be observed during protein intake or glucagon infusion is also thought to be caused by an

enhanced glomerulopressin release [24]. Indeed, we have shown that the infusion of amino acids in healthy individuals increases GFR (median value from 110 to 126 ml/min/1.73 m^2) and ERPF (median value from 431 to 543 ml/min/1.73 m^2) without affecting FF [28]. These values, obtained during amino acid infusion in normal individuals, are comparable with those found in the (near) normoglycaemic patients with Type 1 diabetes of the present study. Interestingly, Bosch et al. [22] found that a protein load did not influence GFR in Type 1 diabetic patients with normal to supernormal GFR. However, to confirm the hypothesis that in Type 1 diabetes a predominantly afferent vasodilatation exists, due to for instance an enhanced glomerulopressin release, more detailed studies are warranted.

A general renal vasodilatation induced by the diabetic state as an explanation for increased ERPF and GFR is not excluded. However, if such a generalized vasodilatation (including the existence of efferent vasodilatation) exists, it seems contradictory that the effect of low-dose dopamine on renal haemodynamics in Type 1 diabetic patients did not differ from the effect observed in healthy volunteers. Finally, an increased kidney weight per se [2,3,20] might explain the supernormal GFR and ERPF. An increased kidney weigth has been found to be associated with a decreased renal vascular resistance in the mature growing rat which results in an increased renal plasma flow [29].

In conclusion, we found a supernormal GFR and ERPF in patients with Type 1 diabetes, even after a long period of fairly well-regulated metabolic control. The hyperfiltration seemed not to be caused by a decrease in renal vascular resistance on the base of efferent vasodilatation. A decreased renal vascular resistance caused by afferent vasodilatation, and an increased kidney weight are remaining possibilities which might explain the supernormal ERPF and GFR in Type 1 diabetes.

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Chapter 7

RENAL RESERVE FILTRATION CAPACITY IN PATIENTS WITH TYPE I (INSULIN-DEPENDENT) DIABETES MELLITUS

Abstract

Roughly 40% of all patients with Type 1 (insulin-dependent) diabetes mellitus will develop diabetic nephropathy. Therefore, it is important to detect the patients at risk. Glomerular hyperfiltration is one of the factors held responsible for the development of diabetic nephropathy. A supernormal glomerular filtration rate (GFR) can be found in diabetic patients even when they are well-controlled. In a recent study we have demonstrated that such glomerular hyperfiltration is not based on a predominant vasodilatation of the efferent arteriole. This is in accord with animal studies, in which it has been demonstrated that the increased GFR in diabetes is caused by a predominant decrease in resistance of the afferent arteriole. Protein loading and infusion of amino acids cause an increase in GFR. This increase also is caused by a dilatation of the afferent arteriole. Thus, protein loading and amino acid infusion may be used to test renal reserve filtration capacity. In this study, we used infusion of amino acids to investigate whether the supernormal GFR in diabetic patients might be caused by the existence of afferent vasodilatation. Furthermore, the effects of amino acid and/or dopamine infusion on renal haemodynamics of diabetic patients were compared with these effects in normal volunteers.

It is concluded that diabetic patients may be subdivided in patients with a normal GFR (in whom a normal reserve filtration capacity exists) and patients with a supernormal GFR (in whom administration of amino acids does not affect GFR). Our results suggest the existence of afferent vasodilatation in diabetic

patients with a high GFR. The cause of this vasodilatation warrants further study.

Introduction

Despite satisfactory metabolic control, a supernormal glomerular filtration rate (GFR) can be found in some but not all patients with Type 1 (insulin-dependent) diabetes mellitus [1-3]. An increased kidney weight with an increased glomerular filtration surface area [4,5], and a decreased renal vascular resistance [6] are held responsible for this glomerular "hyperfiltration" which is considered to be one of the causal factors in the development of diabetic glomerulopathy [7]. In a previous study we have demonstrated that the increased GFR in Type 1 diabetic patients is not based on a predominantly efferent vasodilatation [3]. This is in accord with the hypothesis of Alvestrand and Bergstrom, who postulated that the supernormal GFR in insulin-dependent diabetic patients is induced by a liver hormone which causes afferent vasodilatation [8,9].

The rise in GFR which can be observed after a meat meal [10] or infusion of amino acids [11] is also attributed to afferent vasodilatation. As in healthy individuals values for GFR, effective renal plasma flow (ERPF) and filtration fraction (FF) during infusion of amino acids resemble values for these variables in well-controlled diabetic patients [3], it might be that administration of amino acids has a lesser effect on GFR, ERPF and FF of satisfactory controlled Type 1 diabetic patients because of already existing afferent vasodilatation. Therefore, we undertook such a study, the results of which are dealt with in this paper. Moreover, the effects of low-dose dopamine on renal haemodynamics were compared with the effects of amino acids on renal function of control subjects and diabetic patients.

Patients and methods

In 16 insulin-dependent diabetic patients (eight male and eight female) renal function studies were performed. The median

age of these patients was 31 years (20-51) and the median duration of diabetes 17 years (8-29). After stimulation with glucagon, C-peptide levels were below 0.1 nmol/l in all patients. Diabetic nephropathy was considered to be absent since in all patients proteinuria was <0.5 g/24h, creatinine clearance was above 80 ml/min, none of them had hypertension, and there existed no or only mild background retinopathy. All patients were treated with intensified insulin therapy, i.e. multiple insulin injections and frequent home blood glucose monitoring with reagent strips and adjustment of the insulin dose accordingly. (Near) normoglycaemia (3-10 mmol/l) was pursued for all patients. To check glycaemic control all patients were seen at the diabetes outpatient clinic every four weeks and glycosylated haemoglobin (HbA_1) was measured every two months using the colorimetric method of Flückiger and Winterhalter. Furthermore, at least once a month a 24hr blood glucose profile was obtained by measuring blood glucose in finger prick samples taken at 03.00, 07.00 (fasting), 09.00, 11.00, 14.00, 17.00, 19.00 and 24.00 hr.

The control group consisted of 12 healthy volunteers (eight male, four female) with a median age of 26.5 years (23-50). Median age nor sex distribution differed significantly between the diabetic group and the control group.

On two separate days, renal haemodynamic studies were performed in supine position allowing to void the subjects in upright position if necessary. On day one, a standard procedure was used to measure GFR and ERPF. ^{125}I-iothalamate was used to determine GFR and ^{131}I-hippurate to determine ERPF [12]. The radiopharmaceuticals were infused at a constant rate after the administration of a priming dose. After an equilibration period of 1.5 hr, two 2-hr clearances were determined using the formula UxV/120xP. At the end of this standard procedure, dopamine was infused at a dose of 1.5-2.0 μg/kg/min for 2hr (Braun Unita II pump). GFR and ERPF during these 2hr were compared with the GFR and ERPF preceding dopamine infusion. On day two, infusion of an amino acid solution (Vamin^{R}N) was started at 18.00 pm at a rate of 500 ml/6hr (=83 ml/hr). On day 3, the standard procedure was

repeated and prolonged again for a 2-hr period during which a low dose dopamine was infused while the infusion of amino acids was continued. The coefficients of the day to day variation of GFR and ERPF are ≤2.2% and ≤5.0%, respectively [12]. Filtration fraction was defined as the ratio GFR:ERPF (normal values in our laboratory amount to 0.22-0.28). A diuresis of at least 100 ml/hr was maintained by the oral administration of fluids.

Heart rate (HR) and blood pressure were recorded at 60 min intervals during the infusion of low-dose dopamine and the preceding 2-hr period. Mean arterial pressure (MAP) was calculated by adding one third of the pulse pressure to the diastolic blood pressure. Urinary excretion rate of albumin was measured by radioimmunoassay.

Wilcoxon rank sum tests on paired and unpaired samples were used for the statistical analysis of our data as we considered our data not normally distributed. Deming's method was used to study correlations. A $p<0.05$ was chosen as level of significance.

Table 1

	DM	alb	BL	Do	AA	A+D
1	27	233	90	94	103	110
2	15	154	116	137	146	167
3	29	97	125	141	130	142
4	16	165	107	109	112	118

Duration of diabetes (DM; years), baseline (BL) GFR and GFR during dopamine (Do) infusion, amino acid (AA) infusion and combined (A+D) infusion (ml/min/1.73 m^2) of the four patients with increased microalbuminuria (alb; μg/min)

Results

From the initial investigated diabetic subjects, four had to be skipped because of an elevated microalbuminuria (≥20 μg/min). Individual data on duration of diabetes, microalbuminuria, GFR

Table 2

		BL	ΔDo%	ΔAA%	ΔA+D%
C	median	107.0	10.5**	9.5**	17.5**
	mean	106.6	11.2	12.3	20.6
	SEM (±)	3.3	2.1	2.9	2.7
D	median	129.0	8.0**	4.5*	17.5**
	mean	134.0	10.7	6.9	21.4
	SEM (±)	7.4	2.1	2.8	4.2
ND	median	115.0	7.0*	15.0*	33.0*
	mean	116.0	12.4	14.1	32.0
	SEM (±)	4.1	3.8	3.1	5.0
HD	median	145.5	9.5*	1.0	12.5*
	mean	152.0	9.1	-0.2	10.8
	SEM (±)	9.6	1.7	2.2	2.9

*p<0.05; **p<0.01

The effects of dopamine (Do), amino acid (AA) and combined (A+D) infusions on baseline GFR (BL; ml/min/1.73 m^2) of healthy individuals (C), patients with insulin-dependent diabetes mellitus (D) and these patients after subdivding them in normofiltering (ND) and hyperfiltering (HD) diabetics.

and response of GFR to dopamine infusion, amino acid infusion and combined infusion are given in Table 1. In the 12 diabetic patients left (microalbuminuria <20 μg/min), MAP decreased during the infusion of low-dose dopamine. Median MAP was 97 mmHg (range 83-117) baseline and 90 mmHg during dopamine infusion (range 80-107; $p<0.05$). Infusion of amino acids and the combined infusion of amino acids and dopamine did not affect MAP significantly, values being 96 mmHg (82-115) and 92 mmHg (78-105), respectively. In the healthy volunteers neither dopamine infusion nor amino acid and the combined infusion caused significant changes in MAP. Values were 92 mmHg (78-108) baseline, 93 mmHg (80-105) during dopamine infusion, 93 mmHg (83-107) during amino acid infusion and 92 mmHg (82-105) during the combined infusion. Neither in the

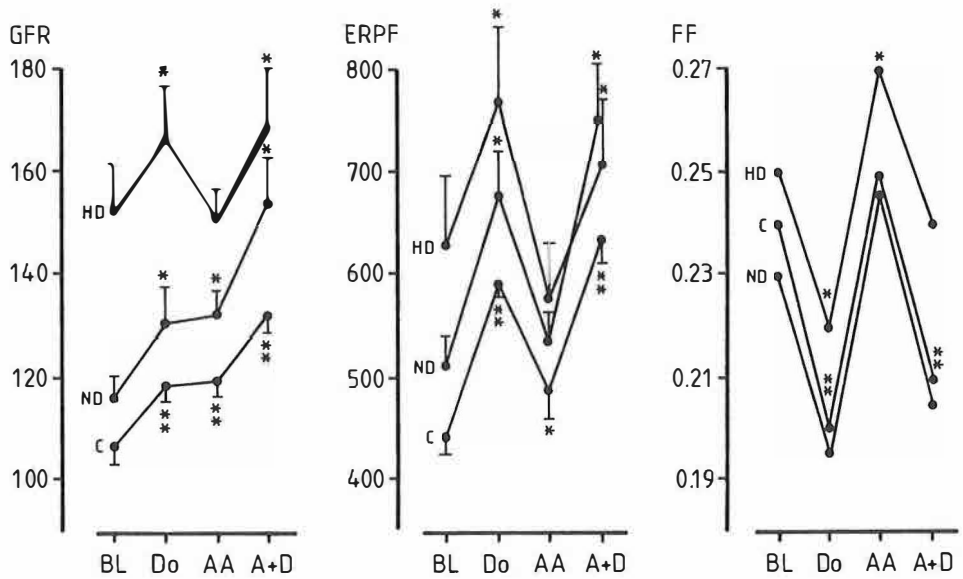

Figure 1
The effects of dopamine infusion (Do), amino acid infusion (AA) and combined infusion (A+D) on baseline (BL) GFR (left panel), ERPF (middle panel) and FF (right panel) of control subjects (C), normofiltering diabetics (ND) and hyperfiltering (HD) diabetics. (GFR and ERPF both in ml/min/1.73 m^2; *p<0.05; **p<0.01).

diabetic patients nor in the control subjects HR changed significantly during dopamine infusion, amino acid infusion or the combined infusion. In the diabetic patients median HR was 76 beats per minute (bpm; 52-92) baseline, 78 bpm (56-100) during dopamine infusion, 72 bpm (64-112) during amino acid infusion and 76 bpm (60-100) during the combined infusion. In the volunteer group those values were 80 bpm (48-92), 80 bpm (60-100), 82 bpm (60-88) and 84 bpm (72-100), respectively. During the four test situations there were no significant differences in MAP or HR between the diabetic patients and the control subjects.

The effects of dopamine infusion, amino acid infusion and the combined infusion of amino acids and dopamine on GFR are listed

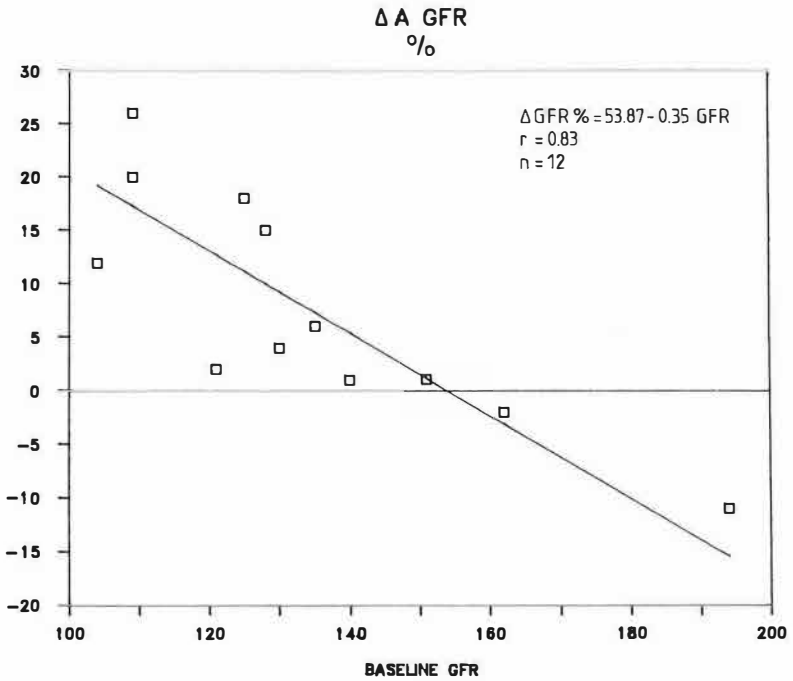

Figure 2
Amino acid-induced change (ΔA GFR%) versus baseline GFR (ml/min/1.73 m^2) in 12 Type 1 diabetic patients.

in Table 2. There tended to be a difference betweeen the diabetic subjects and the control subjects with respect to the response to amino acid infusion: baseline GFR was higher ($p<0.01$) in the diabetic patients and GFR tended to increase to a lesser extent. Therefore, the diabetic patients were subdivided in a patient group (n = 6) with a normal baseline GFR, defined as a baseline GFR below 130 ml/min/1.73 m^2 (130 = mean baseline GFR plus 2x standard deviation of the control subjects), and a patient group (n=6) with a supernormal GFR. A striking difference occurred (figure 1). In the diabetic patients with a normal baseline GFR, amino acid infusion caused a significant increase in GFR which did not differ significantly from the amino acid-induced rise in GFR of the control subjects. However, in the patients with a

Table 3

		BL	ΔDo%	ΔAA%	ΔA+D%
C	median	415	35.5**	6.0*	36.0**
	mean	443	35.9	10.4	42.4
	SEM (±)	16.6	4.2	4.3	7.0
D	median	562	25.0**	0.0	27.0**
	mean	568	28.2	-0.6	30.8
	SEM (±)	40.7	4.1	3.3	7.5
ND	median	538	27.5*	4.5	40.0*
	mean	510	33.3	5.6	47.5
	SEM (±)	29.9	5.0	4.7	9.4
HD	median	587	19.5*	-8.0	8.5*
	mean	627	23.1	-6.8	14.1
	SEM (±)	71.0	6.3	3.3	7.0

*p<0.05; **p<0.01

The effects of dopamine (Do), amino acid (AA) and combined (A+D) infusions on baseline ERPF (BL; ml/min/1.73 m^2) of healthy volunteers (C), patients with Type 1 diabetes mellitus (D) and these patients after subdividing them in normofiltering (ND) and hyperfiltering (HD) diabetic patients.

supernormal GFR, amino acid infusion did not change GFR significantly (Table 2 and figure 1). Interestingly, there appeared to exist a strong negative correlation between the amino acid-induced change in GFR and the baseline GFR: amino acid-induced change in GFR decreased with increasing baseline GFR ($\Delta GFR\% = 53.9 - 0.35 \times GFR$; $r=0.83$; $p<0.01$; figure 2).

On the contrary, dopamine infusion increased GFR to the same extent in as well as the diabetic patients with a supernormal GFR as in the diabetic patients with a normal GFR or the control subjects. The combined infusion of amino acids and dopamine increased GFR most in both the normofiltering diabetic patients and the control subjects. In patients with a supernormal GFR, the rise in GFR during the combined infusion did not differ significantly from the dopamine-induced change in GFR.

Table 4

		C	ND	HD
sex ratio	M/F	8/4	4/2	3/3
BL MAP	median	92	107*	89
(mmHg)	mean	93	106	90
	SEM (±)	2.9	4.9	2.8
age (years)	median	26.5	36.0*	27.5
	mean	31.9	37.3	27.3
	SEM (±)	2.9	3.0	1.8
Duration of	median		18.0	9.5
DM (years)	mean		16.3	12.3
	SEM (±)		2.5	2.2
HbA_1 (%)	median		7.1	7.2
	mean		7.0	7.4
	SEM (±)		0.2	0.3
24-hr gluc	median		9.5	7.8
(mmol/l)	mean		9.4	7.9
	SEM (±)		0.3	1.0
microalb.	median		5.0	6.5
(μg/min)	mean		6.7	7.7
	SEM (±)		2.3	2.4
protein/kg	median		1.3	1.9
	mean		1.5	1.5
	SEM (±)		0.2	0.1
urea excr	median		38.5	44.5
(mmol/2hr)	mean		35.2	48.4
	SEM (±)		7.0	5.0

*ND versus HD $p<0.05$

Data on sex distribution, age, duration of diabetes (DM), dietary protein intake and metabolic control. C = control subjects; ND = normofiltering diabetic patients; HD = hyperfiltering diabetic patiens; BL = baseline; 24-hr gluc = 24-hr blood glucose profile; microalb = microalbuminuria; urea excr = urinary urea excretion.

As can be seen from Table 3 and figure 1, amino acids do affect renal haemodynamics in another way than dopamine. Low-dose dopamine caused a significant increase in ERPF in as well as the control subjects as the diabetic patients. As the percentage increase in ERPF exceeded the percentage increase in GFR, FF fell. During amino acid infusion ERPF increased significantly in the healthy volunteers. However, FF tended to increase (0.24 vs 0.25) indicating a relatively larger increase in GFR than ERPF which is in contrast with the observations during dopamine infusion. In the diabetic patients no significant change in ERPF was found during amino acid infusion whereas FF rose significantly (0.24 vs 0.25; $p<0.01$).

Diabetic patients with a normal baseline GFR were older (median age 36.0 years) than both the control subjects (median age 26.5 years) and the hyperfiltering diabetic patients (median age 27.5 years) although only the difference between the two patient groups was statistically significant ($p<0.05$; Table 4). Duration of diabetes tended to be longer in the diabetic patients with a normal baseline GFR, but the difference was not statistically significant (table 3). Median HbA_1 (normal range 6.0-8.5%) just before the renal function studies was 7.1% (6.1-7.6) in the normofiltering diabetic patients and 7.2% (6.4-8.7) in the hyperfiltering diabetic patients (n.s.). Median 24-hr blood glucose, calculated from the 24-hr blood glucose values of the three months preceding the renal function studies, was 9.5 mmol/l (8.5-10.4) in the patients with a normal baseline GFR and 7.8 mmol/l (4.7-11.4) in the patients with a supernormal baseline GFR (n.s.). From these observations it was concluded that the metabolic control of our patients was satisfactory, though not optimal. Furthermore, we concluded that metabolic control in the patients with a supernormal GFR certainly was not worse than metabolic control of patients with a normal GFR.

Discussion

Diabetic nephropathy does occur in approximately 40% of all patients with Type 1 (insulin-dependent) diabetes mellitus [13]. Glomerular hyperfiltration, which can be found in these patients even during good metabolic control [2], is thought to be an important factor in the development of diabetic nephropathy [7]. Increased kidney weight and glomerular surface area, a decreased renal vascular resistance and several hormones (e.g. glucagon and growth hormone) are considered to be involved in the genesis of this glomerular hyperfiltration. Recently, we demonstrated that infusion of a low dose dopamine, which exerts its effect on GFR by increasing renal blood flow due to a predominant vasodilatation of the efferent arteriole [3], resulted in a rise in GFR and ERPF of healthy volunteers and Type 1 diabetic patients of a comparable magnitude. Thus, it was concluded that glomerular hyperfiltration in insulin-dependent diabetic patients was not based on a decrease in resistance of the efferent arteriole. In the present study this observation is confirmed since dopamine-induced changes in ERPF and GFR of healthy volunteers did not differ from that of Type 1 diabetic patients.

By means of micropuncture studies it has been demonstrated in the rat that a high protein diet results in a rise in GFR because of an increase in net ultrafiltration pressure and glomerular blood flow, both induced by a decreased resistance of the afferent arteriole [14,15]. The FF was slightly higher in case of high protein feeding. In man the administration of amino acids or a meat meal also causes an increase in GFR whereas FF increases slightly or is unaffected. Therefore, amino acids and protein probably affect GFR in man also by the induction of afferent vasodilatation. However, amino acid- or protein-induced changes in the ultrafiltration coefficient are not excluded. Recently, it was postulated that the protein-induced rise in GFR as well as the supernormal GFR in Type 1 diabetic patients are caused by a liver hormone which causes afferent vasodilatation [8,9]. Therefore, a lesser effect of amino acids on GFR might be found

in case of already existing afferent vasodilatation. The observation of the present study that the GFR of hyperfiltering diabetic patients does not increase after amino acid infusion whereas normofiltering diabetic patients have a normal response to amino acid infusion, does favour the hypothesis that in hyperfiltering diabetic patients an afferent vasodilatation exists. Because of this decrease in resistance of the afferent arteriole, glomerular hypertension can occur and persist, and thus, may be involved in the initiation and progression of diabetic nephropathy. Furthermore, it is imaginable that prolonged afferent vasodilatation ultimately may cause damage to the afferent arteriole itself and results in an impaired autoregulation of glomerular filtration rate. In patients with diabetic nephropathy the existence of an impaired autoregulation indeed has been demonstrated by Parving et al. [16].

The four patients with increased microalbuminuria had a relatively long duration of diabetes but showed a normal baseline GFR and seemed to possess a normal reserve filtration capacity. This might point to the fact that glomerular hyperfiltration is not strictly necessary for the development of microproteinuria. Further studies on this subject are warranted, however.

As can be seen in Table 4, several possibilities were excluded to explain the observed difference between hyperfiltering and normofiltering diabetic patients with respect to the effect of amino acids on GFR. Protein intake and urea excretion were not significantly different. The explanation that normofiltering diabetic patients revealed a higher MAP might be that they were significantly older and moreover, had a longer duration of their disease. Why they, despite this, showed no increased microalbuminuria and a normal reaction on amino acid infusion remains at this moment speculative, although it indicates that these patients have "healthy" kidneys.

The observation that GFR rises most during a combined infusion of low-dose dopamine and amino acids can be explained by their different effects on renal haemodynamics [17]. A dopamine-induced efferent vasodilatation resulting in an increased renal

plasma flow and an amino acid-induced afferent vasodilatation causing an increase in the hydrostatic pressure in the glomerular capillary will be additive. The fact that the change in GFR during the combined infusion did not differ from the change in GFR during dopamine infusion in hyperfiltering diabetic patients whereas, on the other hand, in normofiltering diabetic patients the combined infusion resulted in a significant larger rise in GFR when compared with dopamine infusion alone, also favour the assumption of the existence of afferent vasodilatation in insulin-dependent diabetic patients with a supernormal GFR.

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Chapter 8

GENERAL DISCUSSION
(and look at the future)

Based on the results of micropuncture studies Brenner and co-workers have developed a model of glomerular ultrafiltration in the rat [1-4]. This model has deepened our insights in the factors which govern glomerular ultrafiltration. Of these factors glomerular plasma flow appeared to be most important. Since in man, in contrast to the rat, no methods are available to measure single nephron glomerular filtration rate and its determinants, it is questionable whether the observations in the rat model are completely valid in man. For instance, in the dog glomerular filtration rate (GFR) appeared to be only moderately dependent on renal plasma flow [5]. Nevertheless, we assume that the GFR in man also depends on glomerular plasma flow, net ultrafiltration pressure and the ultrafiltration coefficient as long as the oncotic pressure of arterial plasma remains constant. The clearance of PAH or ^{131}I-hippurate can be used to measure the effective renal plasma flow (ERPF). The latter generally is considered to be a valid reflection of the glomerular plasma flow. Thus, changes in ERPF reflect changes in glomerular plasma flow although we have to realize that changes in the distribution of intrarenal blood flow and changes in the extraction of PAH or ^{131}I-hippurate also may have a marked effect on ERPF. It is even more difficult in man to get reliable information about the values for net ultrafiltration pressure and the ultrafiltration coefficient. Changes in the filtration fraction (FF) may indicate whether these variables are involved in changes of the GFR. Again, changes in distribution of intrarenal blood flow might disturb such interpretations. Especially so, since the renal cortex contains two populations of nephrons: juxtamedullary nephrons with a low FF and superficial nephrons with a high FF

[6]. From the above mentioned remarks we have to conclude that in man translation of changes in effective flow and/or FF in changes of the determinants of glomerular ultrafiltration at this moment are more or less speculative.

In order to clarify the basic questions posed in this thesis [p 6] we have tried to manipulate renal haemodynamics. Therefore, changes in haemodynamics were pursued by the infusion of low-dose dopamine and of amino acids, separately or combined administered. Dopamine acts on specific dopaminergic receptors which amongst others are located in the renal vascular bed [7,8]. Stimulation of these receptors results in an increased cortical blood flow and a rise in GFR [9,10]. The observed fall in FF can be explained by a substantially larger rise in ERPF than in GFR, for instance, because of a predominant efferent vasodilatation. However, both a relative shift of blood flow from cortical nephrons to juxtamedullary nephrons and a change (i.e. a decrease) in the ultrafiltration coefficient may account for this fall in FF too. Although dopamine is an endogenous catecholamine, it is not clear yet whether endogenous dopamine is of importance to renal physiology in man. Several investigators have found in animals indications for renal dopamine production [11-14], possibly by the proximal tubule [15]. The results presented in this study show that in man the relative dopamine-induced changes in ERPF and GFR of both kidney donors and renal patients with an apparently normal baseline GFR are less when compared with control subjects. These observations do favour the assumption that endogenous dopamine may have a physiological role. A loss of glomeruli (or glomerular surface area), thus, might cause a release of endogenous dopamine which results in an increase in ERPF (i.e. glomerular plasma flow) in order to maintain GFR. Studies on the effects of low-dose dopamine on renal haemodynamics of kidney donors before and after kidney donation as well as studies on the effects of specific antagonists of renal dopamine receptors might further elucidate this supposition and are warranted, therefore. Regardless a physiological role for endogenous dopamine or not, exogenous dopamine can be used to

test the existence of a renal reserve filtration capacity. The increase in GFR appeared to be largest in healthy individuals and was absent in renal patients with a baseline GFR below 50 ml/min/1.73 m^2. The latter may point to the existence of glomerular hyperfiltration in patients with a GFR less then 50 ml/min/1.73 m^2 [chapters 2,3].

Compared with dopamine, amino acids and protein have different effects on renal haemodynamics as is expressed by the changes in FF. After the infusion of low-dose dopamine FF falls, whereas FF does not change or rises after the administration of amino acids or protein. As can be calculated from the observation of Zatz et al. [16], the increase in GFR during high protein feeding in rats is also associated with a rise in FF. These findings are attributed to an increased net ultrafiltration pressure together with an increased glomerular plasma flow, both as a result of an afferent vasodilatation. In contrast to dopamine, much less is known about the way amino acids or protein cause changes in renal haemodynamics. It is very likely, however, that the rise in GFR observed after administration of amino acids or protein is hormonally mediated. Protein intake causes a postprandial rise in serum glucagon levels [17]. Nevertheless, glucagon itself most likely is not responsible for the amino acid or protein-induced rise in GFR, since direct infusion of glucagon into the renal artery does not change GFR (and ERPF) [18,19]. However, when glucagon is infused into the portal vein, even in doses which result in portal vein concentrations of glucagon as can be found after a meat meal [19], a rise in GFR occurs. This observation points to the existence of a liver-derived substance ("glomerulopressin") [18,19]. The presence of this substance was demonstrated by Uranga in the toad [20] and later on in other animals [18,21]. It exerts its effect on renal haemodynamics by the induction of afferent vasodilatation [22]. Whether glomerulopressin also exists in man is not clear yet, although the observation of Hirschberg et al. [23] that in patients with severe liver disease a meat meal does not affect GFR, favours this possibility. More investigations are necessary in order to

clarify whether a protein/glucagon-mediated release of glomerulopressin indeed exists in man and whether it causes afferent vasodilatation by either a direct or an indirect effect since, for instance, it has been demonstrated that indomethacin blunts the effect of amino acids on GFR as well as the effect of glomerulopressin [24,25]. This indicates that renal prostaglandines may be involved to some extent. Furthermore, studies with specific antagonists (provided they can be found) that cause afferent vasoconstriction and thus reduce glomerular hydrostatic pressure, are warranted in order to investigate whether such antagonists can slow down or even prevent the deterioration of renal function in case of moderate to severe renal failure.

Another explanation for the amino acid-induced rise in GFR was given by Woods et al. [26], who have demonstrated that amino acid infusion causes afferent vasodilatation based on an increased reabsorption of amino acids in the proximal tubule. The latter will be accompanied by an increased sodium reabsorption. This will result in a decrease in sodium delivery at the distal tubule. Therefore, the glomerular tubular feedback will cause afferent vasodilatation and a rise in GFR in order to increase distal sodium delivery. This mechanism may contribute to the amino acid-induced rise in GFR. However, it can not explain the observations of Uranga et al. [18] and Premen et al. [19].

In this thesis we have found that the amino acid-induced rise in GFR was largest in healthy volunteers whereas amino acids did not cause significant changes in GFR of patients with moderate to severe renal insufficiency [chapter 3]. Again, this may point to the existence of glomerular hyperfiltration in these patients. Both Bosch et al. [27] and Rodriquez-Iturbe et al. [28] also noticed that the effect of a protein load was less in patients with renal disease when compared with healthy control subjects. We could not establish a significant difference in amino acid-induced percentage increase in GFR between healthy volunteers and healthy individuals after uninephrectomy. This may imply that mechanisms tested during the administration of amino acid or protein are not involved in the renal adaptation to glomerular

damage. However, our observation is in contrast with the findings of Rodriquez-Iturbe et al. [28] who found a significant difference between healthy individuals and uninephrectomized persons with respect to the protein-induced rise in GFR. Studies in kidney donors before and after kidney donation may provide further information on this subject and thus, may answer the question whether afferent vasodilatation is involved in the renal mechanisms which compensate for a loss of glomeruli (or glomerular surface area).

Apart from a rise in GFR, infusion of amino acids also results in an increased urinary sodium excretion [25,29, chapter 3]. Recently, it was demonstrated that high protein diets cause an impaired autoregulation of renal blood flow in 5/6-nephrectomized rats [30]. Amino acids and protein may impair renal autoregulation by the induction of afferent vasodilatation which will interfere with the glomerulotubular feedback and result in an increased natriuresis. As the effects of protein and amino acids on GFR probably are mediated by a liver substance, this "glomerulopressin" then must have natriuretic qualities. Further investigations on this subject may elucidate this.

In subtotally nephrectomized rats, high protein diets accelerate the down hill course of renal function. As is mentioned before, high protein feeding increases net ultrafiltration pressure and glomerular plasma flow. However, in 5/6-nephrectomized rats low protein diets slow down the progression of renal failure, in association with a normalization of the net ultrafiltration pressure. The glomerular plasma flow on the contrary, remains elevated as a result of a persistent decrease in the resistance of the efferent arterioles [31]. These observations indicate that especially an increased hydrostatic pressure in the glomerular capillaries is harmful to the glomeruli and has to be prevented. Two other observations favour the assumption that especially an elevated hydrostatic pressure is harmful to the glomerulus. Firstly, the fact that antihypertensive drugs (i.e. angiotensin-I converting enzyme inhibitors) which decrease the hydrostatic pressure in glomerular capillaries, are able to

prevent the development of renal failure in 5/6-nephrectomized rats, whereas drugs which do not affect the glomerular hydrostatic pressure have no or less effect [32-34]. Secondly, the observation of De Jong et al. [35] that in a patient with polycythaemia and secondary proteinuria an extremely high FF and a low ERPF were present. After phlebotomy, FF fell while ERPF (and GFR) increased and proteinuria disappeared, all probably because of a fall in the hydrostatic pressure in the glomerular capillaries. Recently, these observations of De Jong et al. were confirmed by Loute et al. [36]. Thus, it seems that glomerular hypertension is the supportive factor in the progression of glomerular damage to end stage renal failure. Therefore, treatment strategies to prevent this glomerular hypertension have to be developed. Furthermore, these observations may lead to a subdivison of the so-called "glomerular hyperfiltration" in glomerular hyperperfusion and the probably more damaging glomerular hypertension.

Table 1

		BL	SP	LP	MM	AA
GFR	mean	110	122*	125*	131**	132**
	SD	11	15	11	12	11
ERPF	mean	462	481	496*	526*	540**
	SD	52	63	54	59	50
FF	mean	.24	.25*	.25	.25*	.25

*p<0.05; **p<0.01

The effects of 85 g soy protein (SP), 85 g lactoglobulines (LP), 95 g red beef protein (MM) and amino acids (AA, Vamin-18, 2ml/min) on baseline (BL) GFR, ERPF and FF of 6 healthy volunteers. (Published with permission of the investigators, Bilo et al. [41]).

The results of several studies in animals and man have shown that dietary protein restriction is an effective treatment in slowing down the deterioration of renal function [37-39] and therefore, may be the initial step in the treatment of patients with renal insufficiency. Interestingly, vegetarians reveal a

remarkably low creatinine clearance [40]. Several investigators have drawn attention to the fact that there appears to be a difference between the several sources of protein with respect to their effect on renal haemodynamics (Table 1) [41,42]. Preliminary results of one of our present studies also indicate that non-red meat ("casilan") protein does increase GFR less than red meat or an amino acids mixture do (median increase 4% versus 12%, respectively). Other workers, however, did not find this difference [43,44]. The possibilty of such a difference has to be investigated further since it may have consequences for the dietary treatment of patients with chronic renal insufficiency. Such a difference might be due to a diversity of amino acid composition of these proteins or to a difference in enteral digestion and absorption.

Another way to treat patients with moderate to severe renal failure in order to prevent the development of end-stage renal failure may be the use of ACE-inhibitors. It has been found that in (subtotally) nephrectomized rats these drugs are capable to slow down the deterioration of renal function possibly by inducing a fall in the glomerular hydrostatic pressure [32,33]. Studies in man on this subject are warranted.

Micropuncture studies in rats have revealed that not only in animals with a substantially impaired renal function glomerular hyperfiltration can exist, but also in rats with insulin-dependent diabetes mellitus [16,45]. The supernormal GFR in these animals is caused by a decrease in vascular resistance of the afferent arteriole and results in glomerular hypertension [16]. In insulin-dependent diabetic patients a supernormal GFR can be found too, despite good metabolic control [46-48, chapter 6+7]. This elevated GFR is associated with an unaffected or slightly increased FF. Alvestrand and Bergström have postulated that this glomerular hyperfiltration in Type 1 diabetic patients also is caused by increased glomerulopressin levels resulting in glomerular hypertension due to afferent vasodilatation [49]. In the dog it has been demonstrated that pancreatectomy caused an increase in GFR which indeed was associated with a rise in glucuronide

levels in hepatic vein blood (glomerulopressin probably is a glucuronide [50]). Infusion of insulin in the portal vein normalized both the GFR and the glucuronide concentration in the hepatic vein [50]. Infusion of insulin into the femoral vein, however, did not affect the supernormal GFR in these pancrectomized dogs. Therefore, del Castillo et al. [50] concluded that a lack of insulin reaching the liver was the cause of the elevated GFR in these animals. On the other hand it was found that glucagon is a potent agent to release glomerulopressin from the liver. Glucagon infusion causes a rise in GFR in healthy volunteers and serum levels of glucagon can be elevated in insulin-dependent diabetic subjects [51,52]. Thus, it is questionable whether a lack of insulin reaching the liver is the only cause of an increased glomerulopressin release (and GFR) in insulin-dependent diabetes. A disturbance in the hormonal balance (i.e. insulin versus glucagon/growth hormone/other agents) more likely might be responsible. Regardless the existence or absence of a glomerulopressin-induced supernormal GFR in insulin-dependent diabetics, the elevated FF in these patients points to the presence of glomerular hypertension. Since the latter, in analogy to renal patients, most likely will be harmful its existence has to be excluded in order to try to prevent the development of diabetic nephropathy.

Until now, in at least two studies it has been demonstrated that good metabolic control does not prevent the deterioration of renal function in existing diabetic nephropathy [53,54]. However, this does not imply that metabolic control would be unimportant since, for instance, especially during poor metabolic control glomerular filtration is increased which may accelerate the deterioration of renal function. Optimal glycaemic control itself, however, seems not to be a sufficient measure to stop the downhill course of renal function in manifest diabetic nephropathy.

In diabetic rats protein restriction increases the resistance of the afferent arteriole and thus lowers the glomerular hypertension [16]. The institution of protein-restricted diets,

therefore, may have a beneficial effect in hyperfiltering diabetic patients too. The latter seems to be in accord with our observation that infusion of amino acids doesnot affect GFR of hyperfiltering insulin-dependent diabetic patients [chapter 7]. A similar observation is the fact that amino acid infusion doesnot have an effect on GFR of patients with moderate to severe renal insufficiency [chapter 4], whereas protein restriction does cause a fall in GFR in these patients [p 5] and has a benefical effect in case of renal failure with respect to the development of end-stage renal disease. Thus, studies on the effect of protein restriction on renal haemodynamics of well-controlled hyperfiltering Type 1 diabetic patients are of interest to investigate whether such diets may prevent the development of diabetic nephropathy.

A second possibility to prevent the development of diabetic nephropathy in well-regulated insulin-dependent diabetic patients with a supernormal GFR may be the use of ACE-inhibitors since these agents cause a decrease in vascular resistance of the efferent arteriole thus reducing the glomerular hydrostatic pressure. It has already been demonstrated in diabetic patients with heavy proteinuria that captopril reduces existing proteinuria. The observation was explained by a captopril-induced reduction in glomerular hypertension [55].

Thirdly, the use of drugs which cause specifically afferent vasoconstriction may be useful to reduce glomerular hyperfiltration in diabetic patients. Indomethacin may be one of these drugs. It normalizes both the hydrostatic pressure and the net ultrafiltration pressure in diabetic rats by inducing afferent vasoconstriction [56]. In hyperfiltering diabetic patients studies on the effects of indomethacin on renal haemodynamics are contradictory [57,58] and, therefore, requires further investigation, taking into account that long-term treatment with this agent may herald certain risks.

Fourthly, studies are necessary to investigate whether low-dose dopamine decreases the hydrostatic pressure in the glomerular capillaries as oral dopamine agonists (e.g. Ibopamine and

Fenoldopam [59,60]) then may be used to decrease glomerular hypertension in diabetic patients with a supernormal GFR.

In this thesis we have shown that both intravenous administration of low-dose dopamine and amino acids increase GFR to the same extent but that the combined infusion of these agents results in even higher values for GFR. Recently, our observations have been confirmed by Allison et al [60]. It might be, however, that administration of amino acids in higher amounts than we used causes even larger increases in GFR. Since several drugs (e.g. ACE-inhibitors/angiotensin-II antagonists and Ca^{++}-antagonists [61-63]) are capable to increase renal blood flow and GFR, it may be that the combination of amino acids, low-dose dopamine and those agents have an additional effect in elevating GFR. Thus, it is not possible yet to answer the question posed in this thesis whether the maximal GFR can be measured. Further studies may provide an answer to this question, although we have to wonder at the same moment whether such manipulations with renal haemodynamics are of physiological importance indeed.

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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 glomerulopathy (chapter 2). In these patients the infusion of low-dose dopamine does not affect effective renal plasma flow (ERPF) and

GFR if baseline GFR amounts to 73 ml/min/1.73 m^2 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 m^2.

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 m^2. 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^{R}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 vasodilatation 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 dilatation of the afferent arteriole since amino acid infusion does not affect GFR in these patients wherease 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 diabets mellitus with or without nephropahty.

SAMENVATTING

De nier bestaat uit een groot aantal functionele eenheden, nefronen genaamd. Een nefron bestaat uit twee delen, het kapsel van Bowman met de glomerulus en de tubulus. In de ruimte van Bowman onstaat de "voorurine" door filtratie door de glomerulaire basale membraan van water, zout en stofwisselingsproducten vanuit de bloedbaan (de glomerulaire filtratie snelheid, afgekort GFR). Vanuit de tubulus wordt het grootste deel van het water, zout en nuttige stofwisselingsprodukten teruggeresorbeerd. Tevens worden in de tubulus andere stofwisselingsprodukten aktief uitgescheiden.

Het is gebleken dat tijdens de zwangerschap de GFR stijgt. Eveneens kan een hogere GFR worden gevonden bij gebruik van een eiwitrijk dieet. Beide observaties geven aan dat er bij de mens een reserve in de filtratiecapaciteit aanwezig is. Het meest overtuigende bewijs voor deze veronderstelling is dat na verwijderen van een nier de GFR ongeveer 70 procent van de waarde van voor de nierdonatie bedraagt. Dit geeft tevens aan dat een verlies van glomeruli deels kan worden gecompenseerd door "hyperfiltratie" van de resterende glomeruli. In rattenstudies is echter aangetoond dat een dergelijke compensatoire hyperfiltratie, bijvoorbeeld geïnduceerd door subtotale nefrectomie, leidt tot een progressieve verslechtering van de nierfunktie en tot het ontstaan van eiwitverlies via de urine (= proteïnurie) en op zichzelf dus schadelijk kan zijn. De beide verschijnselen konden gunstig worden beïnvloed door het geven van een eiwitbeperkt dieet. In een recente studie hebben we aan kunnen tonen dat eiwitbeperking bij mensen met een matige tot ernstige nierinsufficiëntie eveneens een minder snelle verslechtering van de nierfunktie geeft. Dit kan erop wijzen dat mogelijk ook bij de mens "schadelijke glomerulaire hyperfiltratie" kan voorkomen. Derhalve hebben we onderzocht of de reserve filtratiecapaciteit (d.w.z. een afwezigheid van glomerulaire hyperfiltratie) kan worden gemeten bij patienten met een nierziekte. Hiertoe hebben

we geprobeerd de GFR te beïnvloeden d.m.v. een infusie van een lage dosering dopamine en d.m.v. een infusie van aminozuren, welke we afzonderlijk en gecombineerd hebben toegediend.

Dopamine is een endogeen catecholamine. Het werkt op specifieke dopaminerge receptoren en het veroorzaakt in subfarmacologische doseringen (1.5-2.0 μg/kg/min) renale vasodilatatie. Daardoor stijgen de renale bloeddoorstroming en de GFR. Derhalve hebben we gebruik gemaakt van de infusie van dopamine in bovengenoemde dosering om te zien of de GFR hiermee "verbeterd" kan worden. In eerste instantie is dit gedaan bij 32 patienten met IgA-glomerulopathie. Het bleek dat het niet mogelijk was om bij deze patienten een stijging van de GFR te bewerkstelligen als de GFR lager was dan 73 ml/min/1.73 m^2. Boven dit punt bleek een nauwe relatie te bestaan tussen de uitgangs-GFR en de door dopamine veroorzaakte stijging van de GFR, d.w.z. naarmate de uitgangs-GFR hoger was, was er een grotere stijging tijdens dopamine infusie. Ten gevolge van een relatief grotere toename van de effectieve renale plasma doorstroming (ERPF) dan van de GFR daalde de filtratiefractie (FF = GFR:ERPF). Dit kan worden verklaard door een op de voorgrond staande door dopamine geïnduceerde dilatatie van de efferente arteriole. Echter een door dopamine veroorzaakte verschuiving van de renale bloeddoorstroming naar nefronen van de binnenste cortex, welke een lagere FF hebben, kan eveneens een bijdrage leveren aan de daling van de FF tijdens dopamine-infusie. We hebben geconcludeerd, dat bij patienten met IgA-glomerulopathie een verlies aan nefronen gecompenseerd wordt door in gebruikname van reserve filtratiecapaciteit. Wanneer de GFR onder 73 ml/min/ 1.73 m^2 daalt, is de reserve filtratiecapaciteit verbruikt.

In hoofdstuk 3 zijn de resultaten beschreven van de effecten van dopamine-infusie bij patienten met andere nierziekten, personen met een nier en gezonde vrijwilligers. Opnieuw kon worden aangetoond dat de door dopamine geinduceerde stijging van de GFR toeneemt bij een stijgende uitgangs-GFR. Voorts werd gevonden dat de GFR niet meer verbeterd kan worden met dopamine als de uitgangs-GFR lager is dan 50 ml/min/1.73 m^2. De door

dopamine bewerkstelligde stijging van de GFR was het grootst bij gezonde vrijwilligers en was significant groter dan de stijging bij zowel de gezonde personen met een nier als bij de patienten met een nierziekte en een ogenschijnlijk ongestoorde nierfunktie. Derhalve wordt geconcludeerd dat in geval van een nierziekte al in het begin een verminderde reserve filtratiecapaciteit aanwezig is. Tijdens dopamine-infusie veranderde de hartslag niet terwijl de gemiddelde arteriele bloeddruk licht daalde. Het urinevolume en de zoutexcretie namen toe.

Het is al lang bekend dat zowel aminozuren als een vleesrijke maaltijd een stijging van de GFR kunnen veroorzaken. Daarom hebben we ook gebruik gemaakt van de infusie van een aminozurenoplossing (Vamin^{R}N), teneinde de GFR te beinvloeden (hoofdstuk 4). Bij gezonde proefpersonen werd een stijging waargenomen. Bij patienten met een matig tot ernstig gestoorde nierfunktie werd geen effect op de GFR gevonden. In tegenstelling tot dopamine infusie, vertoonde de FF een tendens tot stijgen. Dit is in overeenstemming met de hypothese van Alvestrand en Bergström dat aminozuren een dilatatie van de afferente arteriole veroorzaken waardoor de effectieve filtratiedruk toeneemt. Daar dopamine en aminozuren derhalve de GFR op verschillende manieren lijken te beïnvloeden, werd tevens het effect van gecombineerde infusie van deze stoffen bestudeerd (hoofdstuk 5). Inderdaad kon worden aangetoond dat dopamine en aminozuren een additief effect op de GFR hebben. De grootste stijging werd gevonden bij gezonde vrijwilligers. Wederom bleek dat bij patienten met een matig tot ernstig gestoorde nierfunktie geen verandering van de GFR kon worden bewerkstelligd hetgeen er op kan wijzen dat bij deze patienten glomerulaire hyperfiltratie aanwezig is.

Ook bij patienten met Type 1 (= insuline afhankelijke) diabetes mellitus kan een supernormale GFR worden gevonden. Er wordt verondersteld dat dit berust op een toegenomen niergrootte met een toegenomen glomerulair filtratie-oppervlakte en/of een verlaagde renale vaatweerstand. Om te onderzoeken of de supernormale GFR bij Type 1 diabetici berust op een voornamelijk efferente vasodilatatie, werd het effect van een lage dosering

dopamine op de renale hemodynamiek van 12 goed geregelde diabetici onderzocht (hoofdstuk 6). De door dopamine veroorzaakte veranderingen in de renale hemodynamiek verschilden niet tussen de diabetici en gezonde proefpersonen. Derhalve wordt geconcludeerd dat de supernormale GFR bij patienten met een Type 1 diabetes mellitus niet berust op een op de voorgrond staande dilatatie van de efferente arteriole. Dit is in overeenstemming met een recente hypothese welke er van uit gaat dat zowel de stijging van de GFR na een vleesrijke maaltijd als de supernormale GFR van Type 1 diabetici berust op afferente vasodilatatie hetgeen veroorzaakt zou worden door een uit de lever afkomstige faktor. Vervolgens werd dan ook het effect van aminozuren op de GFR van redelijk goed geregelde Type 1 diabetici onderzocht (hoofdstuk 7). Er wordt geconcludeerd dat patienten met Type 1 diabetes mellitus kunnen worden onderverdeeld in twee groepen. Ten eerste een patientengroep met een normale GFR waarbij een normale reserve filtratiecapaciteit kan worden gevonden, d.w.z. een door aminozuren en dopamine geïnduceerde stijging van de GFR vergelijkbaar met die van gezonde proefpersonen. Ten tweede een patientengroep met een supernormale GFR welke berust op afferente vasodilatatie, dit gezien het feit dat infusie van aminozuren geen invloed heeft op de GFR terwijl dopamine infusie leidt tot een stijging van de GFR vergelijkbaar met die van controlepersonen.

In de "general discussion" wordt erop gewezen dat het waarschijnlijk beter is het begrip "glomerulaire hyperfiltratie" nader te definiëren door bijvoorbeeld onderscheid te maken in glomerulaire hyperperfusie en glomerulaire hypertensie, vooral omdat de laatstgenoemde waarschijnlijk de beschadigende factor is. Tevens worden nadere onderzoeken alsmede eventuele behandelingsmogelijkheden voor zowel patienten met nierziekten als diabetici met en zonder diabetische nefropathie besproken.