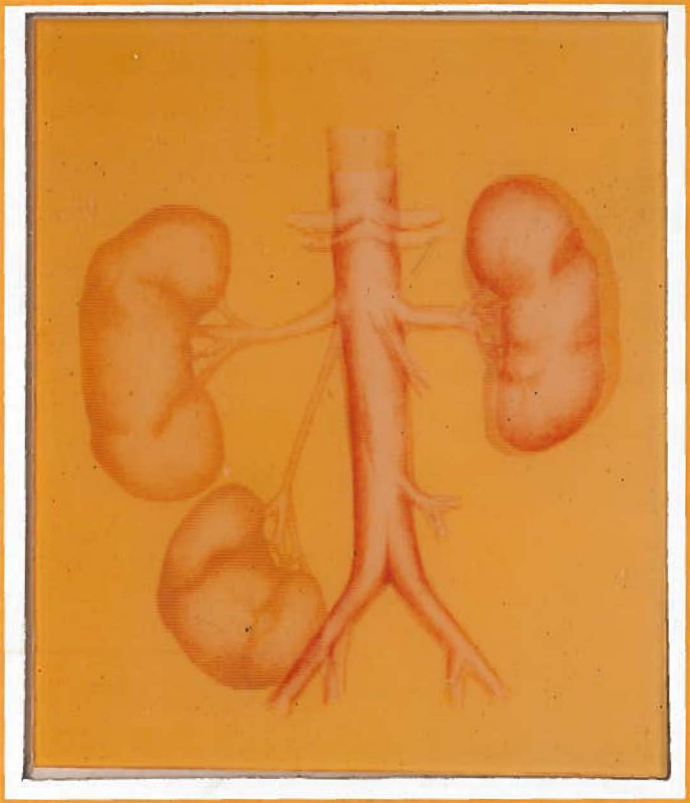
Renal mobility and hypertension

Zeeuw, Dick de

RENAL MOBILITY AND HYPERTENSION



DICK DE ZEEUW

RENAL MOBILITY AND HYPERTENSION

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Stellingen

I.

Het verdient aanbeveling het begrip funktionele nefroptose in te voeren.

II.

Het opsporen en vaststellen van een funktionele nierarteriestenose kan doeltreffender worden door het autoregulatiemechanisme van de nier te belasten.

III.

Men dient zich steeds te realiseren dat het minuten intraveneus urogram bij het onderzoek naar renovaskulaire hypertensie, niet direkt een maat is voor een verschil in doorbloeding tussen beide nieren doch voor een eventueel verschil in glomerulaire filtratie snelheid.

IV.

Het gelijktijdig meten van de glomerulaire filtratie én de renale doorbloeding levert een fraktie meer aan informatie op.

V.

Bij patiënten met een wandelnier en een dientengevolge sterke orthostatische afname van de nierdoorbloeding, dient preventieve nefropexie overwogen te worden teneinde het hypertensierisiko van een wandelnier te keren.

VI.

Een statistikus dient voor een wetenschappelijk onderzoek te worden geraadpleegd (en erna).

VII.

Het ontstaan van het begrip "borderline hypertensie"demonstreert de onoverbrugbare spanning over de grens tussen normotensie en hypertensie.

VIII.

Revaskularisatie van een afgesloten arteria renalis verdient de voorkeur boven nefrektomie.

IX.

In de operatieve strijd tegen de vernauwde koronairvaten dient men de karotiden niet over het hoofd te zien.

X.

De massa elementaire deeltjes ontdekt na het proton, het neutron en het elektron doet vermoeden dat we met renine, prostaglandine en bradykinine nog pas aan het begin staan van een explosie.

XI.

Verzekerd van een uitstekende drukregeling in z'n kop durft de giraffe zijn nek uit te steken.

XII.

De juiste tijd van het digi-ana-chrono horloge is verstreken.

XIII.

De "vrije trap" lijkt bij het huidige voetbalspel meer te slaan op de inhoud van de overtreding, dan op de bestraffing.

Stellingen
behorende bij het proefschrift van
Dick de Zeeuw
Renal mobility and hypertension
Groningen, juni 1980

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		Prof. Dr. E. Mandema
Referenten	:	Dr. A. J. M. Donker
		Dr. G. van Herk

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Contents

List of abbreviations

AI : angiotensin I
AII : angiotensin II
BP : blood pressure
CAI : curve-angle-index
CED : university electronics department
D : doppler flow measurement
D_s : artery diameter in supine position
D_u : artery diameter in upright position
EM : electromagnetic flow measurement
ERPF : effective renal plasma flow
FF : filtration fraction
FMD : fibromuscular dysplasia
GFR : glomerular filtration rate
IVU : intravenous urography
LDH : lactate dehydrogenase
m : mean
MAP : mean arterial pressure
NS : not significant
OCC : oral contraceptives
PAH : *p*-amino hippurate
PRA : plasma renin activity
Q : normalized $^{81}Rb/^{81m}Kr$ ratio
RAL : real artery length
Rb/Kr : ratio of ^{81}Rb to ^{81m}Kr
RVH : renovascular hypertension
SD : standard deviation
UGD : university health care center
VAL : virtual artery length
VRD : right renal vein
VRS : left renal vein

CHAPTER 1

Introduction

1.1 Renal mobility

The kidneys are located retroperitoneally in the lumbar region and are more or less fixed by surrounding tissues. This fixation by the vascular pedicle, fatty capsule, perirenal fascia and intra-abdominal pressure allows a certain movement of the kidneys in their niche.

Normally the respiration and change of body position are accompanied by excursions of the kidneys. This so-called renal mobility appears not only a movement in cephalo-caudal direction, but may include a rotation of the kidneys with changes in position and with respiration. Furthermore a displacement toward or away from the midline can be observed.

History

The earliest report on the subject of renal mobility is said to be that of Meuse in 1495[1]. In 1864 Dietl described the condition and its symptoms, since then known as Dietl's crisis[2]. Hare had advocated in 1860 the use of elastic abdominal belts to support ptotic kidneys[1]. The first surgical suspension is said to be performed by an American surgeon in Mobile, Alabama[3], but others mention Hahn, from Berlin, in 1881[1]. Since then a boom of nephropexies followed in the late nineteenth and the beginning of the twentieth century[4]. This 'over-application' of nephropexy was followed by a period in which the operation became impopular and the nephroptotic patient was surgically neglected[3]. The marked advance in the diagnosis of renal disease led to a more selective use of nephropexy. And until recently the subject had been discussed occasionally by only a few investigators, often meeting criticism from the medical world.

Definition

However simple it seems to describe the 'normal' mobility of a kidney, it is difficult to define its pathological limits. Moody and Van Nuys in 1940, tried to define the normal position and mobility of the kidneys by studying the radiographs of a group of healthy young males and females[5]. They came to the following conclusion: 'the kidneys like other abdominal viscera, should be recognized as normally 'floating viscera''. The mean renal mobility was determined to be 2.5 - 3.5 cm with a wide range (0 - 10 cm). These results indicate that rather extreme excursions of the kidney could be considered as a normal anatomical variant. In 1864 Dietl however, had drawn the attention to some acute clinical effects of this floating, and referred to excessive renal mobility as *nephroptosis*[2]. The controversy in the literature in the following decades about the direct relation between renal mobility and clinical symptoms known as Dietl's crisis (pain, nausea, vomiting, collapse and local tenderness), led to conflicting viewpoints. On the one hand the following opinion could be heard: 'We should like to impress on the student of urology the idea that ptosis should be considered a relatively normal condition ....'[6]; on the other hand a large number of nephropexies had been performed to correct that condition[4].

However, some conclusions can be drawn from the few reports on the subject[7-13]. Various degrees of renal mobility can be observed in healthy males and females; excessive renal mobility (nephroptosis) is observed far more frequently in women, while the right kidney is most often affected. Furthermore it was stated that nephroptosis has to be differentiated clinically into a group with and a group without symptoms or functional disorders[14]. An excursion of less than one vertebra between the horizontal and the vertical position has been suggested as a limit for normal renal mobility[5]. The significance of such an arbitrary figure however, is doubtful.

In conclusion, the definition of renal mobility seems clear with regard to the direction of the movement but unclear as to the normal limits of this movement.

Prevalence

The prevalence of excessive renal mobility (nephroptosis) is obviously depending on how 'excessive' is defined. Apart from this, the large variety in frequencies of nephroptosis (4-50%) reported in medical literature[7] may be

explained by the different populations studied. Moody and Van Nuys for instance, studied healthy young (18-25 yr) volunteers[5], whereas the symptoms of nephroptosis are reported to be manifest in the fourth decade of life mainly[9]. It is however well-accepted that ± 20 per cent of all women have a 'more than normal' renal mobility whereas this condition is found in 2 per cent of all men only[15]. In 70 per cent of the female cases, only the right kidney is excessively mobile, in 10 per cent the left, and in 20 per cent both kidneys are affected[9].

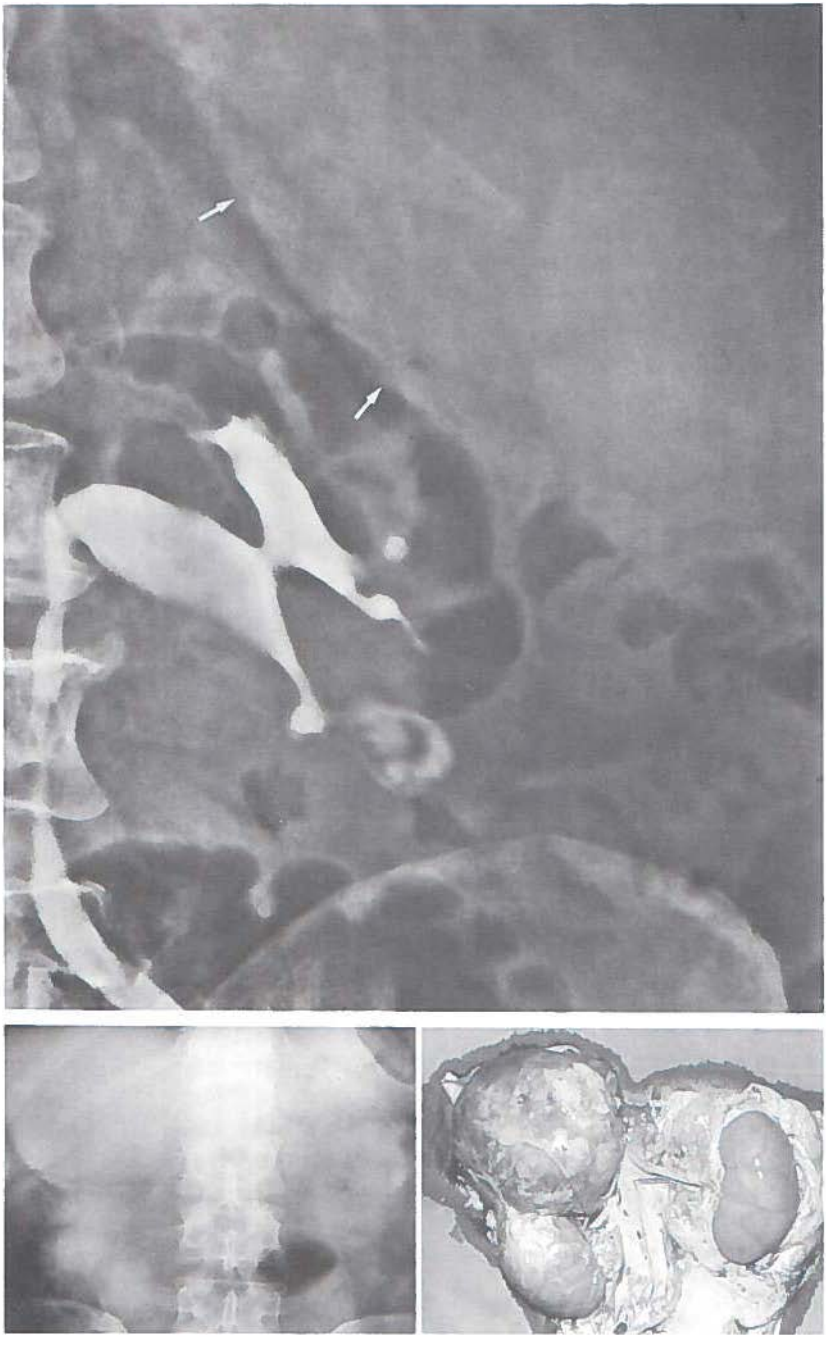
In summary, excessive renal mobility appears to be a relatively frequent condition in women, mainly affecting the right kidney.

Aetiology

The reason for the observed variation in renal mobilities may be found in anatomical variations in the fixation structures of the kidneys. In quadrupeds the anterior sheath of the renal fascia alone supports the animal's kidneys and limits their movement. In man however, an additional fixation is necessary to prevent displacement when in upright position. The anterior and posterior leaf of the renal fascia, which are above continuous with the diaphragmatic fascia, form a sheath for the kidney although they do not completely surround it. This envelope separates the perirenal fat from other extraperitoneal fat. The layer of perirenal fat varies in thickness and is traversed by sparse strands of fibrous tissue, connecting the renal capsula with the perirenal fascia[16]. The combination of these structures together with the vascular pedicle and abdominal muscular tone provide a loose fixation of the kidney to its niche.

An inadequate support could be due to congenital or acquired factors. Of the congenital factors predisposing to mobility of the kidney, certain characteristics of the renal fossa shape apparently play an important role. Volkow and Delitzin concluded that the excessive mobility would result from an anatomical deficiency of the renal fossae, i.e. these are smaller than normal and widely dilated at their lower end[17]. Also a loose renal fascia and a lack of perirenal fat in slim persons, which could stress the fibrous strands, have been mentioned in relation with nephroptosis[1].

The more frequent involvement of the right kidney was attributed by Mathé, at least partly to the fact that the right renal fossa is more shallow than the left one and has a wider lower end[18]. Sir Arthur Keith on the other



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hand was reported to explain this by a downward pressure on the right kidney by the liver, whereas the left kidney would have more sub-diaphragmatic space[1].

One of the acquired factors causing renal mobility could be the loss of abdominal muscle tone, because the intra-abdominal pressure would have a function in preventing visceroptosis and nephroptosis[19]. This was denied however, by Hinman[9]. Other secondary causes of nephroptosis have been reported such as exposure to long-continued forms of vibrations (e.g. motorcycling over rough roads), or repeated violent muscular exertion such as when lifting heavy objects[1]. Occupation has also been mentioned as a contributing factor (long hours of standing or bending)[1]. Excessive renal mobility by these supposed secondary causes has to be differentiated from an acquired dystopia of the kidney. The latter can be observed in patients with intra-abdominal tumours, as illustrated in figure 1.

In summary it has been stated that congenital variations in the shape of the renal fossa predispose to nephroptosis, which itself might be triggered by various secondary factors. Whether these are the true causes for extreme renal mobility remains questionable. First the anatomical preparations in the renal area are reported as very difficult and could be falsely interpreted[16]. Secondly the mentioned exogenous causes for nephroptosis seem to be only surmises instead of results of careful studies. A significant finding is the observation of a different prevalence of nephroptosis in the two sexes. Volkow and Delitzin as well as Southam were able to find a clear difference in the shape of the renal fossae between males and females at autopsy[17,21]. This difference in nephroptosis was said not to be explained by pregnancy[20]. We may therefore conclude that the cause of nephroptosis is likely to be found in an aberrant shape of the renal fossa, but whether this is a congenital or an acquired defect remains to be elucidated.

Figure 1: Two examples of a dystopic kidney. The first (upper part) caused by an enlarged spleen and the second one by a phaeochromocytoma of the right adrenal gland (lower part). The IVU on the left side shows the displacement of the right kidney by a large tumour mass, the right side of the figure illustrates the observation at autopsy.

Symptoms

Symptoms which have been mentioned in relation with excessive renal mobility are:

— (orthostatic) abdominal or flank pain
— pyelonephritis
— haematuria
— hypertension

Flank pain, which may be acute or chronic was described as one of the most common symptoms in nephroptosis[19]. The so-called Dietl's crisis is a severe flank pain which is relieved by lying down. This pain is usually not constant but varies in severity. The acute type would be the result of ureter kinking or of torsion of the vascular pedicle which results in circulatory obstruction[14]. A more chronic dragging pain accompanying nephroptosis is interpreted as a sympathetic nerve irritation by torsion or stretching of the renal pedicle and the embedded nervous plexus[14]. Other vegetative symptoms would accompany this pain and are attributed to a general vegetative or even psychological lability of such patients[1 22 23].

Pyelonephritis has also been often observed in nephroptotic patients[19 21]. The prevailing theory is that it would be caused by a urinary obstruction. In this context the work of Clorius et al. is interesting, who found a relationship between nephroptosis and nephrolithiasis[24].

Haematuria is reported in nephroptotic patients with different frequencies (10%[25], 28%[26] and even 50%[27]). Different aetiological factors are described in these studies: nephritis[25], ruptures of small vessels[26] and circulatory disorders[26 27].

In conclusion it is generally accepted that the above-mentioned symptoms are present with nephroptosis. To what extent those are directly caused by extreme renal mobility is difficult to conclude but it seems likely that a partial obstruction of the renal vessels or the ureter would play a role. Indeed, pathological renal mobility becomes manifest only through those patients that show symptoms. This selection is not likely to represent the total nephroptotic population, as the degree of renal mobility has never been found related to the severity of the symptoms.

1.2 Renal mobility and hypertension

The relation between renal ptosis and hypertension was first mentioned by McCann and Romansky in 1940[28]. Although other authors had previously indicated the possible effect of nephroptosis on the renal pedicle and on the blood flow in the kidney[1 9], McCann and Romansky were the first to suggest a relation with hypertension. They studied the effects of nephroptosis on renal blood flow in hypertensive patients and found renal flow to decrease more in the ptotic patients than in the controls. They concluded that nephroptosis would cause an orthostatic hypertension through a reduction of the renal blood flow in upright position. Abeshouse supported the idea of a relation between nephroptosis and hypertension by including nephroptosis and nephrotorsion in a classification of various types of renal disease that would cause hypertension[29]. The underlying mechanism of renal blood flow decrease due to the ptotic kidney was unclear but was supposed to be the effect of traction on the renal vessels. The observation of Bugbee was thought to confirm this hypothesis since he noticed a sharp rise in a patient's blood pressure when traction was applied to the renal pedicle and a return to a normal level after the traction was released[30].

The idea of nephroptosis causing a traction on the renal vessels and hence triggering hypertension was further extended by Prather and Mathé. Prather reported in 1948 that a shift of the kidney to the contralateral side (medial ptosis) could well cause a traction on the renal pedicle and cause hypertension[31]. Mathé agreed with the hypothesis of renal hypertension due to nephroptosis, and found nephrotorsion equally important with respect to the orthostatic constriction of the renal artery[13].

After the introduction of renal angiography it became possible to visualize the effect of a mobile kidney on its vessels. Indeed, Kaufman et al. and also Hariu et al. observed a narrowing of the renal artery in patients with excessively mobile kidneys[32 33]. The physiological effects of such artery narrowing became apparent as the techniques to assess renal functions advanced. Supine and upright renography revealed an orthostatic reduction of renal function on the ptotic side[34-40]. Schoenenberger even reported posture-dependent changes of urinary lactate dehydrogenase (LDH) in nephroptotic patients which he earlier found to be the result of impaired renal blood supply[41 42 43].

Beside these indirect ways to establish a relation between nephroptosis and hypertension, others have tried to prove this by performing nephropexy

to cure hypertension. Mathé and McCann reported nephropexy in patients with advanced malignant hypertension. Although blood pressure did not become completely normal, it did improve after the operation. Pytel and Lopatkin succeeded in obtaining normotension in 15 of the nephropexies performed on 17 hypertensive females with nephroptosis[44].

Apart from this direct relation between hypertension and nephroptosis another, indirect relation had been mentioned. Derrick and Hanna found that a specific type of renal artery stenosis, fibromuscular dysplasia (FMD), was often accompanied by nephroptosis. They digressed on the suggestive concordance of this FMD and nephroptosis which was prevalent in women in their thirties, in particular for the right kidney[45]. An excessively mobile kidney was suggested to cause a chronic intermittent stretching of the renal artery. This stretching would cause lesions in the arterial wall which subsequently would result in the FMD-type renal artery stenosis, triggering hypertension. Derrick referred to Dahl and co-workers[46] who were able to induce focal intimal and medial proliferation of the external iliac arteries in dogs[45]. This could be attributed to trauma since the proliferation was manifest over torn places in the inner elastic membranes. Lopatkin and Maso as well as Kaufman et al. supported this idea[32 47]. Both found high prevalences of nephroptosis in patients with a fibromuscular dysplastic renal artery. It seems that in most reported cases a medial fibroplasia according to the classification of McCormack[48] was present, which occurs most frequently and comprises 60 to 70 per cent of all idiopathic stenoses.

In summary three possible causes of 'renovascular' hypertension have been attributed to extreme renal mobility: the first two, nephroptosis and nephrotorsion or a combination of both, may cause an orthostatic elongation and narrowing of the renal artery whereas the third one, a renal artery stenosis like FMD, could be caused by the intermittent artery stretching. Supposedly both the *direct* effect of nephroptosis on the renal artery diameter and the *indirect* effect (FMD) will cause a diminished blood supply and a drop of filtration pressure in the kidney. According to the present knowledge of the renin-angiotensin system this (relative) stenosis would stimulate the production of renin by the ischaemic kidney. Through this renin release the kidney tries to maintain its flow and filtration pressure with an angiotensin-induced higher systemic blood pressure.

The multiplicity of causes for hypertension as well as the pivotal role of the kidney in the hypertensive process are well accepted. Nephroptosis may be a neglected factor in this process. The aim of this thesis has been to

restore faith in the hypothesis that excessive mobility of the kidney may contribute to the onset of hypertension.

1.3 Scope of the study

In the following chapters the relation between nephroptosis and hypertension is studied in its different aspects. The second chapter is concerned with the plausibility of the relation through a population study where the coincidence of nephroptosis and hypertension is determined. Besides, a number of concomitant factors and symptoms are discussed.

Chapters 3 and 4 deal with the effects of nephroptosis on renal function and with effects of nephroptosis on the renal artery diameter, respectively. An inventory of the possible screening methods for nephroptosis-induced hypertension is given in chapter 5. Proposals are made to improve the conventional screening methods, which is adstructed by preliminary results of a number of studies. The last two chapters discuss the development and applicability of a new method for continuous measurement of renal blood flow and the results of this non-invasive method in a nephroptotic patient.

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CHAPTER 2

Population studies

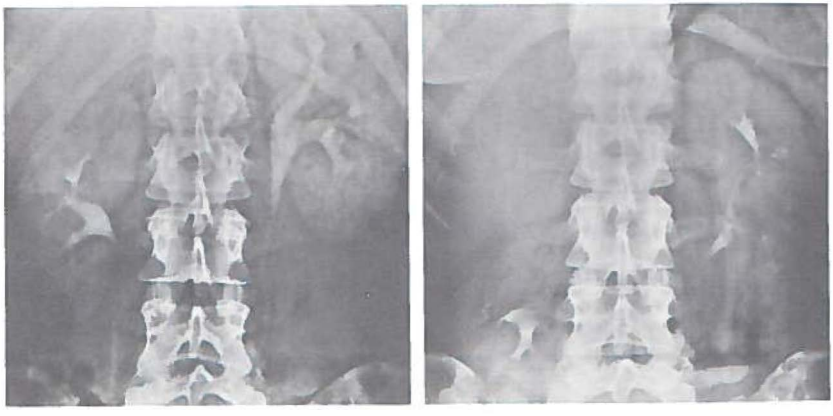
2.1 Introduction

The history and frequency of nephroptosis give rise to some scepticism toward its relation with complaints such as abdominal pain as described in the previous chapter. On the other hand there is the success of nephropexy in individual cases suffering from haematuria[1-4] or recurrent urinary tract infections[1 3 4 5]. This justifies a closer look on renal mobility as a potentially pathological phenomenon, particularly on its relation with hypertension since the prevalence of the latter is also reported to be high, with high overall mortality[6-9].

Despite several reports on the successful anti-hypertensive treatment of nephroptotic patients with nephropexy[4 10-13], and despite the high prevalence of nephroptosis in a healthy population (20%)[12 14-17], we have found no report of any study on the prevalence of nephroptosis in 'essential' hypertensive patients. This might be of interest since a rather straightforward hypothesis could explain the relation between nephroptosis and hypertension (see chapter 1).

Therefore a population study had been set up to investigate the validity of *three* possible mechanisms on which this relation could be based. Firstly, the probability of a *direct* (nephroptosis-induced artery narrowing) relation was checked by comparing the prevalence of nephroptosis in a group of essential hypertensives and a group of normotensive subjects. Secondly, the *indirect* (nephroptosis-induced FMD) relation was evaluated through a measurement of the renal mobility in patients with a FMD-type of renal artery stenosis. Thirdly, a possible predisposing effect of excessive renal mobility on another blood pressure-elevating factor was studied. The latter was done by studying the prevalence of nephroptosis in females who developed hypertension on oral contraceptives (OCC). This criterium has been selected because OCC use is known to induce a mild elevation of blood pressure[18 19] and in some cases hypertension[20 21].

Apart from the measurement of renal mobility in these three groups, additional information was collected in order to evaluate the relation between renal mobility and other symptoms and factors.



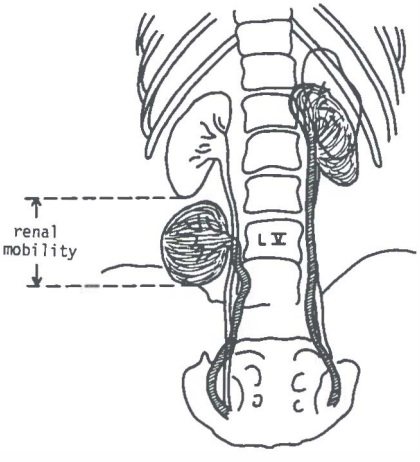


Figure 2: Schematic illustration of renal mobility measurement (lower part): the positions of kidneys in supine (white) and upright (shaded) posture are drawn. The upper part shows a supine (left) and upright (right) X-ray film of a female patient with ptosis of the right kidney.

2.2 Patients and methods

Renal mobility measurement

The degree of renal mobility in all studied persons was measured by comparing the position of the kidney in supine and upright posture. For this purpose an upright X-ray film was added to the conventional supine (rapid sequence) intravenous urography (IVU). The difference in height between the lower pole in supine and upright position was measured and expressed in centimeters vertical shift (figure 2)[22]. Furthermore an estimate of the torsion of the kidney was obtained by comparing the projected kidney sizes in both postures. For this purpose a torsion index was defined as a semi-quantitative measure of nephrotorsion[22]:

$$\text{torsion index} = \frac{\text{kidney length / width (supine)}}{\text{kidney length / width (upright)}}$$

Thus a torsion index greater than one would represent nephrotorsion.

The above-mentioned measurements were all corrected for differences in the X-ray tube distance between supine and upright position, taking the fourth lumbar vertebra as reference.

Groups in the study

Group I (hypertensives)

This group was selected from patients with high blood pressure (BP) referred to the Department of Radiology for a rapid sequence IVU. The selection was made on the following criteria:

— hypertension (BP $\geq$ 160/95 mmHg[23])
— normal creatinine clearance ($>$ 90 ml/min)
— no proteinuria ($<$ 1 g/24 h)
— absence of cell casts in urinary sediment
— no obvious genito-urinary tract disorders on IVU
— no regular medication (except OCC)
— no history of other major diseases
— no history of abdominal surgery
— no signs of renovascular hypertension.

Fourty-two male patients and 102 female patients met these criteria over a survey period of 1 and 1.5 year, respectively.

Group II (normotensives)

A normotensive (BP < 160/95 mmHg) control group was selected from all referrals for IVU in the above-mentioned periods, since it was considered unjustifiable to select them from a random population. The selection was carried out with the same list of criteria used for group I (except item 1). This resulted in a group of 72 normotensive females and 43 normotensive males, with various complaints such as abdominal pain, microscopic haematuria and recurrent urinary tract infections, but without any sign of urinary tract pathology on IVU.

The renal mobility of the patients in group I and II was measured according to the protocol described earlier. Additional data (age, height, weight, OCC use and parity) were obtained from the patient's records. Part of this data was collected through an additional questionnaire, since the necessary information was frequently absent in the patient's record. The high response rate of 75 per cent provided a representative sample of the adressed population (group I and group II).

Group III (FMD patients)

This group consisted of 24 patients known with a renovascular hypertension caused by fibromuscular dysplasia of the renal artery. Unilateral medial fibroplasia[24] was demonstrated with angiography in 22 patients (1 male, 21 females) and bilateral medial fibroplasia in two patients (1 male, 1 female). The right renal artery was affected in 20 patients, 6 patients showed an involvement of the left renal artery. None of them had a history of abdominal surgery and all used antihypertensive medication.

An upright X-ray film was performed after a low dose of contrast medium in those cases where this had not been taken in the past.

Group IV (UGD patients)

The fourth group consisted of young females who had presented a 'hypertensive reaction' on oral contraceptive medication. They were selected from an OCC-using female student population which had a routine check-up every six months at the University Health Care Center (Universitaire

Gezondheids Dienst = UGD). The selected subjects met at least two of the following criteria:

after the start of OCC — a diastolic pressure increase of at least 20 mmHg,
— a mean arterial pressure (MAP*) increase of at least 15 mmHg,
— hypertension (BP $\geqslant$ 160/95 mmHg).

Eighty-one females out of the studied 3684 OCC users (2%) were enrolled. They were asked together with 100 female controls who had no or less blood pressure reaction on OCC, to participate in the study. Positive replies however, were rather poor: only 20 persons (11%) of them did cooperate, seven out of 100 with a minor BP-reaction on OCC and thirteen who met at least two of the above mentioned criteria.

Renal mobility in this last group was measured on supine and upright X-ray films with low dose contrast medium.

Data management and statistical analysis

The data of all groups were stored and processed on a CDC Cyber 74-16 computer. Statistical analysis consisted of the following tests: (paired) Student t-test, testing the significance of any difference between (paired) parameters supposed to be normally distributed, otherwise a (paired) Mann-Whitney rank test; furthermore correlation coefficients were calculated and part of the data was submitted to a multiple regression analysis[25]. Statistical significance was taken at the 5 per cent level.

2.3 **Results**

Group I and II

The results of these two groups are presented together, to enable a comparison between hypertensive patients and normotensive patients with respect to the different parameters.

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* the sum of one-third of the systolic pressure and two-third of the diastolic pressure

Renal mobility

The male subjects in group I and II appeared to have a low renal mobility with no significant difference between normotensive and hypertensive patients (figure 3). High renal mobility was observed only occasionally in both groups and with no apparent preference for either side.

In striking contrast were the results of the renal mobility measured in the female population. As can be seen in figure 4 the mean renal mobility in the normotensive female controls was significantly higher than that in the

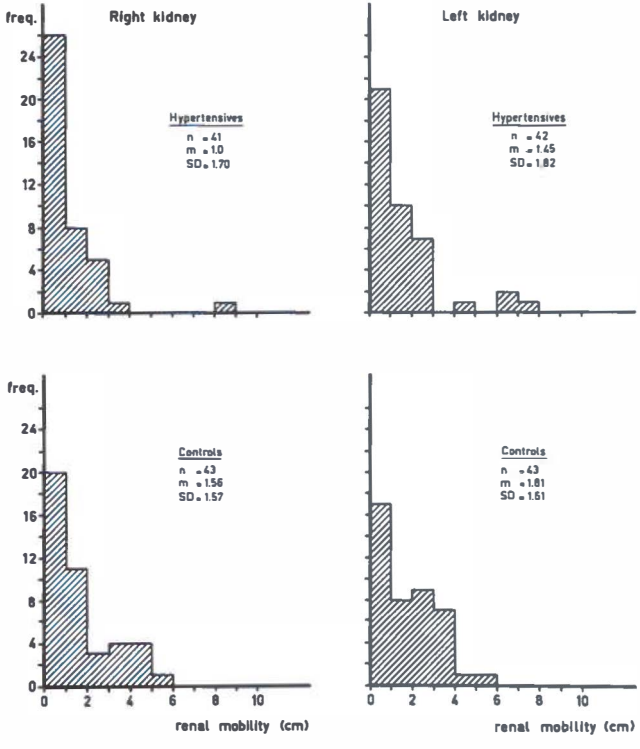

Figure 3: Distribution of renal mobility in *male* hypertensive patients (upper part) and male normotensive subjects (lower part). Mean (m) and standard deviation (SD) are expressed in centimeters.

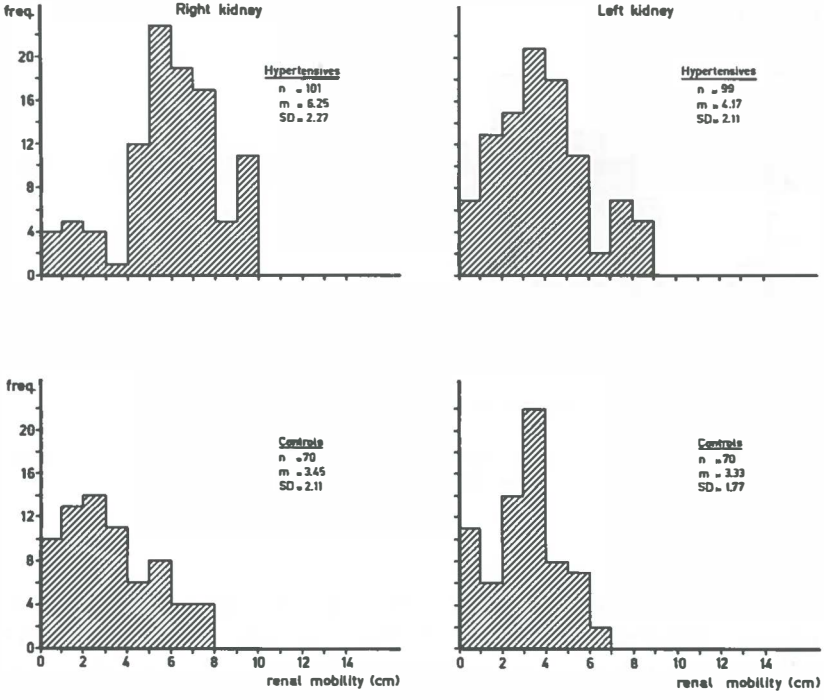

Figure 4: Distribution of renal mobility in *female* hypertensive patients (upper part) and female normotensive subjects (lower part). Mean (m) and standard deviation (SD) are expressed in centimeters.

males. If one assumes a mobility of 1.5 vertebral body (± 5.5 cm) as the 'normal' limit, 20-30 per cent of the female controls had nephroptotic kidneys, whereas only 5 per cent of the male controls showed an excessively mobile kidney. The upper diagram of figure 4 illustrates the distribution of renal mobility in hypertensive females. Both kidneys appeared to be more mobile than in the female controls. The difference in renal mobility between normotensive and hypertensive females was most striking in the right kidney. About 75 per cent of the right kidneys of hypertensive females

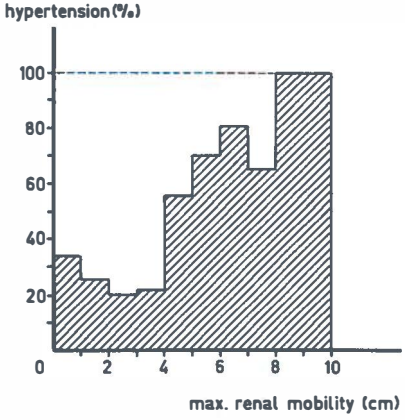

Figure 5: Percentages of hypertensive subjects in the total studied female group (hatched bars), in different renal mobility subgroups.

showed a mobility of more than 1.5 vertebral body. Figure 5 illustrates the relative difference in renal mobility between hypertensive and normotensive females. For this purpose 'maximal renal mobility' was defined as the highest mobility of either kidney in one subject. The percentage of hypertension in the total female population appeared to be higher with higher renal mobility.

Another significant difference between hypertensive and normotensive females was found in the extent of bilateral nephroptosis. An indication for the presence of unilateral nephroptosis is obtained by subtracting the right from the left renal mobility in an individual. The specific unilateral character of the renal mobility in hypertensive females is illustrated in figure 6. The mean absolute difference of left and right renal mobility appeared to be less than 1 cm in the control group, while only very few normotensive females showed more than 2 cm mobility difference (14%). A different situation however, was observed in hypertensive females. Apart from a significantly higher mean mobility difference, only a relatively small fraction had a mobility difference of less than 2 cm (37%).

However, before drawing conclusions on how significant the observed differences between hypertensive and normotensive females may prove to be, the possibility of interference had to be excluded. For instance the arbitrary division of the total female population in normo- and hypertensives

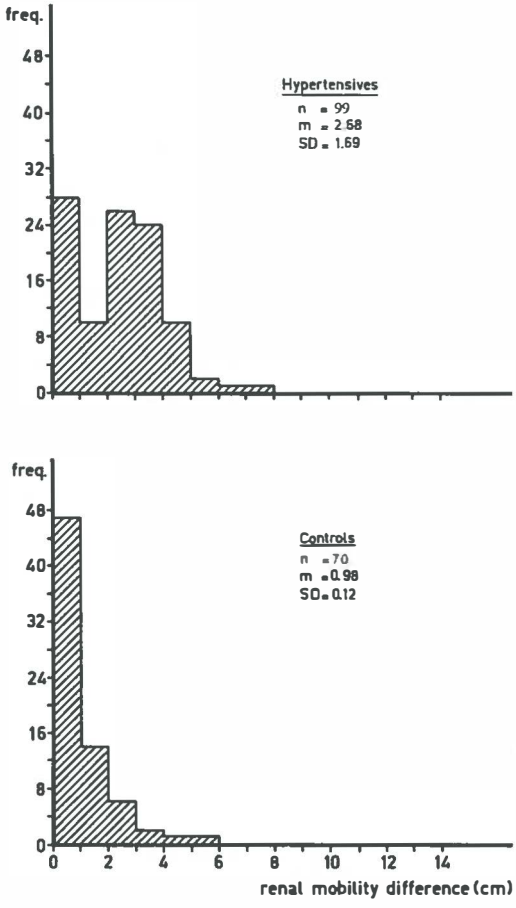

Figure 6: The distribution of the 'renal mobility difference' (absolute value of right minus left renal mobility in cm) in the female hypertensive group and female normotensive group (controls).

could have had an effect on the final results. A change of this limit to 140/90 mmHg or 160/100 mmHg however, did not alter the results essentially. The results could also have been influenced by the fact that the control group was not a 'healthy' group by definition. This fact however, would probably have resulted in an overestimation of the 'true' control renal mobility since the typical complaints of our control group are said to be usually accompanied by increased renal mobility (chapter 1). Furthermore the similarity of the renal mobility distribution in our female control subjects and the distribution in

healthy subjects reported by Moody and Van Nuys[14], confirmed the validity of our control group.

Differences in body height could also have introduced the difference observed in renal mobility between hypertensive and normotensive subjects since both parameters were expressed in centimeters. This however, appeared to be irrelevant since height-adjusted renal mobility had a similar distribution pattern compared to the absolute renal mobility (cf. figures 4 and 7).

Other factors that were likely to have influenced the results could have been age, weight, parity and OCC use. Table I (upper part) shows the mean values of these parameters in both the normo- and hypertensive group. Only weight and height-adjusted weight (Quetelet-index) appeared to be significantly higher in hypertensive than in normotensive patients. This however, could not explain the difference in renal mobility between both groups since no correlation was found between weight and renal mobility, neither in the total group (r = —0.06) nor in either of the subgroups (r = —0.29 in hypertensive patients and r = 0.04 in normotensive patients).

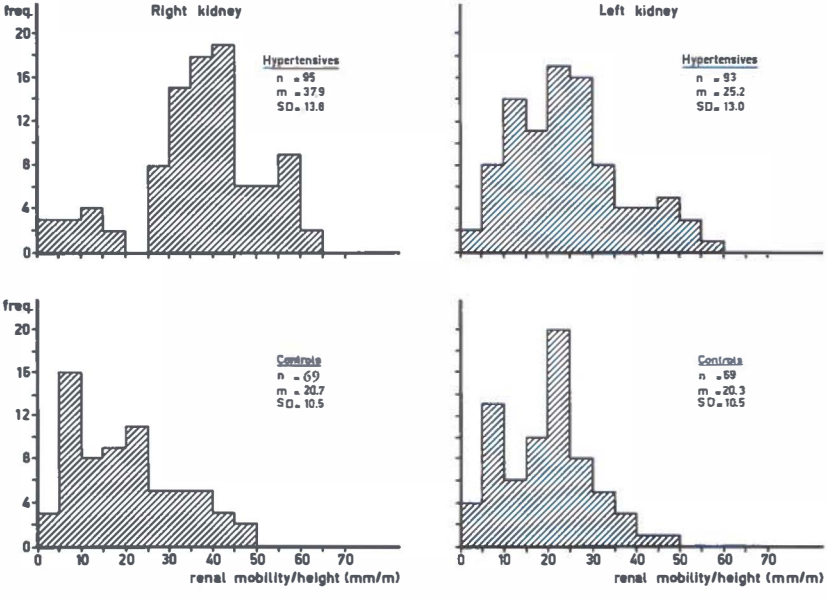

Figure 7: The distribution of body-height corrected renal mobilities in the female hypertensive and female normotensive group (controls).

Table I: Mean ± standard deviation of parameters and frequency of various symptoms in the female hypertensive and normotensive groups.

	Normotensive patients (n = 72)	Hypertensive patients (n = 102)	difference
Blood pressure (mmHg)	134/82 ± 12/7	172/110 ± 22/11	$p < 0.0001$
age (yr)	41.4 ± 13.1	38.7 ± 15.8	N.S.
height (cm)	164.8 ± 6.0	165.9 ± 6.0	N.S.
weight (kg)	66.2 ± 8.8	70.4 ± 12.5	$p < 0.01$
Quetelet index*	241 ± 34	259 ± 49	$p < 0.005$
parity (n)	3.3 ± 2.1	3.9 ± 2.2	N.S.
OCC use (%)**	53	58	N.S.
renal mobility: right (cm)	3.5 ± 2.1	6.3 ± 2.3	$p < 0.0001$
left (cm)	3.3 ± 1.8	4.2 ± 2.1	$p < 0.005$
history of: haematuria (%)	1	0	
urinary-tract infections (%)	39	26	
flank pain (%)	63	41	
urinary-tract calculi (%)	13	5	

* relative weight: $10^5 \times$ weight (kg)/[height (cm)]^2
** OCC use or history of OCC use for more than 1 year

Because the high association between renal mobility and hypertension in females might also be explained by a combination of the above-mentioned variables, a multiple regression analysis was performed to exclude this possibility. The results of a stepwise multiple regression analysis of blood pressure allowing for age, height, Quetelet index, parity and OCC use showed a significant and independent attribution of renal mobility and relative weight to the blood pressure. Moreover two subgroups of the hypertensive and normotensive groups (each 27 subjects) that were matched with respect to the mentioned parameters showed still a difference in renal mobility. It follows that none of the studied parameters alone or any combination of them, could have explained the observed difference in renal mobility between the hypertensive and normotensive population.

Table II: Mean torsion indices (definition in text) of right and left kidneys in the female hypertensive and female normotensive group (controls). The supine and upright values represent the ratio of kidney length to kidney width in both positions.

	Mean torsion index	
	Right kidney	Left kidney
Hypertensives		
supine	2.2 ± 0.2	2.2 ± 0.2
upright	1.7 ± 0.4	2.1 ± 0.3
index	1.3 ± 0.2	1.1 ± 0.1
Controls		
supine	2.2 ± 0.3	2.2 ± 0.2
upright	2.1 ± 0.3	2.1 ± 0.2
index	1.1 ± 0.2	1.0 ± 0.1

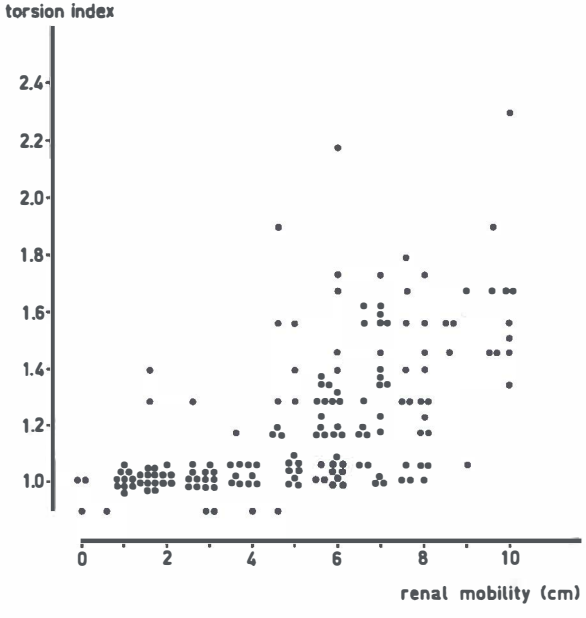

Figure 8: The relation between right renal mobility and nephrotorsion in the total female group (n = 168, r = 0.62).

Renal torsion

Table II gives the mean torsion indices of the kidneys in both the normotensive and hypertensive group. Nephrotorsion appeared to occur predominantly on the right side in hypertensive females. If the torsion index was plotted against the right renal mobility (figure 8) a significant positive correlation was found ($r = 0.62$). Apparently the high mean torsion index could partially be explained by the high mobility of the right kidney in hypertensive females. A similar relation was found with respect to left renal mobility and torsion, however far less explicit ($r = 0.28$) than on the right side.

In summary, nephrotorsion was found mainly with mobile kidneys and particularly on the right side.

Other factors and renal mobility

Tables III and IV give the data on the degree of renal mobility in different age-groups. Although the number of persons in the different subgroups is rather low, one may conclude that renal mobility was not prevalent in a certain age group neither in hypertensives nor in normotensives. However, the low prevalence of high renal mobility in the older normotensive subjects might imply that a young normotensive having nephroptosis would develop hypertension eventually.

The lower part of table I shows the frequency of several symptoms and factors often said to occur in the presence of nephroptosis. The prevalences of these factors however, were found to be similar with different renal mobilities.

Childbirth is said to be a secondary factor in the genesis of nephroptosis (see chapter 1). The majority (80%) of the female subjects in our study had had children. This high prevalence however, appeared not to be related to the degree of renal mobility (figure 9). The fluctuations of this prevalence in the lower range of renal mobilities did not reflect a significant difference ($p < 0.3$). However, the number of persons in the subgroups was rather small. The number of pregnancies also showed no relation with the degree of renal mobility.

As mentioned no significant difference was found in the frequency of OCC use (or history of OCC use) between normotensive and hypertensive patients in our study. Its prevalence in both groups however, appeared to be

Table III: Number of female subjects with low (0-3), medium (3-6) and high (6-10 cm) renal mobility in different age-groups of the total female group.

	renal mobility			
age	0-3	3-6	6-10 cm	
10-20 yr	3	8	0	11
20-30 yr	8	17	16	41
30-40 yr	9	11	13	33
40-50 yr	7	16	20	43
50-60 yr	5	16	11	32
60-80 yr	3	6	5	14
	35	74	65	174

Table IV: Number of female subjects with low (0-5) and high (5-10 cm) renal mobility in different age-groups of our normotensive and hypertensive groups.

	Hypertensives		Normotensives	
age	0-5	5-10 cm	0-5	5-10 cm
10-20 yr	3	2 *(40%)*	6	0 *(0%)*
20-30 yr	1	18 *(95%)*	16	6 *(27%)*
30-40 yr	6	14 *(70%)*	8	5 *(39%)*
40-50 yr	3	27 *(90%)*	11	2 *(15%)*
50-60 yr	6	16 *(73%)*	8	2 *(20%)*
60-80 yr	1	5 *(83%)*	8	0 *(0%)*

related with the degree of renal mobility (figure 10) such that the larger proportion of the females with a high renal mobility had a history of OCC use. This positive correlation between renal mobility and OCC use could not be explained by age difference between the different subgroups. Neither did other factors such as parity or weight show any relationship with the OCC use or renal mobility to explain this curious observation.

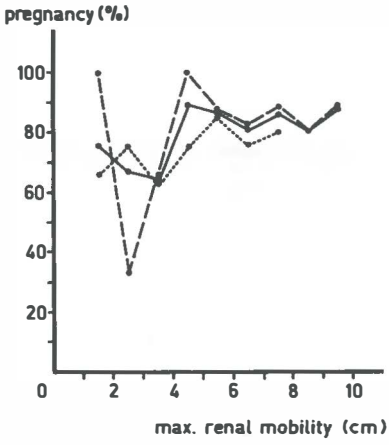

Figure 9: Percentages of female subjects having had children, of the total (●——●), normotensive (●- - - - - -●) and hypertensive (●— — —●) group, in different renal mobility subgroups.

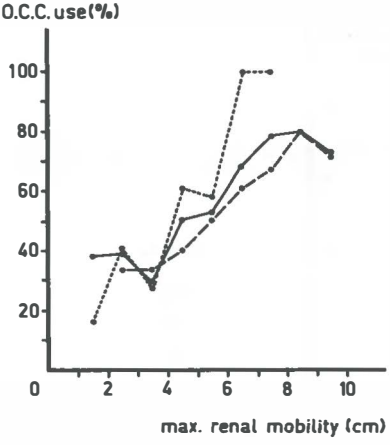

Figure 10: Prevalence of OCC use of the total (●——●), normotensive (●- - - - - -●) and hypertensive (●— — —●) group, in different renal mobility subgroups.

Group III

The mean age of our group of twenty-four FMD patients was 39 ± 6 years. Figure 11 shows the mobility of 26 affected and 20 non-affected kidneys in this group. The mobility of two (non-affected) left kidneys could not be quantified due to intestinal gas. The right renal artery appeared to be FMD-affected far more frequently than the left renal artery (77% versus 23%). Interestingly the measured renal mobility of all except 6 post-stenotic kidneys appeared to be significantly higher than the renal mobility 'range' of the normotensive population (group II). Consequently the mean mobility of the affected kidneys was high (right kidney: 8.4 ± 1.6 cm, left kidney: 5.4 ± 2.4 cm). These results are the more striking as the renal mobilities of the two males were included in this analysis where mean renal mobility in a male population is low (figure 3). Lopatkin and Maso discussed the theory that hormonal factors such as during pregnancy might also contribute to the development of fibromuscular dysplasia, since FMD occurs mainly in female patients[26]. In their study however, only 3 out of 15 FMD patients had been

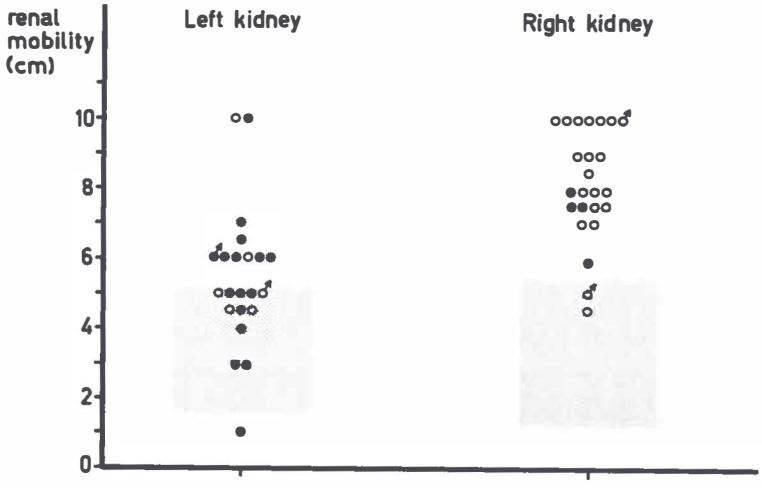

Figure 11: Renal mobility in female hypertensive patients with FMD of the renal artery. Open dots represent mobility of FMD-affected kidneys, black dots that of non-affected kidneys. Shaded areas represent the range (mean ± SD) of renal mobility in female control subjects.

pregnant. In this context it is worth mentioning that 91 per cent of the female patients in our FMD group used OCC at the time or until at most one year before their hypertension became manifest.

Group IV

The results of the renal mobility measured in the two selected groups of UGD-subjects are summarized in table V together with other relevant data. The mean 'maximum renal mobility' in the group having a distinct increase in mean arterial pressure (MAP) during OCC use (group A), was significantly higher than the mean mobility in the group with only a minor rise (group B). Apparently a correlation existed between rise in MAP and renal mobility. This positive correlation as illustrated in figure 12, could not be explained by difference in age or relative weight. The mean nephrotorsion (as expressed by the torsion index) did not differ significantly between group A and B, although excessive nephrotorsion was found in group A only.

Subsequently the renal mobility in group A was compared with the mobility of normotensive and hypertensive OCC users selected from group I

Table V: Mean ± standard deviation of relevant parameters in two subgroups of the UGD-group. MAP 1 is the mean arterial blood pressure before OCC use, MAP 2 during OCC use.

	Group A n = 13	Group B n = 7	difference
age (yr)	24 ± 3	22 ± 2	N.S.
Quetelet index	217 ± 17	227 ± 17	N.S.
MAP 1 (mmHg)	99 ± 6	102 ± 4	N.S.
MAP 2 (mmHg)	117 ± 6	110 ± 4	$p < 0.02$
MAP increase (mmHg)	18.5 ± 3.9	8.4 ± 2.7	$p < 0.0005$
renal mobility (cm)	7.1 ± 1.7	4.1 ± 1.7	$p < 0.001$
torsion index	1.3 ± 0.2	1.1 ± 0.1	N.S.

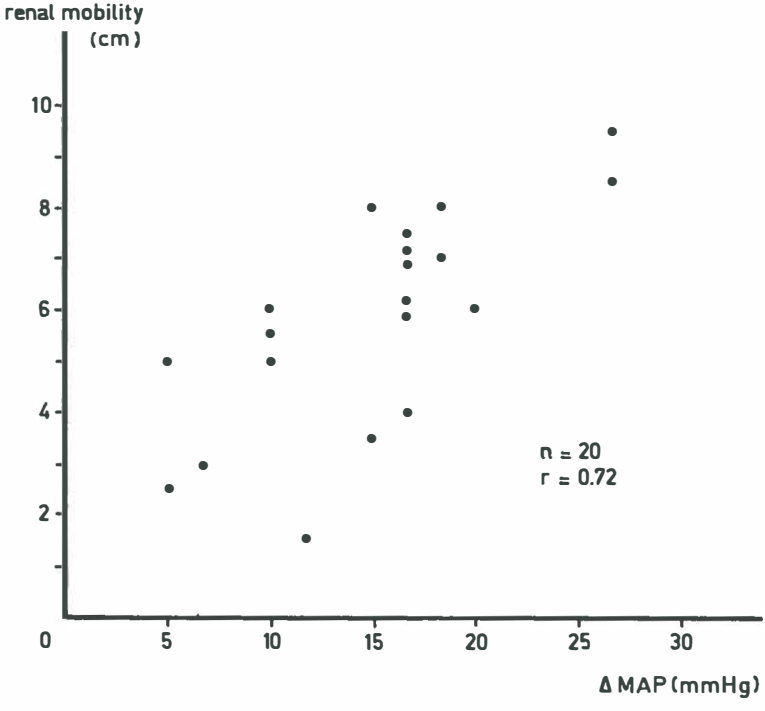

Figure 12: Relation between maximum renal mobility (see text) and increase in mean arterial blood pressure (Δ MAP) after starting OCC.

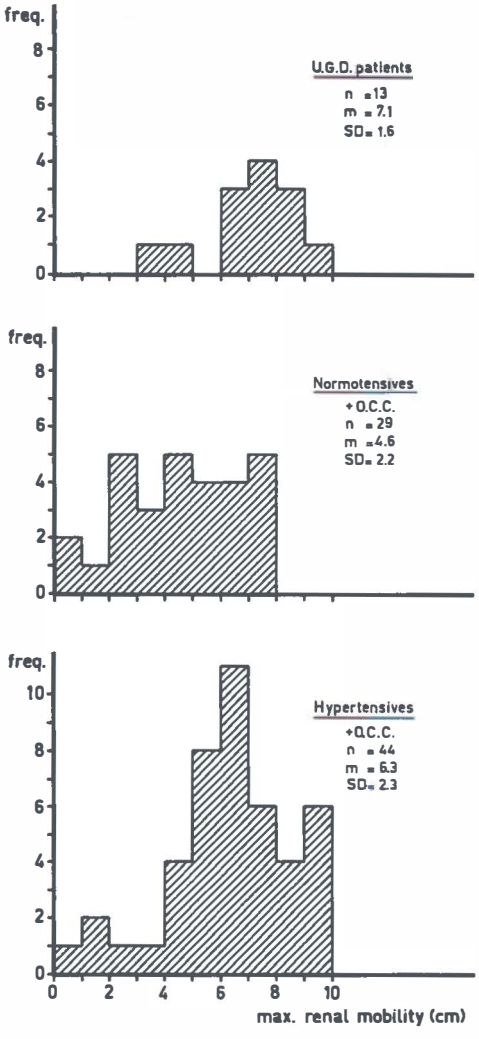

Figure 13: Distribution of maximum renal mobility in UGD group A, OCC-using normotensive subjects and OCC-using hypertensive subjects. Mean (m) and standard deviation (SD) are expressed in centimeters.

and II (figure 13). The distribution of renal mobility in the UGD patients appeared to be similar to that of the hypertensive OCC users in group I, and again significantly different from the distribution in normotensive OCC users.

2.4 Discussion and conclusions

An excessively mobile kidney can be a *direct* cause of hypertension. This has been demonstrated by the anti-hypertensive effect of nephropexy in nephroptotic hypertensive patients[4 10-13] and also by Petrish et al. who found that an excessively mobile kidney caused hypertension in rats through elongation and thus narrowing of the renal vessels[27]. A certain renal mobility can, but not necessarily, play an important role in the development of hypertension, since renal mobility will only show the *direct* effect on blood pressure when the artery is stretched and narrowed. As a consequence it seems that the 'length' of the renal artery should also be included in the definition of a pathological renal mobility. Although our present data do not provide information on the latter subject, a few conclusions can still be drawn on the probability of this *direct* relation.

Excessive renal mobility is seldom found in a male population but it is a relatively frequent condition in females. Assuming a normal renal mobility range to be 0 - 5.5 cm (= mean renal mobility plus standard deviation of the normotensive controls), 19 per cent of our female control group showed a nephroptotic kidney. A similar percentage has also been found by several other investigators[12 14-17]. The renal mobility distribution in our hypertensive population however, had a strikingly different pattern. The majority (75 per cent!) appeared to have a renal mobility of more than 5.5 cm, predominantly unilateral and often accompanied with nephrotorsion. It is not justified to draw a conclusion from our data as to what extent nephroptosis can explain the high blood pressure in this special population. But our observation certainly confirms the role of nephroptosis as a possible cause of hypertension at least in females. The presence of excessive renal mobility in normotensive subjects could imply that nephroptosis might only cause hypertension in predisposed subjects, for instance OCC users. The present data on the renal mobility of OCC-using normotensive and hypertensive patients give the impression that the susceptibility for blood pressure rise on OCC is partially attributable to the degree of renal mobility.

An *indirect* relation between renal mobility and hypertension has also been postulated previously[12 15 16 18 19]. The intermediate condition of the indirect relation is supposed to be fibromuscular dysplasia of the renal artery which is known to cause hypertension. This particular stenosis is suggested to be the result of the irritating effect of frequent intermittent stretching on the renal artery wall. The high renal mobility in our FMD patients

corresponds with the studies quoted. Although these data are no evidence for a cause-effect relation, the high coincidence of FMD and nephroptosis in female subjects on the right side is striking.

The data of our study on the alleged *effects* of nephroptosis such as haematuria, urinary tract infections and flank pain (see chapter 1) do not provide conclusive proof. The vast number of other aetiological factors for these conditions or symptoms could certainly have interfered with our observations.

With regard to the *cause* of the significant differences observed in mobility of the kidneys between the studied groups, pregnancy and/or body weight appeared not to be of significant importance. This observation corresponds with that of Latzko who also concluded that these factors were less important compared to congenitally predisposing factors (see chapter 1)[28]. Of interest however, is our observation of a relation between OCC use and degree of renal mobility. This would imply that OCC use is one of the secondary factors allowing a higher renal mobility. The mechanism of such 'OCC-induced renal mobility' is unclear. There have been reports on the influence of sex hormones on connective tissue[29 30 31] but the extrapolation to oral contraceptives affecting the connective tissue of renal fixation structures would be speculation.

We conclude that, although the degree of renal mobility seems not to be an exclusive factor to predict its pathophysiological effects, the differences between normotensive and hypertensive females suggest a causal role of this condition in the onset of hypertension. This could take place either by a nephroptosis-induced narrowing of the renal artery or by a nephroptosis-induced FMD. The role of OCC in the genesis of renal mobility and FMD needs further study as does its role in the development of elevated blood pressure in patients with nephroptosis. Finally, the effect of different renal mobilities on the renal artery diameter and on the renal blood supply has to be investigated before conclusions can be drawn on the magnitude of nephroptosis as a potential cause of hypertension in the female population.

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CHAPTER 3

Renal mobility and renal function

3.1 Introduction

The striking coincidence of extreme renal mobility and hypertension demonstrated in the previous chapter has reinforced the hypothesis of a causal relation between the two phenomena. A further investigation on the physiological effects of nephroptosis on renal function and renin release might reveal the mechanisms of this relation.

The excessively mobile kidney is supposed to stretch its own artery which would result in a reduction of its diameter. If this were true, a decrease of the blood flow in the shifted kidney would probably take place. This reduction in blood flow in turn will trigger the kidney to maintain its filtration capacity[1 2]. For this purpose the kidney is amongst others equipped with the ability to produce vasoactive substances. One of these is renin, itself capable to stimulate the formation of the vasopressor angiotensin II[3 4]. Other vasoactive substances such as kininogens and prostaglandins appear to have a vasodilating action also on renal level[5 6]. Both groups of vasoactive substances represent a major part of the auto-regulatory mechanism of the kidney with which a sufficient blood supply and a constant filtration is ensured[7].

Several experimental studies have demonstrated the reaction of the kidney to a stenosis of its artery. The production of renin is increased which results in a systemic vasoconstriction by angiotensin II and an increase of the prestenotic blood pressure[8]. At the same time the intrarenal vascular resistance decreases through the local action of kininogens and prostaglandins[6 9]. As a result the renal blood flow may remain constant with a higher systemic blood pressure. These regulatory mechanisms appear to fail however, when the stenosis is further narrowed beyond a certain threshold, and the blood flow decreases[10 11].

If the effect of excessive renal mobility is assumed to be similar to the effect of a renal artery stenosis, an orthostatic reduction of blood flow in the

mobile kidney can be expected together with the consequent release of renin.

The study described in this chapter had been initiated in order to evaluate the hypothesis that nephroptosis would cause a significant reduction in renal blood flow. Since non-invasive methods were not available to determine the changes in unilateral renal blood flow, we were confined to a method measuring the total blood flow in both kidneys together. Therefore orthostatic changes in effective renal plasma flow (ERPF), glomerular filtration rate (GFR) and peripheral plasma renin activity (PRA) have been measured in patients with various degrees of renal mobility. The measurements were performed in both hypertensive and normotensive patients with and without nephroptosis. Thus an answer was sought to the question why a certain renal mobility causes hypertension in one person and leaves another person with a normal blood pressure. Finally, one patient is described who was submitted to selective renal vein catheterization in order to obtain data on the renin release by the mobile kidney in supine and in upright position.

3.2 Patients and methods

Retrospectively, 27 patients were selected from the hypertensive and control groups described in chapter 2. This selection resulted in two groups: 15 patients with hypertension (BP: 152/104 ± 18/5 mmHg) and 12 normotensive patients (BP: 110/68 ± 9/8 mmHg). It was made sure that both the hypertensive group and the normotensive group had virtually a similar wide range of renal mobilities. The mean age in the total group was 31 year at the time of the study (normotensives 28 ± 8 yr and hypertensives 34 ± 9 yr). The renal mobility was measured according to the method described in chapter 2 and expressed in centimeters vertical shift.

All patients were subjected to a similar protocol. None of the normotensive subjects used medication. Three hypertensive patients had a severe salt-restricted diet (< 3 g NaCl/24 h) and two of them used diuretics (hydrochlorothiazide 50 mg o.i.d.).

The study itself lasted 8 hours starting at 9 a.m. The renal function (GFR and ERPF) was determined during 4 hours (after an equilibration period of two hours) in the supine position and during two hours in the upright position, which followed immediately. Urine production was measured every hour and venous blood samples for the PRA determination were

drawn just before changing to the upright position and at the end of the upright period. The PRA was determined by means of a radioimmunoassay and expressed in nmol AI/1/h[12].

The GFR and ERPF were determined simultaneously using ^{125}I-iothalamate and ^{131}I-hippuran, respectively. These radiopharmaceuticals are generally accepted to be good substitutes for inulin and PAH, the latter after correction for the difference in extraction between PAH (0.89) and ^{131}I-hippuran (0.75)[13]. After a priming dose both radiopharmaceuticals were administered by constant infusion (maximum doses of 2.8 MBq (75 μCi) ^{131}I-hippuran and 2.5 MBq (68 μCi) ^{125}I-iothalamate). The ERPF was calculated according to the constant infusion method (IxV/P*). Donker et al. had found a highly significant correlation between the ERPF calculated according to the standard method (UxV/P**) and according to this constant infusion method ($r = 0.998$)[14]. Due to several factors the constant infusion method cannot be used to replace the standard method in the determination of the GFR[14]. However, possible causes of error in the standard method such as incomplete urine collection and dead space are eliminated by correcting the GFR (obtained from the standard method) with the following factor:

$$\text{ERPF (IxV/P)} \;/\; \text{ERPF (UxV/P)}.$$

In this way the estimation of GFR and ERPF appeared to be accurate within 2.2 and 5 per cent respectively, without the need for a meticulous urine collection[14]. This is important in this particular study, where a decrease in urine production could be expected in upright position[15 16].

The GFR and the ERPF were not standardized for body surface area if we were interested in the relative changes of these functions only.

In one patient we investigated the effect of nephroptosis on the renin release by the kidneys. Hypertension (180/105 mmHg) was diagnosed in this 35 year old female using OCC, by her general practitioner. Since extensive anti-hypertensive medication failed to result in a normal blood pressure she was hospitalized. IVU showed a symmetrical nephrography and a delayed contrast excretion in the small right kidney (11 cm vs 15 cm on

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* concentration of the administered substance × volume / plasma concentration
** urine concentration of administered substance × urine volume / plasma concentration

the left side). Radionuclide renography showed a delayed first phase on the right side compared to the left. A renal artery stenosis was suspected since also a vascular bruit was heard over the right kidney region. Because the vascular bruit was more intense in upright position, an upright plain X-ray film of the abdomen was taken. The right kidney appeared to be excessively mobile (10 cm) whereas the left kidney shifted 3 cm only. Angiography was performed and a bilateral renal artery stenosis (FMD) was found in supine position (figure 14). Subsequently, angiography in upright position was performed to assess the effect of the nephroptosis on the renal artery. Figure 14 shows the stretching and narrowing of the right renal artery due to the

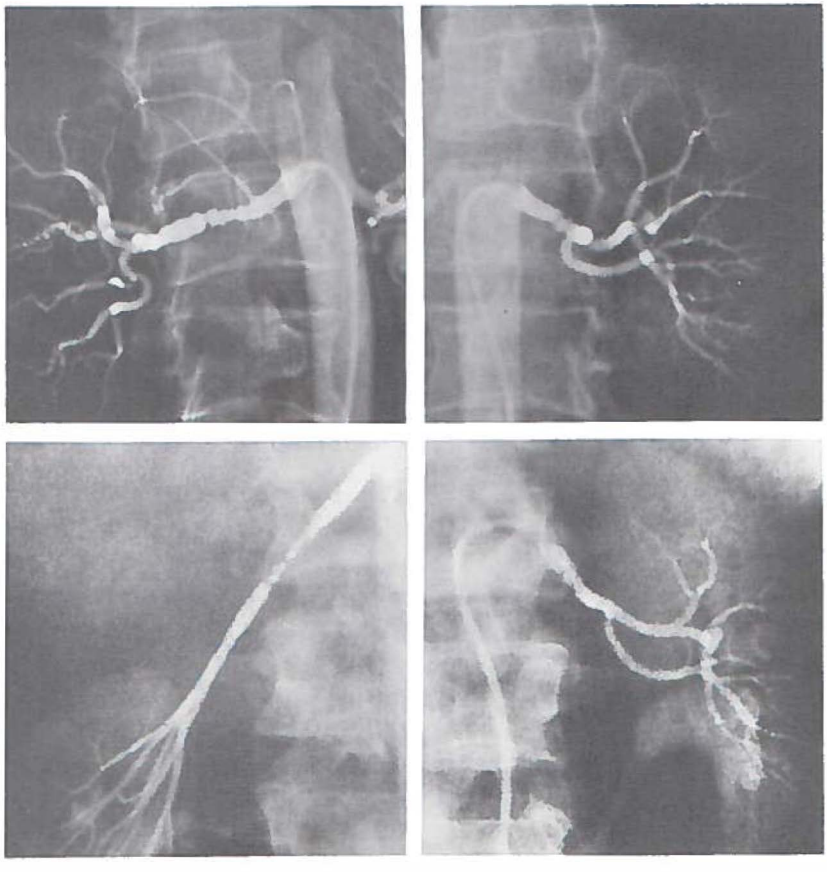

Figure 14: Renal angiography performed in supine (upper part) and upright position (lower part). For details see text.

mobility of that kidney whereas the diameter of the left renal artery appeared unaffected on visual inspection. Consequently catheterization of both renal veins was performed to gather information on the renin release in both positions. After the patient was off antihypertensive medication for two weeks, blood samples were drawn from the right and left renal vein in supine position and after one hour in upright position.

3.3 Results

The results of the renal function studies are summarized in table VI. The ERPF-values represent the results of a measurement at the sixth hour in supine position and the second hour in upright position, respectively. These values appeared to be a true indication of the renal plasma flows during the supine and upright periods in each individual since no significant differences were observed between the ERPF at 4 hours and 6 hours in supine position (figure 15A), nor at 1 hour and 2 hours in upright position (figure 15B). The virtually constant plasma levels of ^{131}I-hippuran in each position, justified the correction of the GFR for incomplete urine collection and dead space with the factor given in paragraph 3.2.

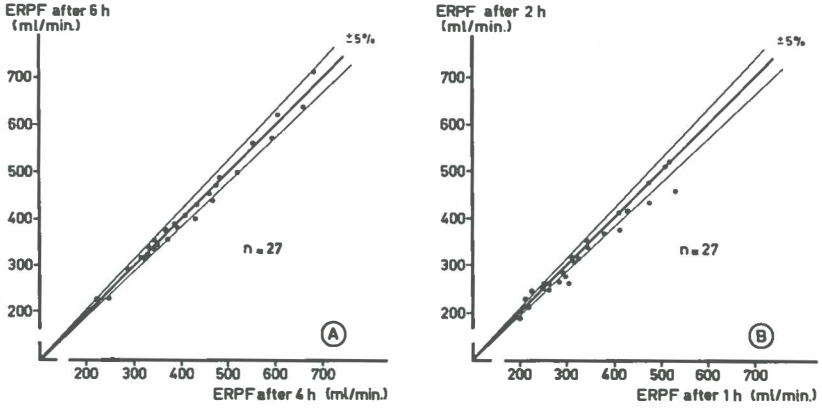

Figure 15: Ⓐ ERPF after 4 hours versus the ERPF after 6 hours in supine position. Ⓑ ERPF after 1 hour versus the ERPF after 2 hours in upright position. The lines of identity are drawn with the 5% 'deviation'.

Table VI: Data on renal function measured in 12 normotensive and 15 hypertensive subjects. GFR and ERPF (*not* standardized for body surface area) are expressed in ml/min, PRA in nmol AI/1/h. Renal mobility is the sum of left and right renal mobility in centimeters.

Patient no.	Age	Sex	GFR sup.	GFR upr.	ERPF sup.	ERPF upr.	FF sup.	FF upr.	PRA sup.	PRA upr.	Renal mob.
NORMOTENSIVES											
1	40	f	111	98	415	336	0.27	0.29	1.0	3.6	11
2	42	f	104	85	353	286	0.29	0.30	0.5	1.4	6
3	21	f	100	82	346	315	0.29	0.26	0.8	1.6	4.5
4	28	f	136	99	470	334	0.29	0.30	0.5	3.8	8
5	22	f	82	71	330	264	0.25	0.27	0.5	1.3	2
6	24	f	155	140	500	410	0.31	0.34	1.5	2.7	9.5
7	24	f	137	110	436	318	0.31	0.35	0.4	2.8	10.5
8	22	f	100	80	314	248	0.32	0.32	2.8	4.3	2
9	26	f	178	135	638	472	0.28	0.29	—	—	9.5
10	34	f	189	164	715	515	0.26	0.32	—	—	13.5
11	16	f	151	94	610	451	0.25	0.21	0.7	7.5	6
12	33	m	143	126	487	429	0.29	0.29	1.3	2.9	5.5
Mean	28		132	107	467	365	0.28	0.30	1.0	3.2	7.3
SD	8		33	29	130	87	0.02	0.04	0.7	1.8	3.6
HYPERTENSIVES											
13	31	f	120	116	389	284	0.31	0.41	0.5	1.9	13.5
14	33	f	99	86	343	261	0.29	0.33	9.9	47.5	5
15	21	f	135	127	430	374	0.31	0.34	1.0	1.5	11
16	33	f	125	103	406	288	0.31	0.36	1.3	3.8	14.9
17	24	f	93	83	387	344	0.24	0.24	1.2	2.3	7
18	37	f	98	79	312	256	0.31	0.31	17.8	20.2	9
19	24	f	60	49	237	197	0.25	0.25	0.6	1.4	9
20	48	f	119	109	435	376	0.26	0.29	2.2	2.9	12
21	46	f	79	71	317	260	0.25	0.27	1.5	2.3	11
22	44	f	110	80	291	215	0.38	0.37	1.1	1.6	10
23	35	m	148	139	568	517	0.26	0.27	1.8	3.2	4.5
24	35	f	72	66	328	227	0.22	0.28	2.8	14.5	14.5
25	22	f	114	111	550	425	0.21	0.26	1.3	2.2	10
26	40	f	99	66	375	224	0.27	0.30	—	—	15
27	32	f	67	67	219	202	0.31	0.33	—	—	3
Mean	34		103	90	372	297	0.28	0.31	3.3	8.1	10.0
SD	9		25	26	99	92	0.04	0.05	4.9	13.2	3.8
DIFFERENCE											
p-value	N.S.		< 0.02	N.S.	< 0.05	N.S.	N.S.	N.S.	< 0.05	N.S.	N.S.

The selected groups of normotensive and hypertensive patients were comparable with respect to age distribution and range of renal mobilities, although the mean mobility was slightly - but not significantly - higher in the hypertensive group. The mean systolic/diastolic blood pressure of the normotensives was 110/68 ± 9/8 mmHg in supine position whereas the hypertensive subjects had a mean supine blood pressure of 152/104 ± 18/5 mmHg. The supine renal functions differed between normotensives and hypertensives. The mean GFR (corrected for body surface area) was significantly ($p < 0.02$) lower in hypertensives compared to normotensives (103 ± 20 ml/min and 125 ± 25 ml/min respectively). The mean corrected ERPF was also lower in hypertensives (363 ± 68 versus 446 ± 95 ml/min, $p < 0.05$). The mean supine PRA was higher in the hypertensive patients, which is however due to the high PRA in two hypertensive patients (no. 14 and 18) who used diuretics and had a severe salt-restricted diet.

The GFR as well as the ERPF appeared to decrease in all patients in the upright position. This is illustrated with figure 16. The relative decrease of the ERPF (upright versus supine) appeared to be equivalent in normotensive (21 ± 6%) and in hypertensive patients (21 ± 9%). The GFR decrease observed in upright position was slightly but significantly higher in the normotensive group (19 ± 8% versus 12 ± 9% in the hypertensive patients). There was however, a wide range in these orthostatic renal function decreases: 9 to 40 per cent (ERPF) and 0 to 38 per cent (GFR) respectively. The decrease of the GFR could be partially explained by the

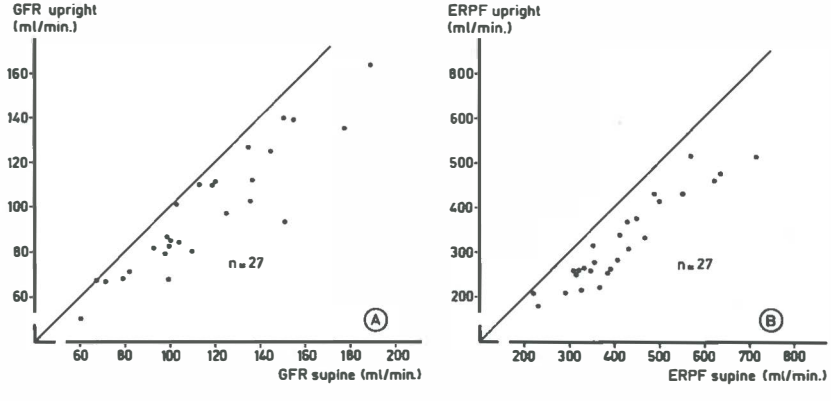

Figure 16: Ⓐ GFR in supine versus GFR in upright position. Ⓑ ERPF in supine versus ERPF in upright position. The lines of identity are drawn.

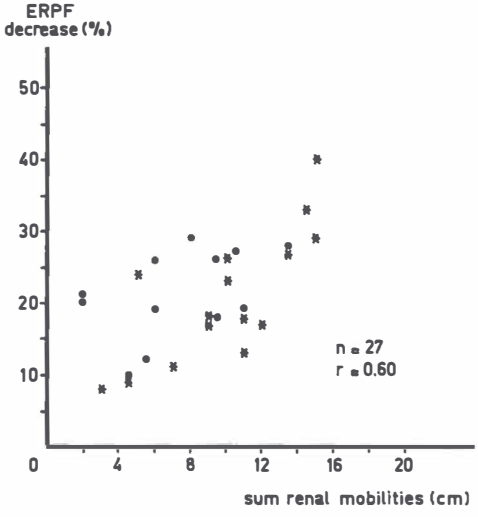

Figure 17: Relation between orthostatic decrease in ERPF (%) and the sum of renal mobilities of left and right kidney. ● = normotensive; * = hypertensive.

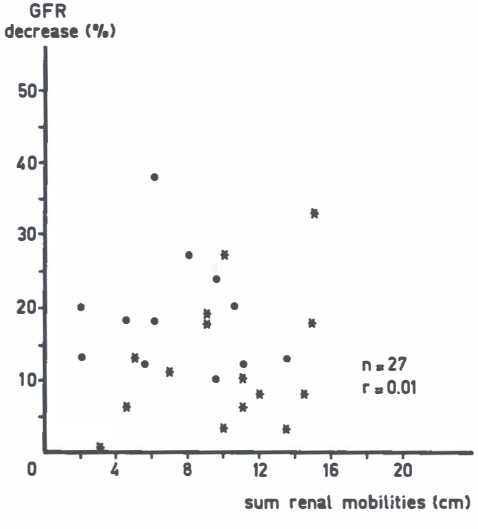

Figure 18: Relation between orthostatic decrease in GFR (%) and the sum of renal mobilities of left and right kidney. ● = normotensive; * = hypertensive.

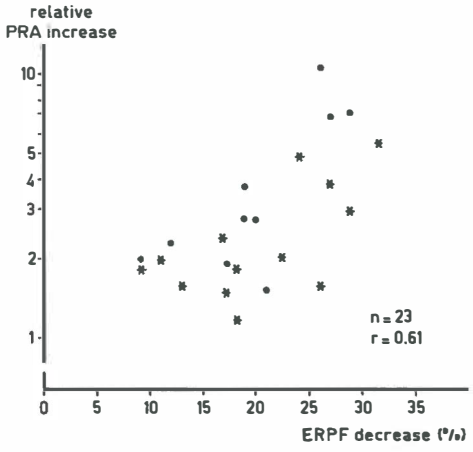

Figure 19: Relation between the orthostatic ERPF decrease and increase in peripheral PRA. ● = normotensive; * = hypertensive.

decrease of the ERPF ($r = 0.51$, $p < 0.05$). That the extent of orthostatic ERPF decrease could be attributed to the degree of renal mobility can be seen in figure 17. The sum of mobilities of the right and left kidney has been plotted versus the orthostatic ERPF decrease. The calculated correlation coefficient confirms the hypothesis that the extent of ERPF decrease may, at least partly, be explained by the corresponding degree of renal mobility. A relation between GFR decrease in upright position and renal mobility was not found (figure 18).

The decrease in renal blood supply in upright position appeared to be a stimulus for the renin production (table VI). Indeed this increase in peripheral PRA was correlated with the decrease in ERPF (figure 19). Although tested *not* to be statistically different ($p < 0.1$), the normotensive subjects showed a higher PRA increase (= PRA upright/PRA supine) than the hypertensive patients (4.2 ± 3.2 versus 2.4 ± 1.4) while the ERPF decrease in both groups was comparable.

Urine production decreased from supine to upright position despite a constant fluid intake. This orthostatic reduction in the urine production appeared to be correlated with the orthostatic decrease in GFR in both hypertensive and normotensive subjects (figure 20).

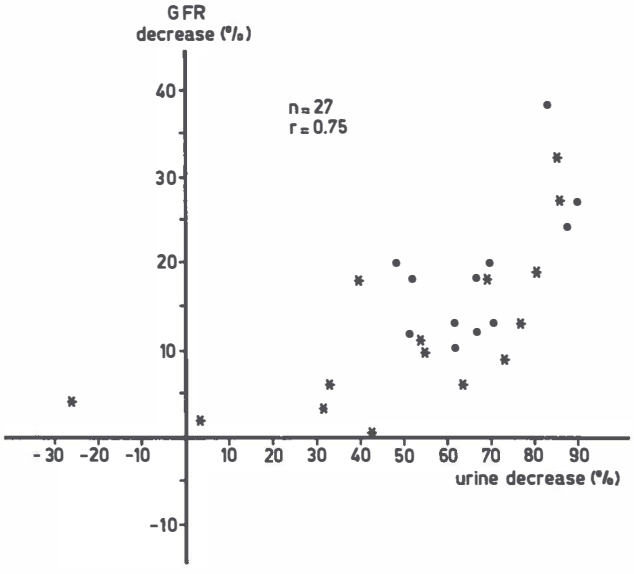

Figure 20: Relation between the orthostatic GFR decrease and decrease in urine production after 2 hours in upright position. ● = normotensive; ✱ = hypertensive.

The reaction of the blood pressure to the change in posture was observed to be different in normotensives and hypertensives. The mean arterial pressure (MAP) of the hypertensive group remained constant in both positions (120 ± 9 mmHg in supine versus 118 ± 10 mmHg in upright position), whereas the supine MAP was significantly lower than the upright MAP in the normotensive group (82 ± 8 mmHg versus 90 ± 11 mmHg). The blood pressure changes in both groups showed no relation with one of the other mentioned parameters.

The results of the PRA measurements in renal vein blood samples of the one hypertensive female patient with FMD and nephroptosis are summarized in table VII. The presence of a functional renal artery stenosis at the left side was likely in the supine position although the ratio of the renin release of left to right kidney was a little less than 1.5. After 1 hour in upright position however, a totally different picture was seen. The renin release of the right ptotic kidney had increased tenfold whereas the renin release of the left kidney not even doubled.

Table VII: Data of the renin measurements in supine and upright position in the right renal vein (VRD), the left renal vein (VRS) and in the brachial artery (arterial).

PLASMA RENIN ACTIVITY (nmol AI/l/h)

	VRD	VRS	arterial	VRD/VRS
	19.5	27.9	17.3	0.70
	194.5	43.2	25.9	4.50

3.4 Discussion and conclusions

Changes in renal blood flow are common under various circumstances such as physical strain, nutrition, temperature, posture and also age[1]. The kidney is supposed to be equipped with regulatory mechanisms to deal with these changes in order to maintain a constant filtration[1 2]. When normal subjects are exposed to a change in posture by tilting, the renal blood flow decreases as does the cardiac output whereas heart rate, peripheral resistance and PRA all increase [15-22]. The kidney, together with other regulatory systems such as baroreceptors and the central nervous system[23], apparently tries to restore its blood supply and filtration. Although there are controversies about the individual importance and the interrelation of the pressure-regulatory mechanisms it is generally accepted that there is a sustained decrease in renal blood flow in upright position.

McCann and Romansky made the interesting observation that the orthostatic reduction of the renal blood flow was more pronounced in nephroptotic patients compared to subjects with a 'normal' renal mobility[24].

This implies that nephroptosis would have an additive effect to the orthostatic reduction in renal blood flow. The studies of Schoenenberger et al. are in agreement with the observation of McCann and Romansky. The former found that the excretion of urinary lactate dehydrogenase (LDH) reflected ischaemic renal tissue damage [25]. A swinging pattern of the LDH excretion was observed during postural changes in nephroptotic patients only, which disappeared after nephropexy had been performed[26 27]. Both studies demonstrate the possible effect of nephroptosis on renal blood flow. The results presented in this chapter confirm these observations, since we also found that the ERPF decrease was more pronounced in nephroptotic subjects. Moreover a linear relation was found between the degree of renal mobility and the decrease in renal plasma flow. Since this ERPF decrease in turn correlated with the increase in PRA, it looks as if the nephroptotic kidney has an effect similar to a renal artery stenosis.

Glomerular filtration was also affected by changes in posture. This orthostatic decrease of the GFR has been reported by several authors[15 17 18]. The GFR decrease is most probably the effect of the ERPF decrease, since Brenner et al. found the autoregulation of the GFR to be a consequence of the factors that maintain a near-constant level of renal blood flow over a wide range of perfusion pressures[28]. According to the results of our study described in this chapter, the autoregulatory capacity of a kidney with respect to its GFR seems to show individual variations since no high correlation (0.51) was found between the orthostatic ERPF decrease and GFR decrease. This would also explain the absence of a relation between renal mobility and GFR decrease in our patients. In this respect the results of the study of Bianchi et al. disagree with our observation[29 30]. Bianchi reported a significant decrease of the GFR in nephroptotic patients (11 normotensives and 1 hypertensive) whereas the non-nephroptotic controls (5 subjects) showed no orthostatic GFR change. The explanation for this discrepancy in results is most likely found in the different approach to the problem. Bianchi investigated the GFR in subjects as they changed from the *upright* to the *supine* position. This direction of changing the posture might have a different effect on the GFR compared to the other way around, which is illustrated by the studies of Epstein et al.[15] and Goodyer et al.[16]. Both latter groups measured the GFR in normotensive subjects that changed from supine to upright and back to supine position. They observed a decrease of the GFR after the first posture change and an even larger decrease after the patient lied down again. After 1½ hour the GFR was still about 85 per cent of the initial supine GFR.

The change in ERPF in relation to the different renal mobilities was found to be similar in hypertensives and normotensives. So there is no evidence for a different effect of renal mobility on the artery diameter as an explanation for the difference in blood pressure. It seems that in a normotensive person the mobile kidney is (still?) able to react adequately to the 'attack' on its blood supply, such that the blood pressure does not rise to a pathological level. The orthostatic rise of the MAP and peripheral PRA in the normotensive subjects might well reflect such an adequate autoregulatory mechanism of the ptotic kidney. This despite the fact that a correlation between renal mobility and MAP or PRA has not been found.

The differences in the supine GFR and ERPF between hypertensives and normotensives and the differences in orthostatic changes in GFR and PRA, are most probably a secondary effect of hypertension instead of a cause of the high blood pressure[31], although arguments against this hypothesis have been reported[32 33]. The difference in supine PRA between the two groups can be explained by the high values of two hypertensive patients, who had a severe salt-restricted diet and a diuretic medication[34].

In summary we conclude that a patient with a mobile kidney shows a more pronounced orthostatic decrease in total renal blood flow compared to non-nephroptotic subjects. The present study has not given the answer to the question whether this blood flow reduction is larger in the mobile kidney compared to the contralateral non-mobile kidney. It would be desirable to measure the blood flow changes both separately and continuously. On the other hand the observed relation between the sum of renal mobilities and ERPF decrease is already suggestive for the blood flow-reducing effect of the mobile kidney. This is even more so if one realizes that the observed correlation might still be confounded by individually different effects of nephroptosis and nephrotorsion on the renal artery diameter. The theory is strengthened by one observation of a ten-fold PRA increase in a mobile-kidney vein after tilting to upright position, whereas in the vein of the contralateral non-mobile kidney the PRA increased only to nearly twice the supine value.

In conclusion, a mobile kidney in upright position seems to have effects equivalent to a renal artery stenosis although hypertension is not always the consequence. Other congenital or blood pressure-raising factors could add to this intermittent renal blood flow decrease in the eventual onset of hypertension[31].

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CHAPTER 4

Renal mobility and the renal artery

4.1 Introduction

An excessively mobile kidney can cause an orthostatic reduction of its own blood supply, as demonstrated by the results in the previous chapter. The mechanism of this effect had been partially elaborated in several other studies. Kaufman et al. and Hariu et al. found the artery of a ptotic kidney elongated and narrowed in the upright position[1,2]. Clorius et al. like others, observed a posture-dependent reduction of hippurate uptake in the ptotic kidney[3-9]. Although the radionuclide renogram has a limited accuracy to quantify renal blood flow[10], the results after nephropexy reported by Clorius et al. did show a qualitative improvement of the renal uptake of hippurate[9]. It looks as if patients *selected* on extreme renal mobility, have an orthostatic renal blood flow decrease due to an elongated and narrowed renal artery in the upright position.

A serious drawback of these studies in selected patients is that no information was available on the anatomical and physiological effects of a 'low grade' or a 'medium grade' renal mobility. The relation observed in our study (chapter 3) between renal mobility and renal blood flow decrease in upright position did not show a high correlation coefficient. This indicates that the degree of renal mobility is not a parameter to unambiguously predict the effect of renal mobility on renal blood flow.

The latter is not unexpected since the effect of a certain renal mobility on the artery diameter is unknown. The diameter-reducing effect of a mobile kidney is probably related with the 'stretchability' of the renal artery: a relatively low renal mobility could have a stretching and thus narrowing effect on a short renal artery, whereas an excessively mobile kidney could shift without stretching its long vessel.

With this consideration in mind a study was set up to assess the effect of a mobile kidney on the renal artery diameter. For this purpose the diameter of

the vessel had to be measured accurately over its total length from aorta to kidney. Therefore, angiography was performed in supine and upright position and the diameters of the vessels were quantified by means of a computer-linked digitizer.

4.2 Patients and methods

The 17 patients in this study, 12 females and 5 males were selected from a hypertensive group on the following criteria: age < 40 years, untreated blood pressure $\geqslant 160/110$ mmHg, normal renal function and 'high' renal mobility or orthostatic nephrotorsion. Informed consent was obtained from all patients.

Aortography was performed in supine position after percutaneous transfemoral catheterization. A 100 mm camera registered the aortograms at 3 second intervals following the contrast injection. Subsequently the patient was tilted to 90° and an upright series completed the investigation.

The supine and upright aortograms were enlarged to the size of the IVU-radiograph using a vertebra as reference. The contours of the renal arteries and aorta were then converted to numerical values by means of a digitizer (Ferranti-Cetec model orthodontix PF). The data were subsequently processed by a computer program we developed on the CDC Cyber 74-16 computer of the Groningen University Computer Center. This resulted in diameter profiles of each renal artery in supine and upright position. These profiles represent the diameter of the renal artery as it varies from the aorta to the kidney. The mean diameters of each renal artery in supine and upright position can only be compared if computed over an equal distance. Therefore two reference points were chosen: one at the projected origin of the artery at the aorta and the other at a well-defined bifurcation close to the kidney (figure 21). The ratio of the supine to upright aorta diameter at the level of the first reference point served as a normalization factor for differences in enlargement. This way of processing resulted in the diameter profile, length and mean diameter of the renal arteries in supine and upright position. Furthermore the renal mobility caused by the tilting during the aortographic study was calculated from the difference of the vertical distance between the two reference points in both positions.

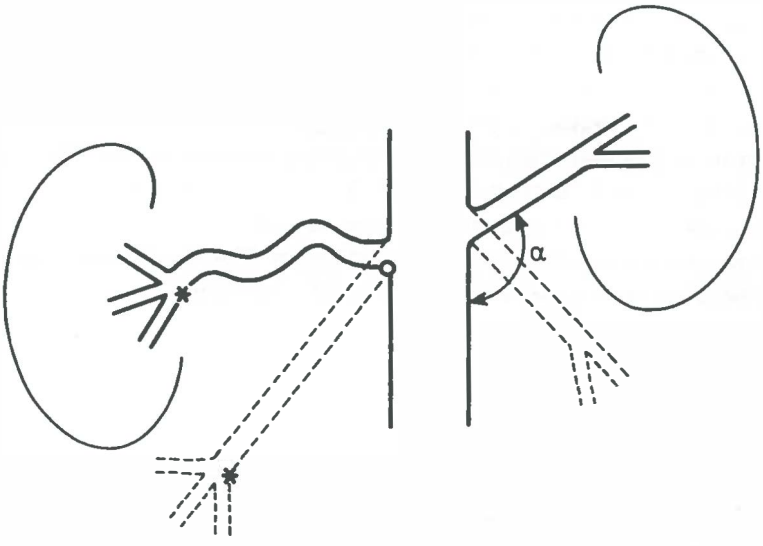

Figure 21: Schematic drawing of renal arteries in supine position (solid lines) and upright position (dotted lines). Open circle represents reference point 1, asterisk reference point 2. Angle between abdominal aorta and renal artery is indicated by α.

In addition a 'curve-angle-index' (CAI) was defined in order to get an impression of the two-dimensional course and hence the 'stretchability' of the renal artery. The CAI included the angle between aorta and renal artery and an index of the artery curving, and was defined with the following equation:

$$CAI = \alpha \times 100 \left[\frac{RAL}{VAL} - 1 \right]$$

RAL represents the full length (mm) of the renal artery as it winds from reference point 1 to reference point 2, and the virtual artery length (VAL) is the shortest distance between the two reference points (figure 21). The angle between the aorta and renal artery is represented by α (in degrees). It follows that the CAI is higher with more curving present or with a larger angle between the aorta and renal artery.

These two factors are essential because they substantially influence the effect of renal mobility on the artery diameter. Figure 21 gives a schematic

example. The 'unfolding' of the right artery as well as the decrease of the angle on the left side allow for a certain renal mobility before stretching and possibly narrowing of the artery will take place. It should be realized that the CAI is only an arbitrary index, which is a useful tool in the qualitative evaluation of the effect of renal mobility on artery diameter change. The true contribution of each factor in this index is not easily estimated.

The digitizing and data processing were tested on a number of model drawings and aortograms by different observers. The results had a good reproducibility with a maximum deviation of 4 per cent.

4.3 Results

Twenty-five arteries from 17 aortograms appeared suitable for the digitizing procedure. Adequate digitizing of the right renal artery was

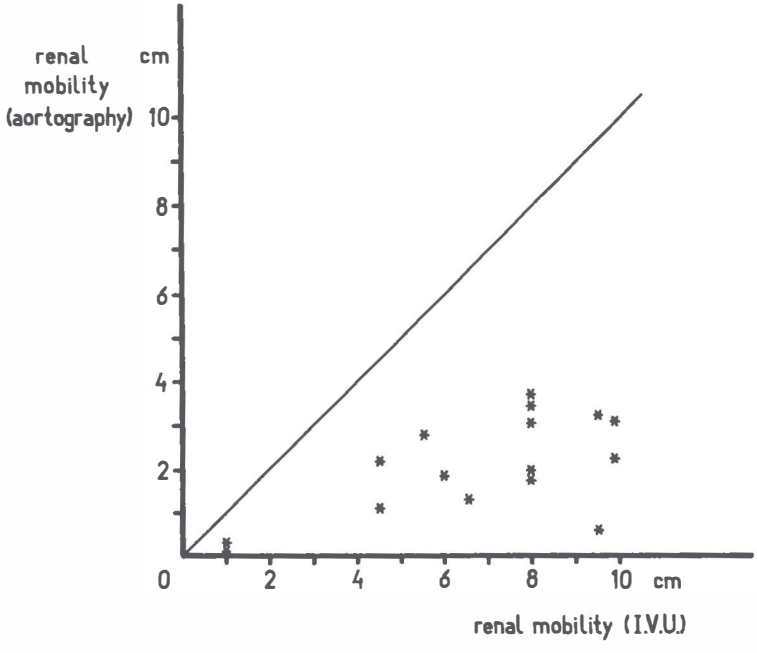

Figure 22: Mobility of right kidney as derived from intravenous urography (x-axis) versus renal mobility of the same patient found in the aortographic study (y-axis), the latter corrected for differences in enlargement.

possible in 16 patients. Digitizing of the left renal artery succeeded in 9 patients. The 9 remaining arteries showed single or multiple overlaps and/or a lack of adequate reference points in supine position.

The mobility of the kidneys derived from the aortograms varied from 0 to 4 cm, reflecting the shift of reference point 2 (see figure 21) during tilting. These mobilities appeared to correlate poorly with those observed earlier with intravenous urography. The latter were measured from the shift of the lower kidney pole after active rising. The discrepancy between the mobilities (right kidneys only) measured with these different techniques is illustrated in figure 22.

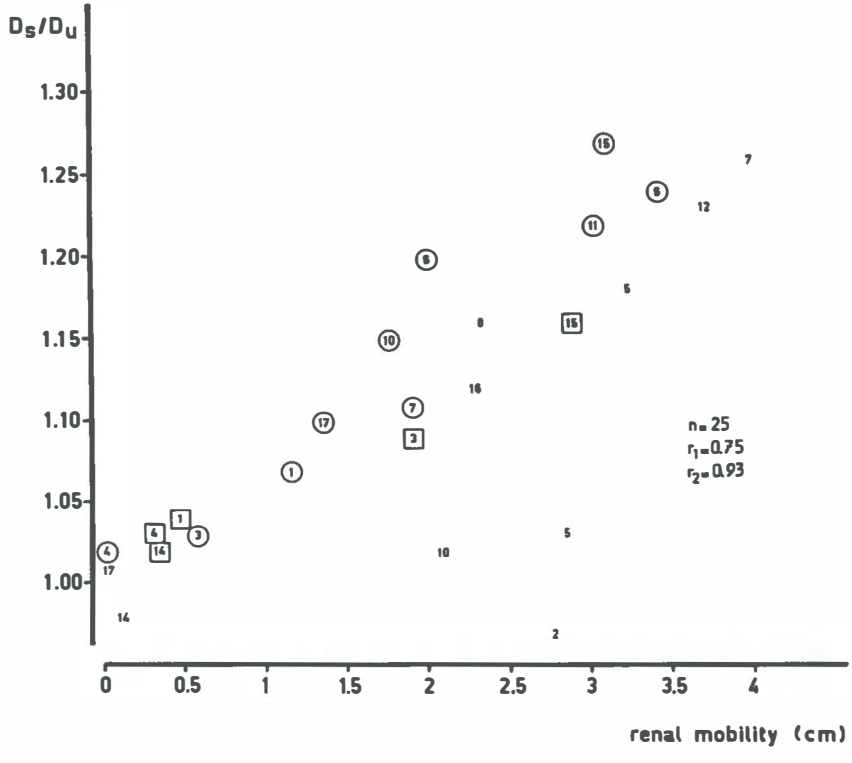

Figure 23: Relation between renal mobility (from aortographic study) and orthostatic diameter changes of the renal artery, represented by the ratio of the mean renal artery diameter in supine position and upright position (D_s/D_u). Non-circled figures represent arteries with a high CAI (> 1000). Circled figures represent right arteries and squared ones left arteries, both with a low CAI. r_1 is the correlation coefficient of all 25 points and r_2 of 15 points with a low CAI (< 1000).

Table VIII: Curve-angle-indices (CAI) in supine position of all digitized renal arteries and the corresponding renal mobilities (cm). The CAI's are an estimate of artery stretchability, including both renal artery curving and the angle with which the artery stems from the abdominal aorta. The figures in parentheses represent the CAI in upright position.

	Curve-Angle-Index		Renal mobility	
Pat. no.	right artery	left artery	right	left
1	540 *(355)*	212 *(131)*	1.2	0.5
2	1625 *(350)*	—	2.8	—
3	68 *(54)*	128 *(45)*	0.6	1.9
4	608 *(595)*	79 *(79)*	0	0.3
5	1748 *(216)*	7800 *(30)*	3.2	2.8
6	656 *(28)*	—	3.4	—
7	228 *(87)*	2565 *(22)*	1.9	3.9
8	1792 *(128)*	—	2.3	—
9	44 *(35)*	—	2.1	—
10	264 *(29)*	1722 *(224)*	1.8	2.1
11	72 *(72)*	—	3.1	—
12	1700 *(192)*	—	3.6	—
13	—	—	—	—
14	1274 *(1276)*	656 *(596)*	0	0.3
15	350 *(66)*	660 *(24)*	3.1	2.8
16	1775 *(495)*	—	2.3	—
17	750 *(148)*	2730 *(2826)*	1.4	0

The effect of the downward shift of all 25 kidneys on their renal artery diameters is illustrated in figure 23. The change in mean diameter of the vessel, represented by the ratio of the diameter in supine to the diameter in upright position (D_s/D_u), showed a linear relation with the degree of renal mobility calculated from the aortogram ($r_1 = 0.75$). Apart from minor variations in the diameter changes between cases with a similar renal mobility, the absence of a diameter change in case 2, 5 and 10 had a clear negative influence on the mentioned correlation. The vessels of these three cases however, appeared to have high CAI's allowing those kidneys a certain shift without a consequent decrease in artery diameter. The same reasoning, although to a lesser extent, seemed to hold for the remaining cases with high

CAI's. The correlation between diameter change and renal mobility did markedly improve ($r_2 = 0.93$) if calculated in a selected subgroup ($n = 15$) with a low (< 1000) CAI (see table VIII and figure 23). Both the orthostatic 'unfolding' of the winding artery and the change of the angle by the mobile kidney, are illustrated by the decrease of the CAI's in upright position (table VIII).

As for the mean diameter, the maximum decrease in upright position was as high as 30 per cent. A local diameter decrease of 60 per cent however, has been recorded in the diameter profiles. Such an exceptional local change in diameter was seen in one patient only (case no. 12). The other patients showed moderate or no local changes of the diameter profile in upright position compared to the supine position.

The effect of a mobile kidney on its artery diameter appeared to be partially the result of an elongation of the vessel. A moderate correlation ($r = 0.69$) was found between the decrease of the artery diameter and the increase of artery length.

4.4 Discussion and conclusions

Posture-dependent changes in renal artery diameter play an essential role in the discussed relation between renal mobility and hypertension, because an orthostatic diameter decrease might function as an intermittent renal artery stenosis. The causal relation between hypertension and a renal artery stenosis is widely accepted. However, several studies have clearly demonstrated that a renal artery stenosis does not necessarily lead to the onset of hypertension immediately[11-13]. These interesting observations may shed light on the paradox of excessive renal mobility with decrease in renal blood flow observed in *normotensive* subjects. Hypertension could be the eventual effect of an orthostatic renal artery stenosis, despite the intermittent character of the stenosis (see paragraph 5.5).

Concluding from the results of our study, a mobile kidney indeed can cause a narrowing of the renal artery. Moreover, the degree of diameter reduction appears to be closely correlated with the mobility of the kidney. The consequences of such an intermittent orthostatic artery stenosis with respect to renal function are not exactly known. According to Poiseuille's law, an average of 30 per cent diameter decrease should result in a considerable

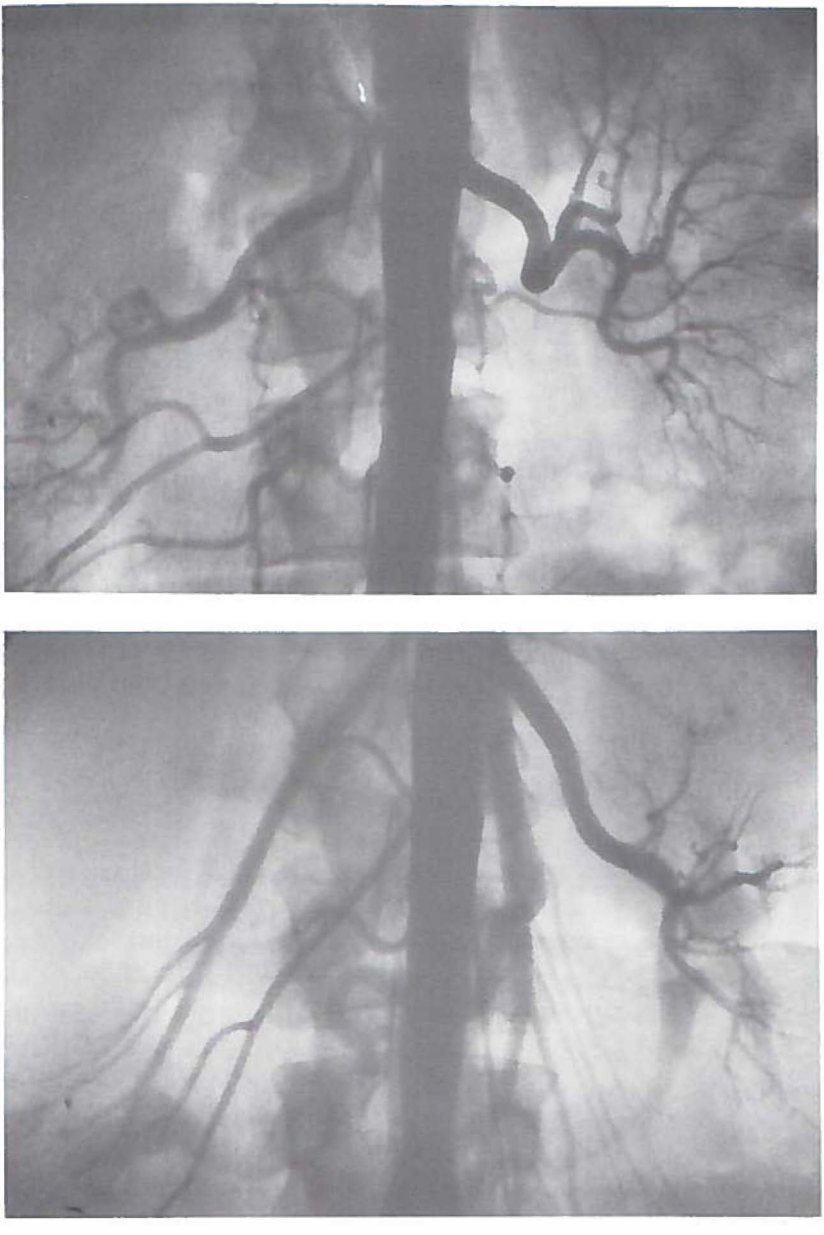

Figure 24: Aortography of a 35-year old woman in supine position (upper part) and upright position (lower part).

reduction of flow. However, the results of animal studies have shown that the effect of a 30 per cent diameter decrease of the renal artery on renal blood flow is negligible. Only a more than 60 per cent reduction in diameter will have a measurable reducing effect on the renal blood supply[14 15]. Once such a so-called 'critical stenosis' has been reached, the length of the stenosis section would have an additional reducing effect on the flow[16].

Renal regulatory mechanisms protect the kidney against blood flow reduction and fall in filtration pressure. The release of different humoral factors causes systemic vasoconstriction and renal vasodilation[17 18]. The degree of artery stenosis, the systemic blood pressure and the vasopressor-depressor balance in the kidney together determine the ultimate renal blood flow.

The effect of a mobile kidney on its artery diameter may lead to an intermittent release of vasopressor substances in the systemic circulation. Thus a rise in systemic blood pressure might occur despite only minor changes in the resulting renal blood flow. Indeed we earlier found a correlation between the increase in plasma renin activity and the decrease in renal blood flow in nephroptotic patients during changes in posture (chapter 3).

The two-dimensional imaging of a three-dimensional phenomenon could have introduced systematic errors in the measurement of the renal artery diameter. The distance between a mobile kidney and the X-ray film is higher in upright position, as the downward shift of the kidney is generally accompanied by an anterior movement. This would however, result in an overestimation of the renal artery diameter of this mobile kidney in upright position, and could have led only to an underestimation of the observed diameter decrease. The accuracy of the measurement of renal artery length may be influenced also by these changes in geometry, although not necessarily to the same extent as the diameter. This would explain the relatively poor correlation between the change in artery diameter and length. Therefore the mean diameter decrease is concluded to be the most representative parameter to predict orthostatic flow reduction.

Unfortunately, the digitizing procedure does not allow diameter measurements of segmental branches of the renal artery where overlaps are frequently present. Changes in 'intrarenal' vasculature as shown in figure 24, could be an even more important factor in reducing renal blood flow compared to the diameter changes in the renal artery itself.

In conclusion, a mobile kidney can cause a narrowing of the renal artery when in upright position. Although the degree of mobility reflects the degree of diameter reduction in most patients, the measurement of renal mobility alone does not provide an adequate screening method for its pathophysiological effects. Other factors have to be taken into account. Firstly, the course of the artery, or 'spare' length, in supine position as illustrated by the absence of a diameter reduction in three patients with a 'high' renal mobility. Secondly, the technique of measuring renal mobility is important. This was demonstrated by the discrepancy between the renal mobility in the same patient during active rising (IVU) and during passive tilting (angiography). A third complicating factor is nephrotorsion. Apart from the difficulty of quantifying renal torsion, its effect on the renal vasculature is hard to assess. Altogether it seems that aortography in supine and upright position is presently the only method for estimating the possible effect of a mobile kidney on its artery diameter and hence on its blood flow. Accurate monitoring of the individual blood flow in two kidneys separately during postural changes will ultimately be the most appropriate method to reveal the effect of a mobile kidney on renal perfusion and systemic blood pressure.

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CHAPTER 5

Unilateral renal function studies

5.1 Introduction

The studies reported in the previous chapters have confirmed the existence of a relation between nephroptosis and hypertension. This relation seems to be based largely on the orthostatic narrowing of the renal artery. It is therefore important to establish whether a mobile kidney indeed shows the characteristics of a functional renal artery stenosis. This may be achieved with a simple technique that measures renal blood flow differences. The methods available at present that can differentiate between a ptotic kidney with and one without an orthostatic effect on its blood flow are briefly summarized:

Invasive:

— electromagnetic flow measurement
— ultra-sound flow measurement (Doppler)
— xenon-133 wash out[1]
— angiography[2]
— renal vein renin measurement
— indicator dilution[3]
— micro-particle trapping[4]
— ureteric catheterization[5]

Non-invasive:

— rapid sequence IVU
— radionuclide renography
— initial uptake of radionuclide tracer
— transit of vascular tracer[4]

The methods that require an invasive catheterization are obviously less attractive as a screening test. This leaves us with the non-invasive methods of which serial IVU and renography are at present frequently used to test for a renal artery stenosis in a hypertensive patient.

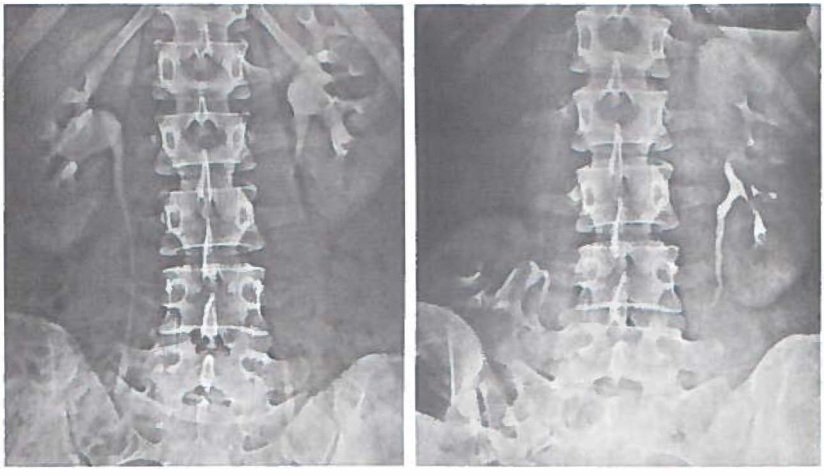

Figure 25: Intravenous urogram in supine (left panel) and upright position (right panel) For details see text.

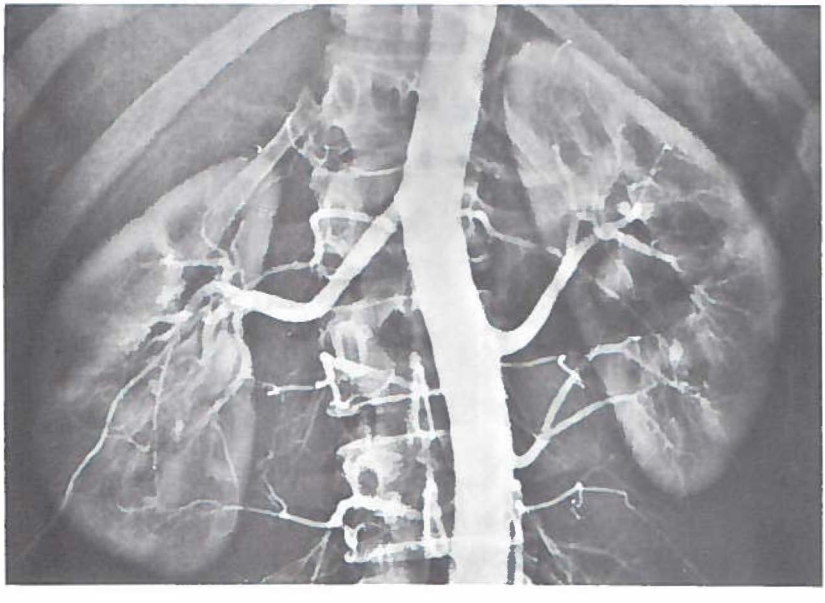

Figure 26: Supine renal angiography. For details see text.

The merits and demerits of the other radionuclide tracer techniques will be discussed in chapter 6. This chapter will be confined to the first two methods, serial IVU and radionuclide renography.

5.2 Serial IVU

The use of serial IVU for the detection of a renal artery stenosis is based on the difference in function between a stenosed and a non-stenosed kidney. Unequal kidney sizes may reflect a renal artery stenosis because kidneys shrink when their arterial pressure and flow are reduced[6]. Furthermore a delayed visualization of contrast material in the stenotic kidney and a prolonged disappearance of the material thereafter can be seen, due to nephron hypoperfusion[6]. Although serial IVU has proven its value with respect to the diagnosis of renovascular hypertension, extensive studies have also revealed certain limitations. Apart from the drawback that differences in blood flow or filtration pressure are not determined quantitatively, a substantial number of false negative results has been reported, ranging from 13 to 47 per cent[7-10]. Besides, Bookstein et al. found a false positive IVU in 10 per cent of the subjects with essential hypertension[9]. It is still unclear whether these false results are due to the limited sensitivity of the method or that they do reflect the actual *absence* of a flow difference between the kidneys[11]. Therefore the use of a serial IVU in 'nephroptotic hypertension' will be mainly limited to those cases where the mobile kidney causes a severe orthostatic reduction in renal blood flow and fall in filtration pressure, whereas the contralateral kidney is less or not affected by the posture change. The usefulness of serial IVU in the latter category of patients is illustrated with the following case history:

> A 24-year old female visited the out-patient clinic with complaints of chronic headaches. She had been taking oral contraceptives for a few years. On physical examination an elevated blood pressure (165/100 mmHg) was found. Serial IVU revealed no signs of renal artery stenosis, nor did renography. An upright X-ray film showed nephroptosis (10 cm) and nephrotorsion on the right side, whereas the left kidney dropped only 4 cm in upright position (figure 25). Renal angiography was performed and no renal artery stenosis was found (figure 26). The patient refused renal angiography in upright position.

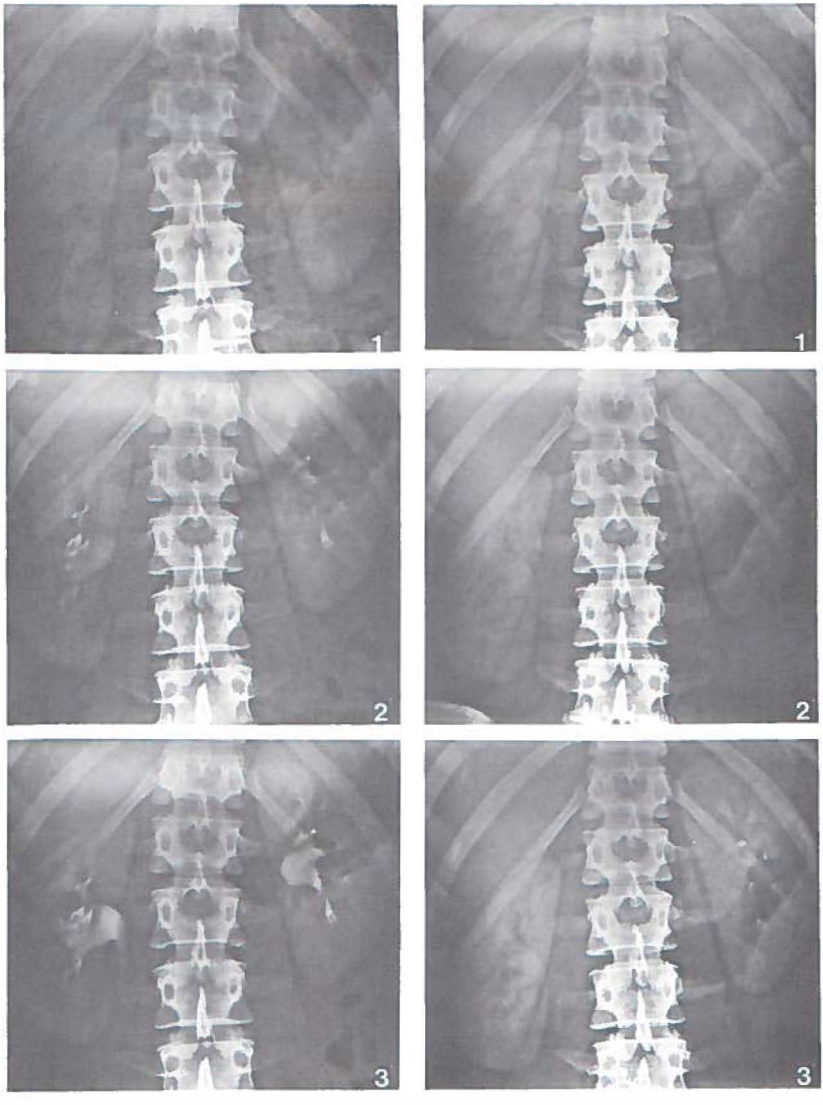

Figure 27: Rapid sequence IVU after three hours in supine position (left panel) and after three hours in upright position (right panel). The X-ray films were taken at 1, 2 and 3 minutes after injection of the contrast medium. For details see text.

Because of the high mobility of the right kidney and its short and 'unfolded' renal artery in supine position, an orthostatic narrowing of the renal artery was suspected (see chapter 4). Peripheral PRA was indeed high in upright position (6.9 nmol AI/1/h), although the value was also elevated in supine position (4.7 nmol AI/1/h).
Rapid sequence IVU in *upright* position was not possible at the time of this study. Therefore serial IVU was performed in supine position after the patient had been so for three hours, and a second supine serial IVU after the patient had walked around for three hours. Figure 27 shows the results of both serial IVU studies. No discrepancy in nephrography or contrast excretion between the left and right kidney was observed after the supine period (left panel). After three hours in upright position however, the right kidney showed a delayed nephrography and excretion compared to the left side (right panel).

This observation suggests that serial IVU in supine *and* upright position can give additional information not only about the presence of nephroptosis but also about its possible haemodynamic implications on renal level.

5.3 **Radionuclide renography**

Renography is applied equally for the detection of a renal artery stenosis. It is based on a similar principle as serial IVU. Instead of contrast medium, a tracer dose of radioactive hippuran is used. The time-activity curve of the hippuran tracer recorded over the kidneys separately provides qualitative information on the uptake, secretion and excretion of the tracer. Differences in the initial phase of the hippuran uptake curve can be interpreted as the effect of a renal artery stenosis[12]. Maxwell et al. however, stated that renography would be even more unspecific than serial IVU, since they observed false positive results with the former more frequently [12 13]. They found that renography could compete with IVU only if the stenosis had reduced the artery diameter to 50 per cent or less. Despite this, renography has been used in a number of studies on nephroptotic kidneys[14-20]. In all these studies patients are presented with extremely mobile kidneys. The blood flow of these ptotic kidneys indeed was found decreased in upright position according to the initial phase of the renogram. This is also illustrated with the observation described below.

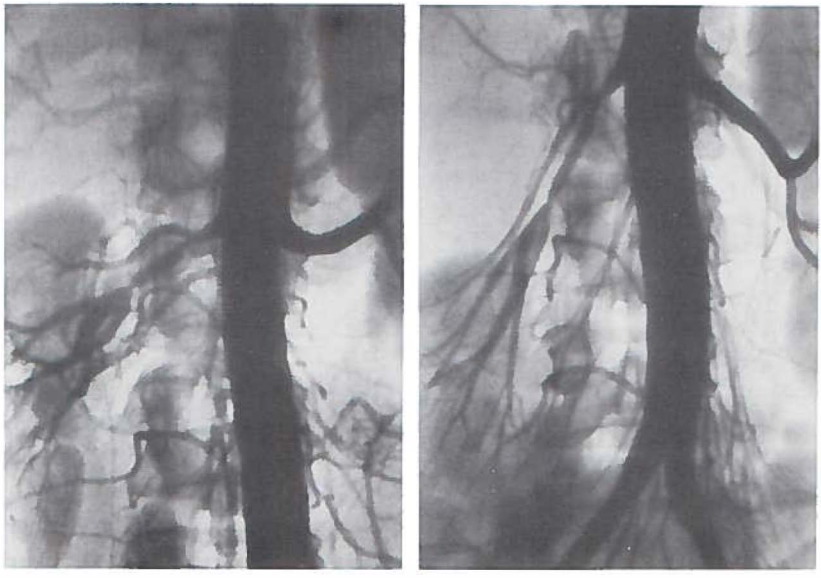

Figure 28: Renal angiography in supine (left panel) and upright position (right panel). The right renal artery shows stenoses at two locations, and in upright position a narrowing of the extrarenal and intrarenal arteries can be seen on the right side. For details see text.

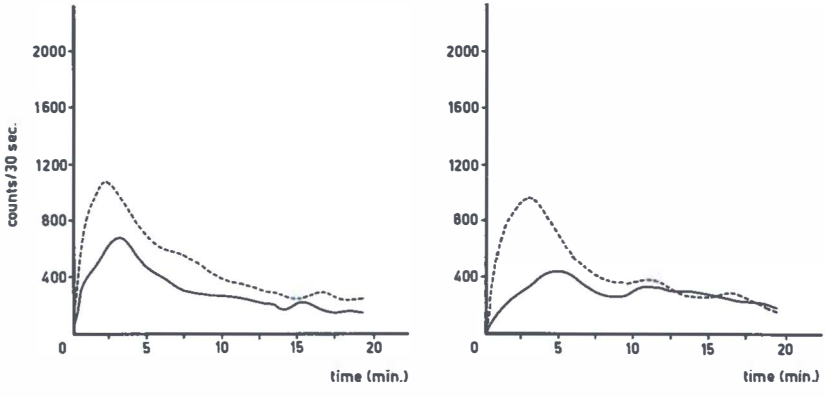

Figure 29: Renograms from a patient with a stenosis of the right renal artery and a nephroptotic right kidney. The left panel shows the renogram in supine position, and the right panel that in upright position. Solid lines represent the time-activity curves of the right kidney, dotted lines that of the left one.

In a 35-year old female with renovascular hypertension (210/125 mmHg), serial IVU had shown no difference between right and left kidney with regard to nephrography and contrast excretion. The right kidney measured 12 cm and moved downwards 10 cm in upright position, whereas the left kidney (13.5 cm) dropped only 4.5 cm. Renal angiography in supine and upright position revealed the presence of a renal artery stenosis (FMD) on the right side and an additional 20 per cent reduction of the mean diameter in upright position (figure 28). The ERPF was reduced to 70 per cent in upright position compared to supine. Consequently the peripheral PRA rose from 2.8 in supine position to 14.5 nmol AI/1/h in upright position. The renal artery stenosis appeared to be 'non-functional' in supine position, because no significant difference was found between the renin secretion of the stenotic and the non-stenotic kidney (PRA in right renal vein, left renal vein and artery: 3.9, 3.2 and 2.7 nmol AI/1/h, respectively). Renography was performed in supine position after the patient had been so for 3 hours. The same day, after an ambulatory period of 3 hours, renography was repeated in upright position.

The results of both studies are shown in figure 29. The left panel shows the time-activity curves recorded in supine position. The right kidney (solid line) appeared to have a slightly delayed uptake and secretion compared to the left kidney, which is suggestive for a renal artery stenosis. In upright position the additional artery narrowing might have caused the further impairment of the blood flow on the right side concluded from the further delay in uptake and secretion of the hippuran tracer (right panel). The curve of the left kidney in upright position is virtually identical to that in supine position.

One may conclude that the reduction of the ERPF observed in upright position had been caused mainly by a reduction of blood flow in the right kidney.

In conclusion, both serial IVU and renography appear to provide a way of recording orthostatic blood flow changes in a nephroptotic kidney. However, whether these methods will prove to be useful in nephroptotic patients with a less pronounced orthostatic blood flow reduction and fall in filtration pressure, remains to be elucidated.

5.4 Renal artery stenosis and renal adaptation

Apart from renal vein renin measurements, the screening for a renovascular cause of hypertension is based on the assumption that a stenosis would cause a lasting decrease in renal blood flow at the stenosed side in comparison with the contralateral kidney. Animal experiments however, have shown that the renal blood flow-reducing effect of an artery stenosis is only discernable if the artery diameter was reduced to below 40 per cent of the original diameter[21 22]. A lesser diameter reduction had no effect on the nephrographic or excretory phase of the stenosed kidney in comparison with the non-stenosed kidney[21 23]. These findings suggest that the serial IVU only detects renovascular hypertension due to a marked stenosis with haemodynamic consequences for the ipsilateral kidney. Apparently the post-stenotic kidney is able to maintain its filtration pressure after a mild to moderate constriction of its artery. This may be caused by the release of renin which results in a rise of the pre-stenotic blood pressure through a systemic vasoconstriction mediated by angiotensin II[24-26]. Moreover, the ischaemia itself and the intrarenal vasopressive activity of angiotensin II trigger the release of vasodilator substances within the kidney[27-32].

In order to improve the detection threshold of simple screening methods for renovascular hypertension, it might therefore be useful to deprive the post-stenotic kidney of its adaptive mechanisms. This can be achieved by e.g. the inhibition of the prostaglandin synthesis because prostaglandins are known to be vasodilating substances on renal level, counteracting the renin-angiotensin system[32]. To verify the usefulness of this suggestion, renographic studies were performed in volunteers as control subjects and in patients with a renal artery stenosis, all before and after administration of a prostaglandin synthesis inhibitor (indomethacin[33]).

> Renography was performed in three healthy normotensive male volunteers and three female hypertensive patients with an angiography-proven stenosis of the right renal artery. The following protocol was used: the subjects walked around and were adequately hydrated two hours prior to the first renographic study. Renography was performed with the subjects in supine position and the gamma camera at their back. After intravenous injection of 2.7 MBq (74 μCi) ^{131}I-o-iodohippuran, scintigraphic data were accumulated by a computer linked to the gamma camera. The renal time-activity curves

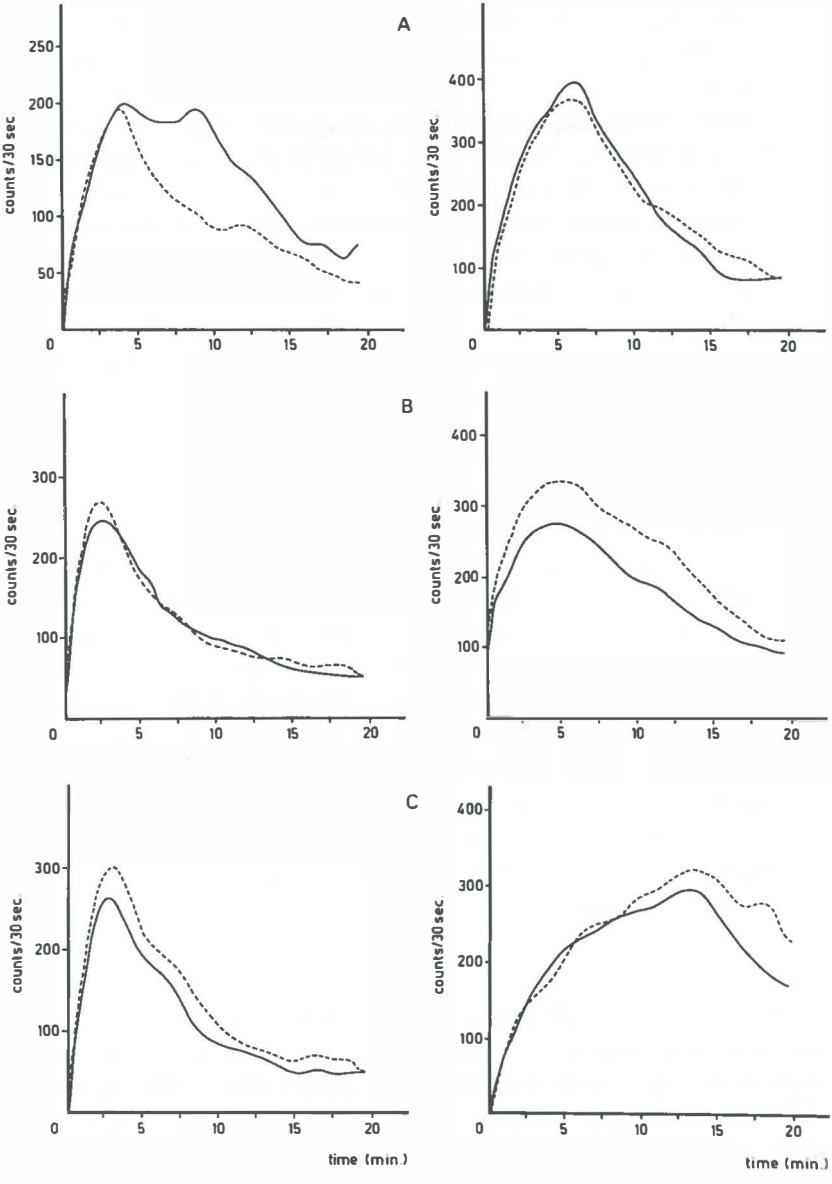

Figure 30: Renograms from three healthy volunteers (A, B, C). The curves on the left side represent the renograms of each subject before indomethacin, the right side after indomethacin administration. Solid lines represent the right kidney curves.

were computed after choosing 'regions-of-interest' over the kidneys and an appropriate background area. Indomethacin (50 mg) was administered orally, immediately after the first renogram. After another ambulatory period of two hours and adequate hydration, a blood sample was drawn for the determination of the indomethacin level in serum. This was followed by a second supine renogram.
The results of these renographic studies are shown in figures 30 and 31. The first renograms of the control subjects were all interpreted as 'normal' (figure 30, left panel). After 50 mg indomethacin however, both right and left kidney showed a delayed uptake and secretion of tracer (figure 30, right panel). In addition, the degree of this delay appeared to correlate with the measured indomethacin serum level. The latter was 0.6, 0.9 and 1.2 mg/l at the time of the second renograms which are displayed in the upper, middle and lower right part of figure 30, respectively.
A similar effect of indomethacin was observed in the renograms of the three patients with renovascular hypertension. The first renograms (figure 31, left panel) showed subtle signs of the stenosis of the right renal artery in all three patients (solid lines). The 'indomethacin renograms' however, showed the left-to-right difference more pronounced (figure 31, right panel). The curves of the post-stenotic kidneys (solid lines) showed a delayed uptake and secretion of tracer compared to the contralateral non-stenotic kidneys (dotted-lines). The degree of this left-to-right difference again appeared to correlate with the indomethacin serum levels (1.6, 1.7 and 2.5 mg/l during the studies, which are displayed in the upper, middle and lower right part of figure 31, respectively).

In conclusion, these preliminary results show that care should be exercised with the interpretation of renographic curves in general, since anti-inflammatory agents such as indomethacin, aspirin and phenylbutazone are used frequently and all markedly inhibit the prostaglandin synthesis. The benefit of this mechanism on the other hand may be to prevent false negative results in screening for renovascular hypertension. In addition a possibility might be present to gain more insight into the function of renal prostaglandins.

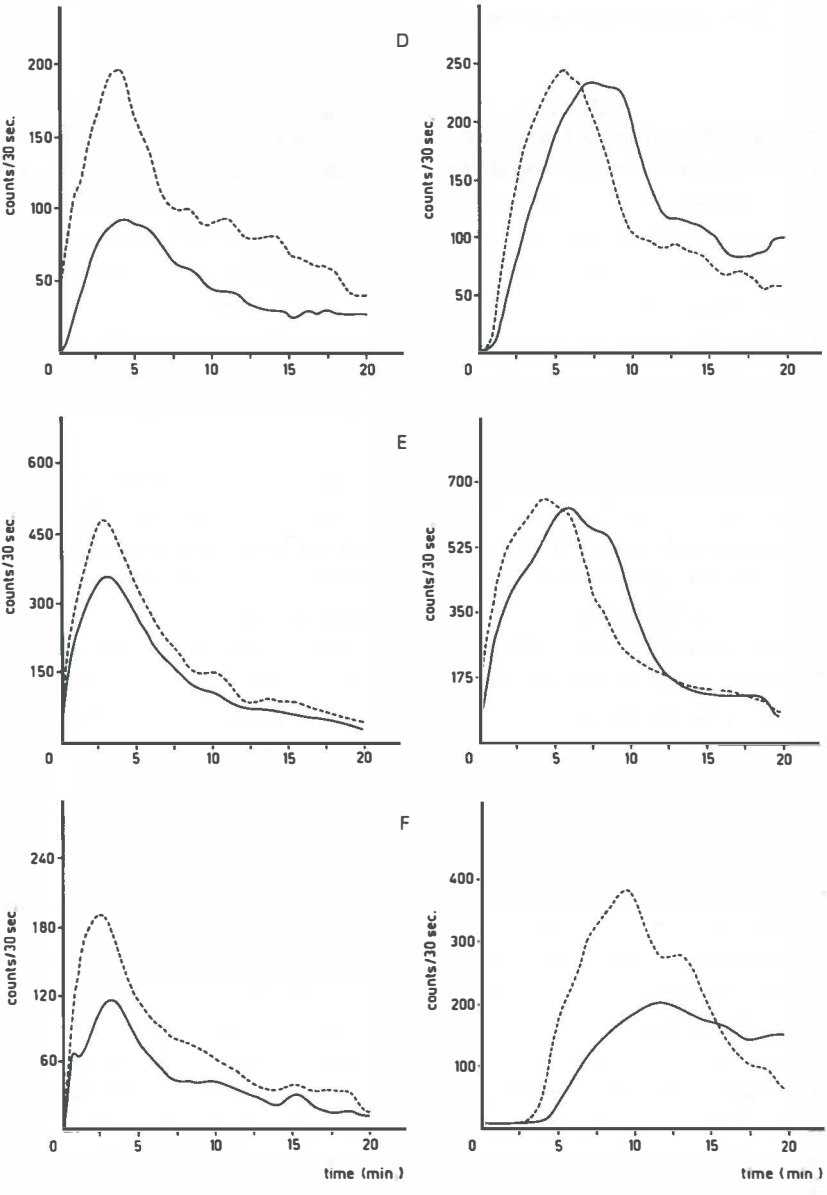

Figure 31: Renograms from three hypertensive patients (D, E, F) with a stenosis of the right renal artery. The left side shows the renograms of each patient before indomethacin, the right side after indomethacin administration. Solid lines represent the right kidney curves.

5.5 Discussion and conclusions

Nephroptotic hypertension seems to be based on a mechanism similar to that of renovascular hypertension. This is illustrated by the cases presented in this chapter in which upright serial IVU and renography showed left-to-right differences in comparison with supine studies. This similarity however, implies that a potential screening test for nephroptotic hypertension will meet similar problems as reported with renovascular hypertension. Serial IVU and renography in upright position might therefore be useful in hypertensive patients with an excessively mobile kidney, like they are useful in patients with a severe renal artery stenosis. However, in less severe cases these methods may fail to demonstrate the effect of nephroptosis on renal function.

There is however, an essential difference between a renal artery stenosis caused by a vascular disease and that caused by a mobile kidney. This very difference could make the screening test more useful in nephroptotic than in renovascular hypertension. The development of a renal artery stenosis caused by atherosclerosis or FMD is in general a gradual phenomenon, whereas nephroptosis causes a recurrent and sudden artery narrowing. Referring to the former situation the kidney has the opportunity to adapt gradually to the pressure fall, and maintain its blood flow and filtration pressure at a constant level by increasing the systemic blood pressure. Nephroptosis on the other hand has the effect of an acute renal artery stenosis every time the kidney drops.

In this context the animal experiments of Anderson et al. are interesting[26]. Although they studied the effects of an acute stenosis and repeated stenoses in a one-kidney model in the dog, the results give some information on the time it takes for a kidney to recover from an acute stenosis. In the case of a mild stenosis (post-stenotic pressure 60 mmHg) the renal blood flow recovered to 90 per cent of the initial value within 15 minutes while the mean arterial pressure rose only slightly. In the case of a reduction of the post-stenotic pressure to 20 mmHg, the renal blood flow and post-stenotic pressure recovered to 87 per cent within 30 minutes and the mean arterial pressure was 18 mmHg above the control value. When the stenosis was further narrowed every 15 minutes during one hour to a post-stenotic pressure of 20 mmHg, the systemic blood pressure rose with 40 mmHg. In this situation the renal blood flow only partly recovered between the repeated adjustments of the artery constriction.

The condition of nephroptosis could well be comparable to this experiment with acute stenoses. This would mean that in cases of mild orthostatic narrowing of the renal artery in upright position the effects on renal blood flow and filtration pressure could be demonstrated best within 15 minutes after active rising. Furthermore the effect of kidney movements during daily activities could resemble the repeated stenoses. This would result in a decrease of the renal blood flow and a fall in filtration pressure as the kidney would have no time to recover from the repeated 'attacks'. Besides, if indomethacin or other aspirin-like drugs could deprive the kidney of its adaptive mechanism as suggested by our study, the conventional methods for RVH-screening might appear to be more useful as a screening method for nephroptotic hypertensive patients.

However, the supposed stenotic effects of nephroptosis and the subsequent adaptation of the affected kidney are yet to be demonstrated. For this purpose a renal blood flow measurement method would be required that would allow a monitoring of renal blood flow changes with a better time resolution. The following two chapters will deal with the development of such a method for clinical application.

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CHAPTER 6

Evaluation of renal blood flow measurement with the $^{81}Rb/^{81m}Kr$ ratio

6.1 Introduction

The conventional methods for renal blood flow determination have been summarized in chapter 5. Most of them have the drawback of being either invasive, nonspecific or inaccurate.

In nuclear medicine a number of different kidney tracers are applied. In general two distinct approaches may be recognized in renal tracer functions:

1. Initial uptake of tracer such as labelled macro-aggregates or microspheres[1] and potassium-analogue isotopes (e.g. rubidium[2,3]). Difficulties in absolute calibration of the uptake have limited a general application of these methods.
2. Washout of an inert gas tracer such as xenon and krypton isotopes[4-6]. A serious drawback of this method is the invasive arterial injection required.

Apart from the difficulties to quantify renal blood flow with these methods, the recording of *changes* in renal blood flow is even more difficult. This would require repeated injections of the tracer in the different flow situations, while rather long time intervals are needed to avoid interference of the previous tracer dose.

Jones and Matthews proposed in 1971 the theory for a new method ($^{81}Rb/^{81m}Kr$ ratio) of blood flow measurement which would provide essential advantages over the conventional tracer methods[7]. The different aspects of the practical application of this $^{81}Rb/^{81m}Kr$ ratio method have been elaborated by Van Herk[8] and co-workers[9-11]. The aim of the study presented in this chapter was to develop the theoretical principle into an applicable clinical procedure.

Theory of the $^{81}Rb/^{81m}Kr$ method

The radioactive tracer rubidium-81 is at any time in 'radioactive equilibrium' with its decay product krypton-81m, because of the short half-life of ^{81m}Kr (13 seconds) compared to ^{81}Rb (4.6 hours). After intravenous injection rubidium-81, as any potassium analogue, is actively taken up by the cell, predominantly in highly-perfused organs such as the kidneys and the myocardium, within which it decays to ^{81m}Kr. After its formation this inert gas immediately diffuses over the tissue and is subsequently washed out by the blood. Thus the organ is offered a continuous 'infusion' of the inert gas by the ^{81}Rb which is present in situ. With no blood flow through the organ the radioactive equilibrium of ^{81}Rb and ^{81m}Kr will be unaffected, i.e. their activities are equal. However, with increasing blood flow ^{81m}Kr is washed out proportionally before its decay. Only a blood flow-dependent *fraction* of the ^{81m}Kr emits its radiation within the organ, whereas the remainder decays in the lungs or after exhalation. This leads to a linear relationship between the $^{81}Rb/^{81m}Kr$ ratio of activities measured over the organ and the specific blood flow (expressed in ml/min/g tissue)[8]. The activity of the two nuclides can be detected selectively outside the body by virtue of their different gamma radiation[8].

In summary, it seems possible to monitor changes of renal blood flow after an intravenous injection of ^{81}Rb by external measurement of the activity ratio of ^{81}Rb and ^{81m}Kr. However, a few practical problems had to be solved to achieve a successful clinical application. These are discussed in the next paragraphs.

6.2 Measurement and calculation of the ratio

The $^{81}Rb/^{81m}Kr$ ratio (Rb/Kr ratio) measured over the kidney outside the body should represent the actual ratio of activities *within* the organ. The accuracy of this measurement however, is hampered by three obstacles:

a. the gamma radiation of both nuclides is scattered by surrounding tissue before it reaches the detector outside the body. As a result only a part of the emitted gamma radiation has the original energy of ^{81}Rb (446 and 511 keV) and ^{81m}Kr (190 keV), the remainder has a lower energy or is absorbed. The actual krypton photopeak is thus 'contaminated' with so-called Compton-scattered rubidium gamma

rays. Van Herk has extensively studied this problem and came to the conclusion that the use of 'pure' ^{81}Rb, uncontaminated by the usual impurities as ^{82m}Rb, and a sophisticated spectrum analysis are mandatory[8], if one utilizes NaI (Tl) scintillation detectors. Thus the ^{81}Rb activity is assessed in a straightforward way and the ^{81m}Kr activity is derived after a non-linear correction for the Compton background.

b. The different absorption of the gamma radiation emitted by both nuclides presents a second problem. The lower gamma energy of ^{81m}Kr causes that a smaller fraction of its radiation reaches the detector compared to ^{81}Rb. Thus the ratio of the count rates measured is higher with increasing tissue thickness between detector and organ. This problem can be solved if one combines the response of two opposite detectors[8].

c. Tissue background: this problem will be discussed in paragraph 6.3.

Instrumentation

For the monitoring of changes in renal blood flow, we found a two-probe system most adequate. Two 5 × 5 cm NaI (Tl) scintillation detectors are mounted on a detector stand at 30 cm distance facing each other. The signals from both detectors are fed (via a mixer-router) into a multi-channel

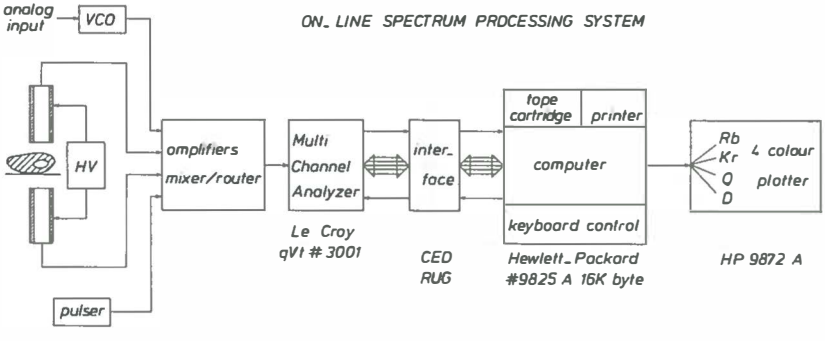

Figure 32: Block-diagram of instrumentation for measurement of the Rb/Kr ratio in the kidney. Analog signals (such as Doppler and EM), detector signals and a pulser signal (for dead-time correction) are input to the processing system, the former via a voltage-controlled oscillator (VCO). The Multi-Channel Analyzer is linked to the computer via an interface developed by the University Electronics Department (CED RUG).

analyzer which is interfaced with an on-line spectrum processing system as illustrated in figure 32. This set up allows the dynamic selection of different windows, a sequence of analytical operations and corrections, and a plotting of the final results momentarily. The gamma spectrum is processed simultaneously with and independent of the acquisition of new data. No 'dead time' results from the processing.

Calculation of the ratio

The ^{81}Rb to ^{81m}Kr ratio is calculated as follows: the gamma spectra detected by both NaI (Tl) detectors are analyzed separately. The ^{81}Rb activity is represented by the total counts in the photopeaks between 430-540 keV. The ^{81m}Kr activity is represented by the Compton-corrected total counts in the photopeak between 170 and 210 keV. Compton correction is performed by subtraction of the counts below the line that is extrapolated as a logarithmic function from the Compton continuum between the two photopeaks. The geometrical mean of the count rates from the two detectors is calculated and represents the total, position-independent ^{81}Rb and ^{81m}Kr count rates of the source. In situations of zero flow the ratio of these two activities has to be equal one. However, the actual results of the measurement depend on geometrical and other factors. Therefore it is necessary to normalize the ratio to a zero-flow ratio in each different geometrical situation.

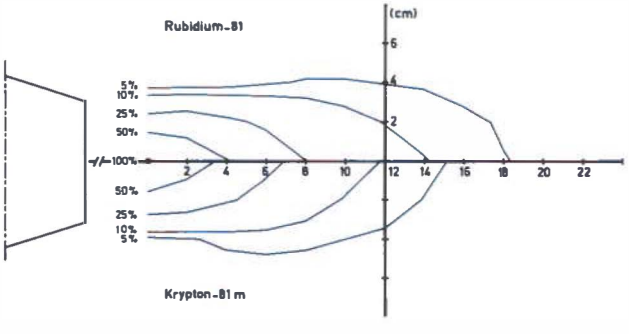

Figure 33: Iso-response curves of one NaI (Tl) detector to a ^{81}Rb point source in water. The upper part shows the ^{81}Rb response, the lower part that of ^{81m}Kr.

System properties

The response of the two-detector system had been tested by phantom studies. The disadvantage of using one probe is illustrated in figure 33. This figure shows the iso-count curves of a ^{81}Rb point source in water, a tissue-equivalent medium. Rubidium-81 counts were reduced to 50 per cent by each increase of 4 cm 'tissue' and the ^{81m}Kr counts to 50 per cent by each 3.5 cm

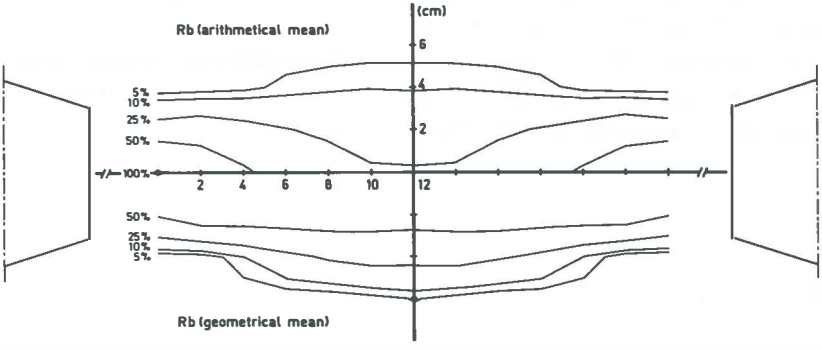

Figure 34: Iso-response curves of two opposite (30 cm distance) NaI (Tl) detectors to a ^{81}Rb point source in water. The arithmetical mean of the ^{81}Rb response of both detectors is drawn in the upper part, the geometrical mean ($\sqrt{\text{Rb det 1} \times \text{Rb det 2}}$) in the lower part.

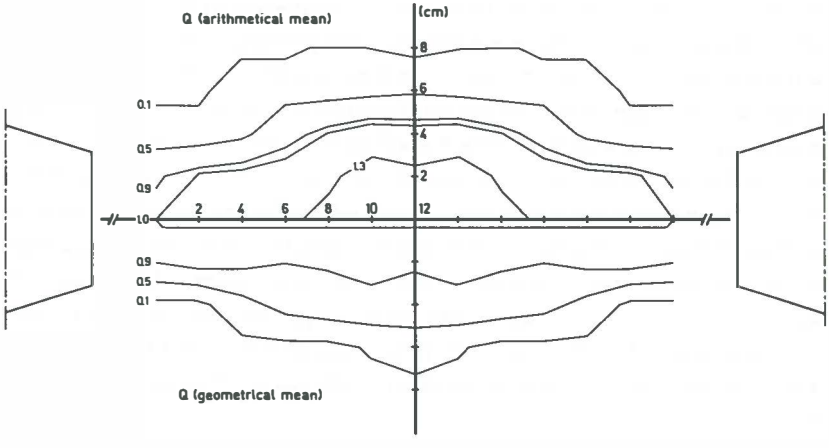

Figure 35: 'Iso-ratio' contours of a ^{81}Rb point source. The Rb/Kr ratio (Q) curves calculated with the arithmical mean of both detector responses are drawn in the upper part, geometrical-mean-calculated ratio curves in the lower part.

increase. As a consequence the Rb/Kr ratio is higher with increasing source-detector distance. The summed response of two opposite detectors was significantly less sensitive to variations in tissue thickness (upper part of figure 34). When using the geometrical mean of the response of both detectors[8], the position of the source in the center line had virtually no effect on the total ^{81}Rb counts (figure 34, lower part). The same was true for the geometrical mean of the ^{81m}Kr counts since the ratio (Q) of the geometrical means of ^{81}Rb to ^{81m}Kr was constant and virtually independent of the source position (figure 35, lower part).

In summary, the use of opposite detectors and their geometrically summed response yields a Rb/Kr ratio that is virtually insensitive to the position of the source between the detectors.

6.3 **Experiments**

Ex-vivo studies

A series of five experiments has been performed on mongrel dogs. The aim was to continuously measure the ^{81}Rb and ^{81m}Kr activity over the kidney at different perfusion rates and to compare it with a Doppler flow recording as independent reference. For this purpose a so-called 'ex-vivo' animal model was used to avoid problems with tissue background. A schematic example of the ex-vivo model is given in figure 36. After the dog was anaesthesized with Fluothane® and heparinized, bilateral nephrectomy was performed. After perfusion with Collins' solution®, one of the kidneys was transplanted to the groin and anastomosed with the femoral vessels via silicone tubing. A Doppler flow probe was placed around the arterial tube together with a clamp, which allowed variable constrictions. The response of the Doppler unit and that of the two detectors placed over the kidney, were on-line processed by the spectrum-processing system. The Doppler probe was calibrated prior to the experiment with similar tubing using whole blood.

Since pure ^{81}Rb, i.e. containing less than 10 per cent contamination with other rubidium isotopes, was not commercially available, we prepared the tracer at the cyclotron of the University of Groningen (KVI) in cooperation

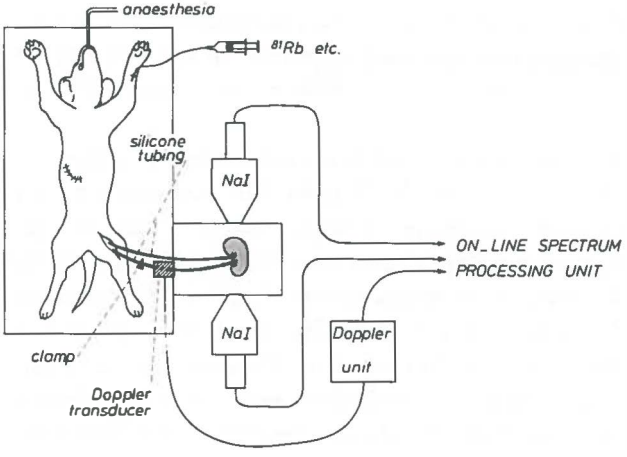

Figure 36: Schematic drawing of a model for the ex-vivo renal blood flow measurement with the Rb/Kr ratio and a Doppler flow probe.

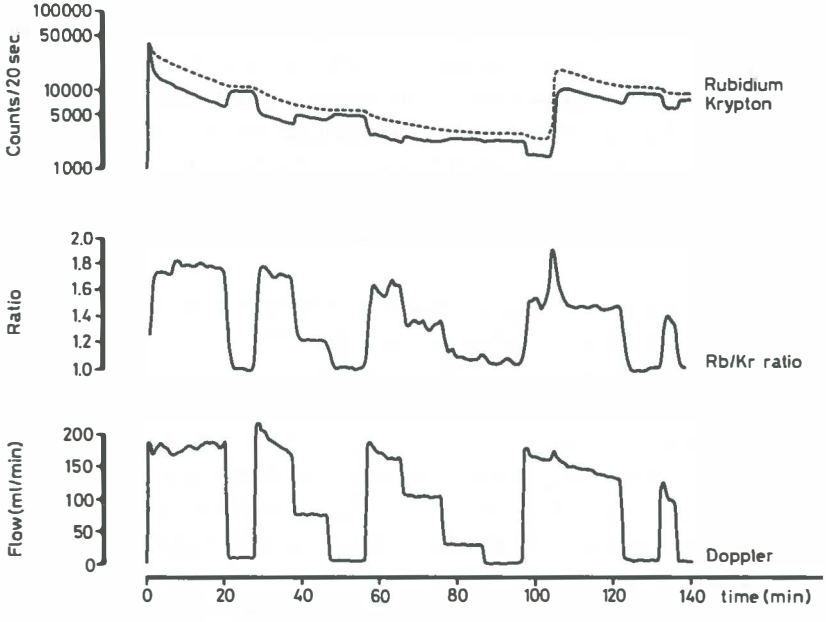

Figure 37: Time activity curve of dead time-corrected ^{81}Rb and ^{81m}Kr counts on logarithmic scale, of the normalized Rb/Kr ratio and of the renal artery flow measured with a Doppler flow probe. Arterial injection at time 0 and peripheral intravenous injection of ^{81}Rb at time 105 min.

with the Department of Nuclear Medicine. The production method and the chemical preparations have been described elsewhere[8]. With this set-up we were able to produce a maximum of 37 MBq (1 mCi) pure ^{81}Rb per production 'run'.

The results of one of the animal experiments are presented in figure 37. Both the ratio of ^{81}Rb to ^{81m}Kr, and the Doppler flow measurement were recorded during two hours, as changes of renal blood flow were brought about by varied constrictions of the arterial tube. The upper curve (dotted line) shows the count rate of ^{81}Rb measured over the kidney after an intra-arterial injection of 5 MBq (140 μCi) ^{81}Rb. The count rate is plotted on logarithmic scale versus the time after injection. The time interval of data sampling was 20 seconds. After the initial bolus peak, the ^{81}Rb activity is seen to decrease slowly with a half-time of approximately 15 min. This is due to a redistribution of rubidium from the renal tissue to the diffuse potassium pool throughout the body[8].

The second activity curve (solid line) is that of the Compton-corrected ^{81m}Kr count rate. Each time the blood flow was reduced by the clamp (compare lower Doppler curve) a clear build-up of ^{81m}Kr could be observed in the kidney. The ^{81m}Kr was apparently washed out to a lesser extent and a new equilibrium was reached. At each subsequent increase of the renal blood flow a larger fraction of the ^{81m}Kr was washed out and as a consequence its count rate was reduced. Indeed the Rb/Kr ratio (normalized to the zero-flow value of 1.0) appeared to follow accurately the changes in the renal blood flow recorded by the Doppler flow transducer (middle and lower curve, respectively).

From this example one may appreciate that, in spite of the disappearance of ^{81}Rb from the organ to approximately 5 per cent of the initial value, the ratio of the remaining ^{81}Rb to ^{81m}Kr activity was at any time proportional to the momentary value of the blood flow. The stability or precision of the ratio however, decreased with reduced counting statistics. Repeated injections however, are possible if needed and do not alter the relation between blood flow and Rb/Kr ratio[8]. This is illustrated by the second -intravenous- injection of 29 MBq (775 μCi) ^{81}Rb, which indeed improved counting statistics (figure 37). Apart from a transient peak value - which might reflect the cortical flow - the ratio did remain constant.

The mean values of the observed ratio at each different level of constant flow appeared to correlate well with the corresponding values of the Doppler measurements. A linear correlation was found with a correlation coefficient of 0.98 (n = 12).

In summary, injection of pure ^{81}Rb either in the renal artery or in a peripheral vein enables a monitoring of the blood flow in an ex-vivo kidney. The precision of the measurement of the Rb/Kr ratio over a certain period of time depends on the activity present and hence on the injected dose. On the other hand counting statistics and hence precision may be improved by measuring the radioactivity over a longer time interval.

Flow phantom studies

The accurate measurement of blood flow changes in the 'in-situ' kidney will obviously be affected by background activity in the surrounding tissue. After an intravenous injection the surrounding tissue will also take up ^{81}Rb tracer. As a result the Rb/Kr ratio measured over the kidney region will be a composite of the actual kidney ratio and the ratio of an unknown amount of overlying and underlying background tissue. To study this problem a flow phantom was constructed and studies were performed to assess the effects of background tissue on the accuracy of the measured kidney ratio.

The construction of this flow phantom is illustrated in figure 38. A small perspex cylinder (13 × 5 cm) represents the kidney. It was filled with water containing a small amount of pure ^{81}Rb. Air was dispersed through this solution, washing out the ^{81m}Kr gas which left the cylinder via an outlet. In

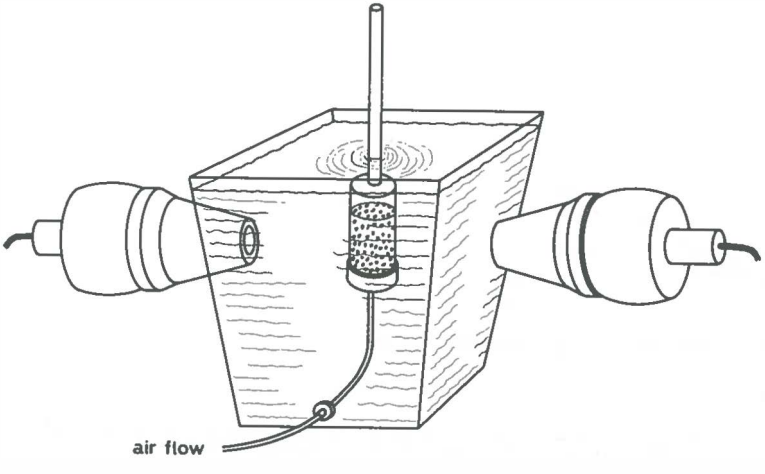

Figure 38: Kidney flow phantom. For details see text.

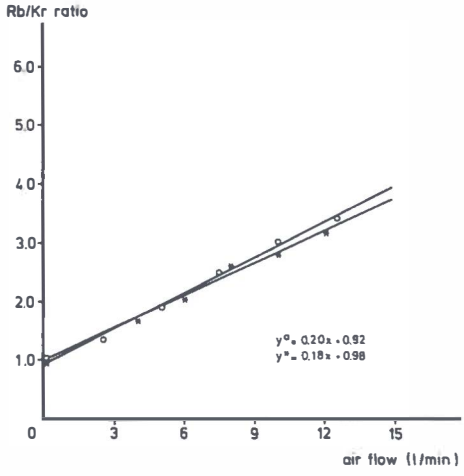

Figure 39: Relation between normalized Rb/Kr ratio and air flow through the kidney model suspended in air (open dots, r = 0.99) and suspended in water (asterisks, r = 0.99).

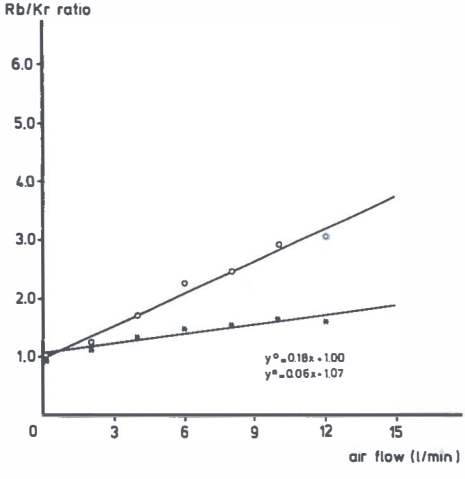

Figure 40: Relation between normalized Rb/Kr ratio and air flow through the kidney model suspended in ^{81}Rb-containing water. Asterisks represent the normalized Rb/Kr ratio at corresponding air flow levels (r = 0.96). Open dots the Rb/Kr ratio corrected for background activity (r = 0.99).

this way the blood flow through an organ was simulated[12]. The kidney was suspended in a perspex box (30 × 30 × 40 cm) and detectors were placed around this box. The Rb/Kr ratio was measured at different air flow values through the kidney which was first suspended in air. Subsequently the box was filled with water representing surrounding tissue and again the Rb/Kr ratio was measured at different air flow levels. The results are presented in figure 39. The normalized Rb/Kr ratio appeared to increase with increasing air flow both with and without the presence of water in the box. The normalized ratio appeared unaffected by the scattering medium.

When however, a small amount of ^{81}Rb was added to the water in the box around the kidney model (simulating tissue background) the Rb/Kr ratio measured outside the box was clearly affected. Although the correlation between the normalized ratio and air flow was still present, the regression coefficient of this relation was drastically lowered (figure 40). This in fact implied that the 'tissue background', having a zero-flow ratio, contributed to the Rb/Kr ratio of the kidney in proportion to its activity. When the kidney was removed from the box, the actual background activity could be measured. Subtraction of the background ^{81}Rb and ^{81m}Kr count rates (1/3 of the total activity) from the total count rates measured with the kidney still in place, caused the original relation to be restored (figure 40).

One may conclude from these measurements that the relationship between flow and the Rb/Kr ratio is linear even at 'high flow values'. Tissue background however, obscures the sensitivity of the ratio measurement. The actual effect of the tissue background depends on the proportion of the background activity in the total counts. Since it was possible in this experimental situation to remove the kidney from the background medium, the original kidney ratio could be easily recovered by correction for the background activity.

In-vivo studies

Four animal experiments have been performed with the kidneys left in situ. The aim was to monitor blood flow changes of a kidney surrounded by background tissue. For this purpose the right renal artery of an anaesthesized dog was made accessible and an electromagnetic (EM) flow transducer was placed around the vessel. Distal to the EM-probe a variable constrictor was placed. The two NaI-detectors were placed over the right

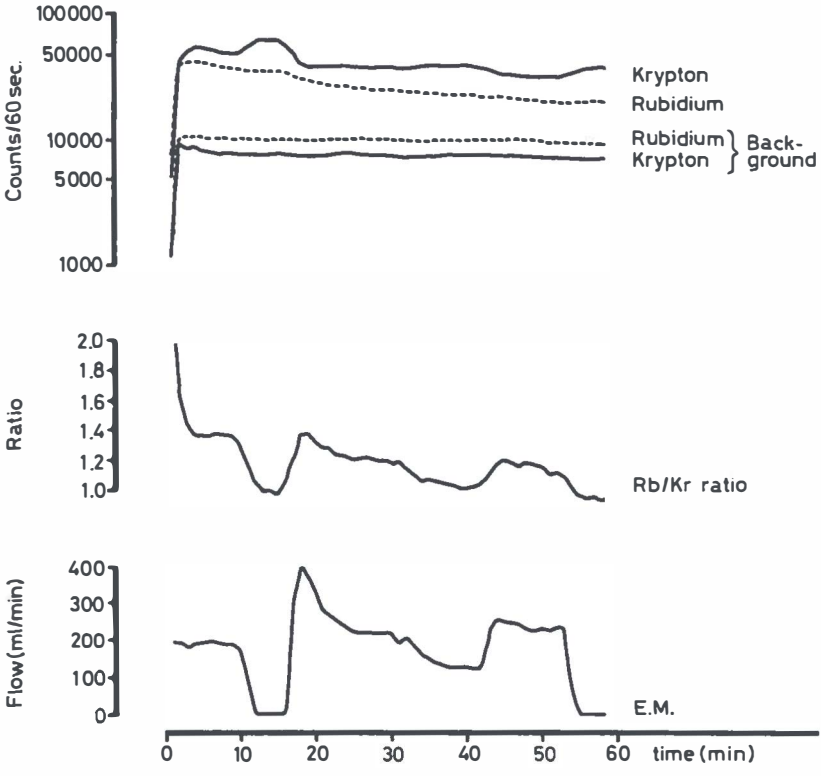

Figure 41: Time activity curve of ^{81}Rb and ^{81m}Kr counts on logarithmic scale, measured over the kidney and over a background region. The normalized Rb/Kr ratio has not been corrected for background activity. Lower part shows the corresponding renal blood flow values measured with an electromagnetic flow transducer.

kidney and a third detector over a background area caudal to this kidney. Although the third detector would not record the true activity of the right kidney background, it would give a general impression of the time-activity curve of the abdominal background.

After intravenous injection of 37 MBq (1 mCi) ^{81}Rb both the Rb/Kr ratio and EM flow value were recorded every 60 seconds during one hour. During this monitoring the renal blood flow was manipulated by varied constrictions. The plot of one of the experiments is drawn in figure 41. The upper curves in the figure show the ^{81}Rb and ^{81m}Kr activities measured over the kidney region and over the background area. The rubidium activity of the background area reached a plateau shortly after the injection, and remained

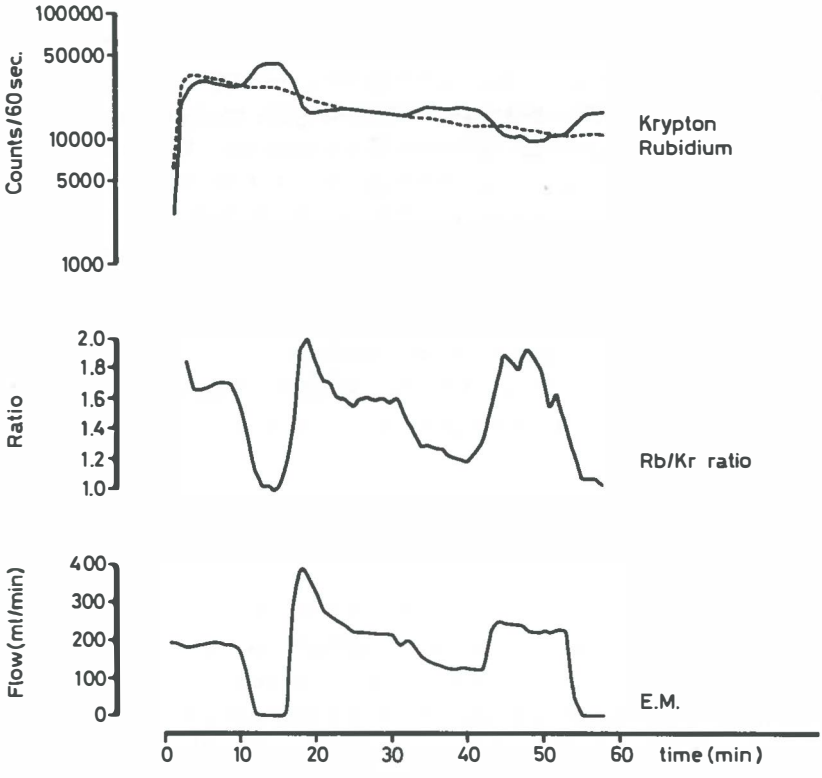

Figure 42: Plot of the experiment illustrated in figure 41 after subtraction of the ^{81}Rb and ^{81m}Kr background count rates in their zero-flow proportion.

constant during the experiment. In contrast, the total Rb-activity measured over the kidney *including* background decreased with time, certainly due to redistribution similar to in the ex-vivo studies. This implied that the relative contribution of the background ratio, i.e. zero-flow ratio, to the total ratio increased with time. Accordingly, the normalized Rb/Kr ratio measured over the right kidney area decreased in time, where the renal blood flow (EM measurement) was virtually equal at the beginning (0-10 min) and near the end of the experiment (45 - 55 min). Despite this gradually diminishing sensitivity in time, the ratio followed the trends in the renal blood flow changes, which were recorded with the EM transducer (middle and lower panel of figure 41).

Similar to with the flow-phantom study, a background subtraction was performed. The background ^{81}Rb and ^{81m}Kr count rates were subtracted from the total ^{81}Rb and ^{81m}Kr counts in their zero-flow proportion. The background counts measured with the third detector were used, normalized to the efficiency of the kidney detectors. The sensitivity of the ratio appeared indeed to increase (figure 42). Although it still followed the EM flow registration, the ratio at each flow level did not have a high correlation with the corresponding EM values. It was hard to distinguish whether this was due to incorrect background correction or to variations in the EM measurement.

In conclusion, the Rb/Kr ratio method enables a monitoring of changes in blood flow of the in-situ kidney. However, adequate background subtraction will be necessary if an accurate quantification is sought.

6.4 Discussion and conclusions

The method described in this chapter appears to provide a number of distinct advantages over conventional methods for the measurement of renal blood flow. It is non-invasive since administration of the tracer requires only an intravenous injection. The total body dose of ^{81}Rb with 10 per cent ^{82m}Rb contamination, is calculated to be 70 mSv/GBq (250 mrem/mCi) which is comparable with one plain X-ray film of the abdomen with optimal radiation protection[8 13 14]. The possibility of a continuous, separate renal blood flow monitoring during one hour after ^{81}Rb-administration is the most attractive property of the Rb/Kr ratio method. The precision of a measurement at constant blood flow and the sensitivity to blood flow changes depend on the amount of ^{81}Rb present in the kidney and on the required time resolution. A longer counting time improves the precision of the measurement, provided the actual blood flow does not change during that time. At least two drawbacks exist which should be mentioned. The production of pure ^{81}Rb is a cumbersome procedure. Secondly, the relatively increasing tissue background interferes with an accurate measurement and is still to be dealt with adequately. With the present radiochemical properties of the tracer, the Rb/Kr ratio method will be limited to monitoring blood flow changes in highly perfused organs such as the kidney.

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CHAPTER 7

Human studies with the $^{81}Rb/^{81m}Kr$ ratio method

7.1 Introduction

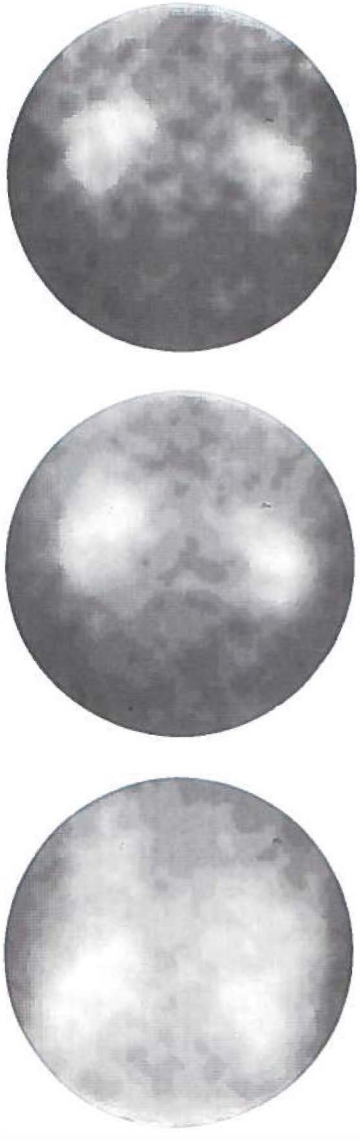
The $^{81}Rb/^{81m}Kr$ ratio (Rb/Kr ratio) had proved a reliable index of renal blood flow changes in the animal studies (see chapter 6). The applicability of the method in man however, had yet to be demonstrated. Inhomogeneous background activity such as in the liver, might interfere with the external measurement over the kidneys (see paragraph 6.3). Therefore the distribution of intravenously administered ^{81}Rb in the abdominal organs and tissues had to be assessed first. Secondly, proof was required that the Rb/Kr ratio would reflect changes in renal blood flow also in man.

Consequently two experiments were set up: first a gamma camera study in order to determine the ^{81}Rb distribution in the abdomen as a function of time and secondly, a measurement of the Rb/Kr ratio over the kidney with the two-probe system (see paragraph 6.2) during a drug-induced change in renal blood flow. These two studies were performed prior to the final object of our research on the Rb/Kr ratio method, viz. to demonstrate its use in screening for nephroptosis-induced blood flow changes. For this purpose a third study was performed monitoring the blood flow in a ptotic kidney during changes in posture.

7.2 Human studies

^{81}Rb production and yield

The production of 'pure' ^{81}Rb for the human studies was carried out at the cyclotron in Louvain-la-Neuve, Belgium. With this cyclotron we were to



time interval (min)	Rubidium-81 (counts/min) kidney left	kidney right	background
0-2	1160	951	540
2-4	1220	1142	571
24-27	757	668	560

Figure 43: ^{81}Rb distribution in the abdomen (posterior view) at different times after injection (left part). The corresponding ^{81}Rb count rates at the right are calculated over a small square region in the left and right kidney and in the background between the kidneys. (The scintigram after 25 minutes was recorded at a higher position over the abdomen).

produce a higher yield of ^{81}Rb than with the Groningen cyclotron, since a higher external beam current (10 μA) of the 65 MeV proton beam was available. In spite of the long distance and time for transportation and consequent decay of ^{81}Rb to half the produced activity, the final yield was expected to be approximately 110 MBq (3 mCi) from a two hour run. Due to technical and as yet unsolved problems we were limited to a third of the desired activity. It implied that longer time intervals for the measurement of the Rb/Kr ratio were required to attain adequate counting statistics. Prior to the injection of ^{81}Rb, the solution was checked for pH, osmolality and for undesired contamination with other radio-isotopes.

According to the accepted procedure for short-lived radiopharmaceuticals[1], a sample of the solution was checked for the presence of bacteria, pyrogens or heavy metals after the study. The results of the tests met the requirements (pH 7.3, osmolality 250-300 mosm/kg H_2O, less than 10 per cent ^{82m}Rb contamination, no bacterial growth and no detectable pyrogens nor heavy metals).

Rubidium distribution in the abdomen

A gamma-camera study was performed to assess the ^{81}Rb distribution in the abdominal tissues. For this purpose we used a gamma camera with a high-energy collimator at the Department of Nuclear Medicine. The camera was linked to an image-processing computer system, with which scintigraphic data were acquired for later review and analysis. After injection of 37 MBq (1 mCi) ^{81}Rb data were recorded with the gamma camera placed at the back of one of us as a volunteer. Every thirty seconds the energy window was alternated between 170-210 and 420-540 keV in order to acquire data from ^{81m}Kr and ^{81}Rb, respectively.

The initial uptake of the tracer was observed predominantly in the kidneys. Within two minutes however, a homogeneous background activity was distinguishable around the kidneys (figure 43). While this background activity remained nearly constant during the experiment, the activity over the kidneys diminished gradually (figure 43) as the tracer redistributed over the total potassium pool in the body. Thus the activity ratio of kidney-to-background decreased with time as had been observed in the animal experiments. Whereas the distribution of ^{81}Rb over the background tissue appeared homogeneous from the back, the anterior view 15 minutes after

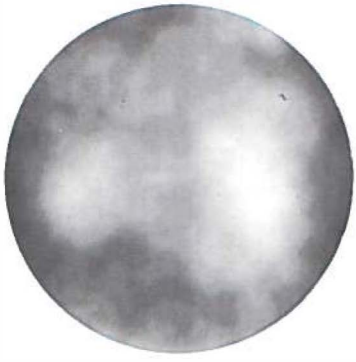


Figure 44: Anterior view of the ^{81}Rb distribution in abdominal tissues, 15 minutes after injection.

Figure 45: Functional image of the Rb/Kr ratio (posterior view), after appropriate smoothing of the image and masking of the background.

injection showed a different picture (figure 44). Although both kidneys are well distinguishable there seems to be more background activity above the left kidney. Presumably this represents uptake in the small intestine rather than in the spleen.

A so-called 'functional image' was created by arithmetical division of a ^{81}Rb image by a ^{81m}Kr image after appropriate image smoothing and masking of the background[2]. This provided a qualitative information on the distribution of the Rb/Kr ratio and thus of the blood flow in the kidneys and background tissue (figure 45). Indeed the highly-perfused kidneys appeared to have a higher ratio than the background tissue, although the data do not lend themselves to any reliable quantification.

In conclusion, the results of this gamma-camera study demonstrated that the Rb/Kr method could be used in humans. However, it might well be that due to background activity the Rb/Kr ratio measured over the left kidney area will not be as accurate as that over the right kidney.

Renal blood flow monitoring

The effect of renal blood flow changes on the measured Rb/Kr ratio was studied in the author as a volunteer. The on-line spectrum processing system and the NaI (Tl) detectors were applied as described in the previous chapter.

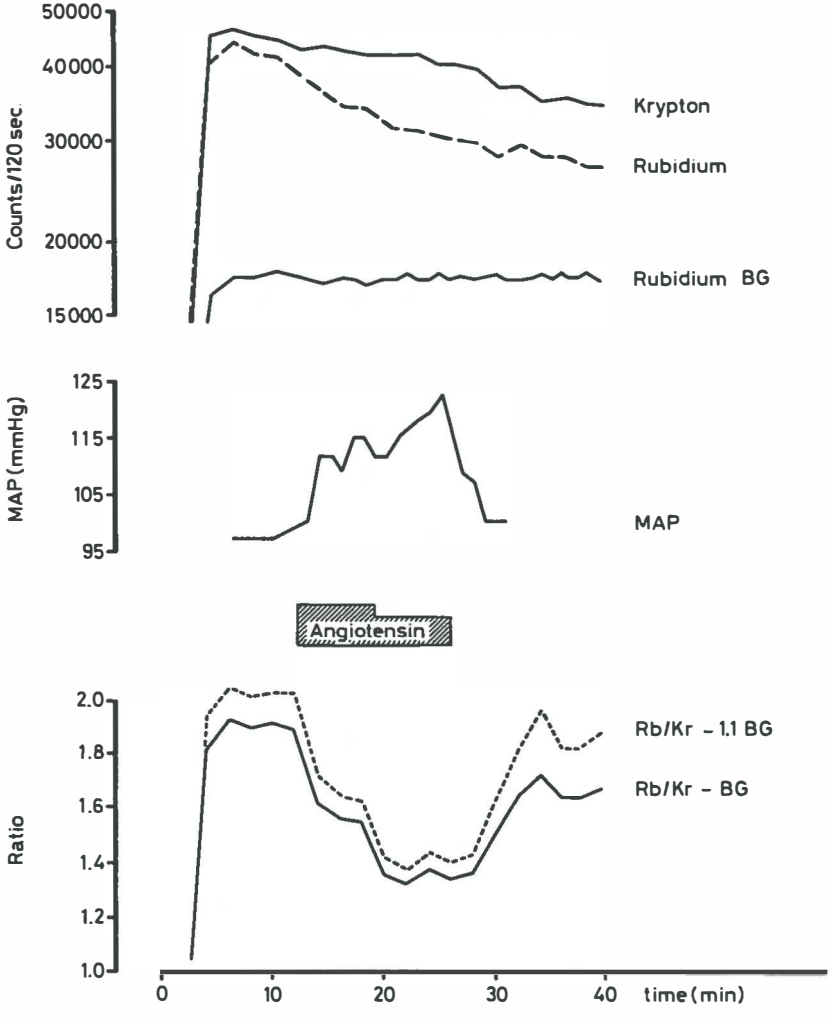


Figure 46: Time-activity curve of the ^{81}Rb and ^{81m}Kr count rates on logarithmic scale, and of the background(BG)-corrected Rb/Kr ratio, during infusion of angiotensin I. The dotted curve (lower panel) represents the Rb/Kr ratio after a higher background subtraction (1.1×). The course of the mean arterial pressure (MAP) is plotted in the middle part.

The detectors were placed over the right kidney which had been localized prior to the experiment with a kidney scintigram using 7.5 MBq (0.2 mCi) ^{99m}Tc-DMSA. After intravenous injection of 55 MBq (1.5 mCi) ^{81}Rb, the rubidium-81 and krypton-81m count rates were recorded simultaneously in two-minute time intervals. Infusion of a vasopressor (angiotensin I) was started after 10 minutes with a pressor-dose (8 ng/kg/min) and lasted 14 minutes. Angiotensin I is known to increase the blood pressure and to reduce the renal blood flow[3 4]. Blood pressure was measured every minute. Figure 46 shows the changes in blood pressure and Rb/Kr ratio during the vasopressor infusion. The solid curve (lower panel) is that of the background-corrected Rb/Kr ratio which was normalized to the background ratio. The background activity and no-flow ratio were measured over the lower right part of the abdomen with a third detector and were normalized for efficiency to the kidney detectors. Exogenous angiotensin I increased the mean arterial blood pressure (MAP) and consequently the Rb/Kr ratio curve did reflect the expected prompt decrease in renal blood flow. Shortly after the end of the infusion the Rb/Kr ratio rose again, while the blood pressure returned to pre-infusion values. In contrast to the animal experiments there was no reference method available to calibrate or only to verify these ratio changes. Therefore the weight of the background in the ratio over the right kidney area could only be estimated. The dotted ratio curve (figure 46) illustrates the effect of an arbitrarily-chosen higher background subtraction (1.1 × background count rates). Although the qualitative change in the ratio on angiotensin remained as clear as with the ratio corrected with the factor one, the accuracy seemed to be improved with the higher factor.

In conclusion, *monitoring* of changes in renal blood flow appears feasible in humans even if the exact contribution of background activity is unknown. *Quantification* of the changes in blood flow however, will be possible only if more accurate background information will be available.

The ^{81}Rb/^{81m}Kr ratio method in a nephroptotic patient

The accurate measurement of orthostatic changes in the blood flow of a ptotic kidney with the Rb/Kr ratio method is expected to be hampered by the difference in supine and upright geometry. With the change to upright position the ptotic kidney moves to a location with possibly less absorbing

tissue between the detectors. Therefore we redesigned the detectors such that an equal amount of absorbing medium would be present between the two NaI probes in both postures. This was achieved by placing water-inflatable cylinders in front of both detectors.

The change in position of the ptotic kidney on the other hand offered a unique possibility to assess the true kidney background activity. In *supine* posture it was possible to measure the background activity over the area where the kidney would be in upright position, and the other way round.

The monitoring of orthostatic changes in renal blood flow with the Rb/Kr ratio method was performed in a 40-year old hypertensive female patient with unilateral nephroptosis (renal mobility at the right side 11 cm and the left side 4 cm). Renal angiography and renal vein PRA measurement had demonstrated a functional stenosis of the right renal artery (ratio of the PRA right renal vein to left was 1.8). In upright position an additional 30 per cent diameter reduction of the right renal artery was found (figure 47). This additional orthostatic narrowing had a distinct effect on the haemodynamics of the kidney(s): the ERPF decreased with 40 per cent and the peripheral PRA increased six-fold. Supine and upright renography had demonstrated that these orthostatic changes could be attributed predominantly to the stenotic and ptotic right kidney (figure 48).

The Rb/Kr ratio was measured after intravenous injection of 22 MBq (0.6 mCi) ^{81}Rb. The kidneys had been localized in both positions with IVU which was verified by ultrasound prior to the experiment. Subsequently, the Rb/Kr ratio was measured in 4-minute time intervals over the right and left kidney in both supine and upright posture and finally once more over the right kidney in both postures. The results of these measurements are given in figure 49. The Rb/Kr ratio's drawn, have been normalized to the background 'zero-flow' value and corrected for the background activity. In supine position the Rb/Kr ratio of the right kidney appeared to be a little lower than that of the left kidney. After the change to the upright position a fall in the right kidney ratio value could be observed followed by a slight but significant increase within a period of approximately 10 minutes. This observation could be reproduced during a second sequence of posture changes. The orthostatic decrease of the Rb/Kr ratio of the left kidney appeared far less pronounced.

In conclusion, despite the relatively small amount of injected ^{81}Rb and hence poor counting statistics, the Rb/Kr ratio method did monitor changes in blood flow adequately. It appeared possible not only to demonstrate an

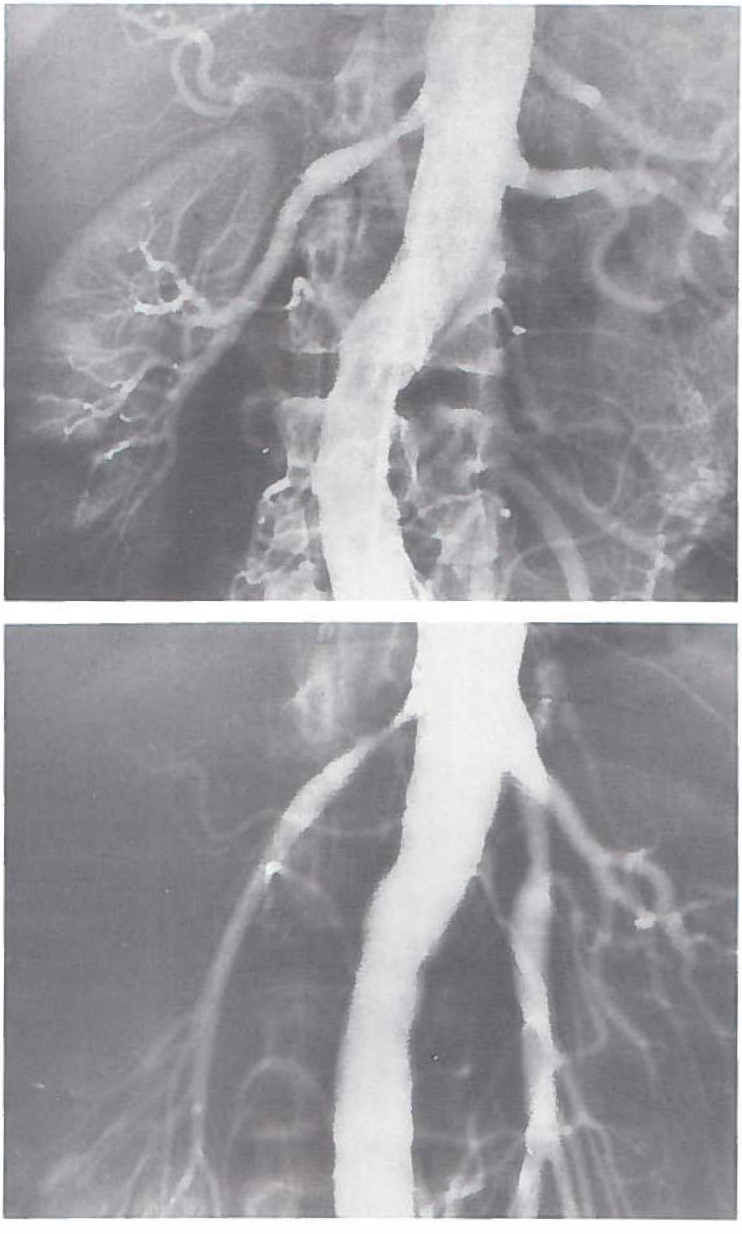


Figure 47: Supine (upper part) and upright (lower part) renal angiography. For details see text.

orthostatic blood flow decrease in the stenotic and ptotic kidney but also the presence of a functional renal artery stenosis on the right side. The subsequent increase of the Rb/Kr ratio in the right kidney on both occasions after the patient remained upright, is an interesting observation. This could well reflect the adaptation of the kidney to acute stenosis (see chapter 5, paragraphs 5.4 and 5.5).

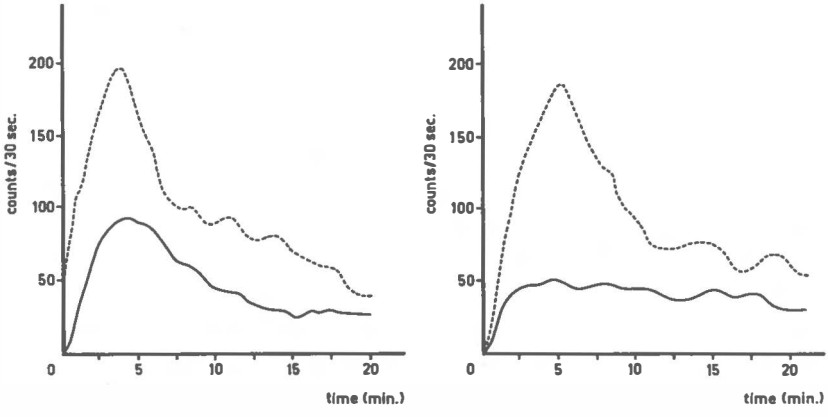


Figure 48: Supine (left panel) and upright (right panel) radionuclide renograms. The solid lines represent the time-activity curves of the right kidney, the dotted lines that of the left kidney. For details see text.

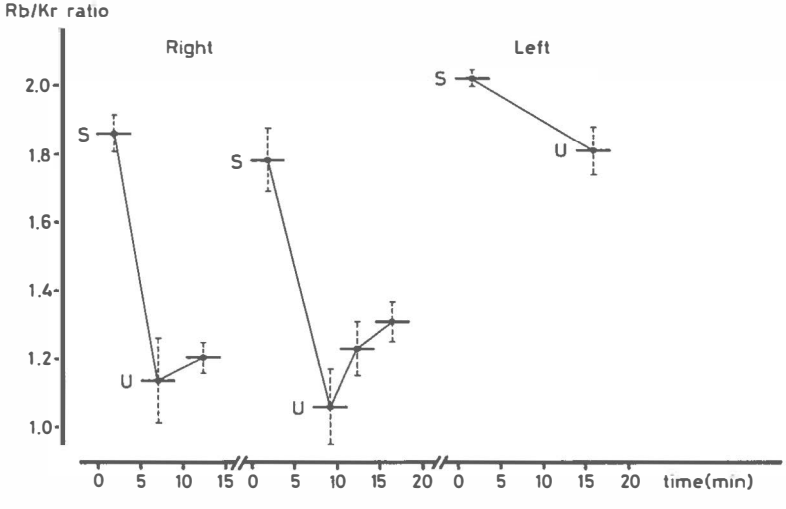


Figure 49: Rb/Kr ratio (normalized and background-corrected) of the stenotic and ptotic right kidney in supine (S) and upright (U) position (repeated studies) and of the left kidney in both postures. Mean and standard error of the Rb/Kr ratio's sampled in four one-minute time intervals, are drawn.

7.3 Discussion and conclusions

The Rb/Kr ratio method had been applied previously to determine the blood flow in the myocardium and spleen[5-8]. In these studies problems had been encountered caused either by the unavailability of pure ^{81}Rb, by inadequate spectrum analysis or by interference of tissue background. The kidney being the organ of interest in our studies offered a definite advantage, since it has a high specific blood flow compared to e.g. the myocardium (3.67 versus 0.83 ml/min/g[9]).

In spite of the relatively small amounts of ^{81}Rb that we had available for our case studies, the Rb/Kr ratio appeared to be a useful tool for the external monitoring of renal blood flow changes in man. The marked results of the measurement of orthostatic blood flow changes in a stenotic, ptotic kidney were promising. The Rb/Kr method appears to provide a way to record transient blood flow changes in the kidneys. Therefore the method could be useful in screening for nephroptotic hypertension. Possible ways to improve the accuracy of the Rb/Kr method will be discussed in the following chapter.

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CHAPTER 8

Summary, conclusions and a look toward the future

8.1 Summary

The subject of this thesis is the relation between hypertension and the excessively mobile kidney (nephroptosis). In the past a variety of complaints and symptoms, apart from hypertension, have been attributed to nephroptosis. However, the varying effect of numerous surgical fixations of the mobile kidney to relieve these conditions has led to some scepticism toward the pathogenetic role of nephroptosis. Apparently the degree of renal mobility is a poor indicator of the alleged effects of nephroptosis and therefore it was supposed to occur with or without symptoms or complaints.

As a result of this 'history of nephroptosis', described in chapter 1, further research on this phenomenon and its significance for the development of hypertension had become neglected. This is remarkable realizing that the condition is found rather frequently (20%) in the general female population. The high prevalence of both nephroptosis and 'essential' hypertension should be a compelling reason to investigate the causal relation between the two phenomena.

The results of our study on the frequency of nephroptosis in a normotensive and essential hypertensive population have indeed confirmed the existence of such a relation (chapter 2). Nephroptosis appeared to be present in 75 per cent of hypertensive females and in 20 per cent of a normotensive female control group.

Two possible mechanisms are thought to underlie the causal relation between nephroptosis and high blood pressure. The first is a *direct* relation, i.e. a narrowing of the artery of a mobile kidney through traction on its vascular pedicle in the upright position. This might cause a rise in blood pressure analogous to a 'Goldblatt hypertension'. The second mechanism may be an *indirect* relation, viz. nephroptosis causing a specific renal artery

stenosis (fibromuscular dysplasia) in the long run through an intermittent stretching of its artery. The high renal mobility observed in patients with FMD-affected kidneys supports the hypothesis of such an indirect relation (chapter 2).

Further investigations on a *direct* relation are described in chapters 3 and 4. The renal plasma flow (ERPF) in upright position appeared to be more reduced in nephroptotic patients than in subjects with a less mobile kidney. Moreover, a positive correlation was found between the degree of renal mobility and the degree of orthostatic ERPF-decrease. Computerized quantification of the artery diameter of kidneys with different degrees of renal mobility confirmed the earlier observation: the mobile kidney indeed caused an orthostatic diameter decrease of its artery. A positive correlation was found between the degree of artery narrowing and the degree of renal mobility. The 'length' of the renal artery however, had to be taken into account: a curved longer artery allows the kidney more movement without a reduction in the diameter than a shorter one. The effect of this artery narrowing was further confirmed by the observation that upright renin release (PRA) increased significantly more in nephroptotic patients.

The feasibility of relatively simple diagnostic tests to screen for 'nephroptotic hypertension' is discussed in chapter 5. Serial IVU and radionuclide renography, generally used for the detection of a renal artery stenosis, appeared to be adequate in patients having excessively mobile kidneys. The use of these methods however, is probably limited to cases with severe artery narrowing since the adaptive mechanisms of the kidney, maintaining a constant filtration pressure, seem to obscure the effects of a milder stenosis. Consequently, a study was performed to improve the benefits of these diagnostic procedures by interfering with the adaptive mechanisms of the post-stenotic kidney. Oral administration of a prostaglandin-synthesis inhibitor (indomethacin) prior to renography improved the detection sensitivity for a renal artery stenosis. However, a *continuous* monitoring of the blood flow in a ptotic kidney during posture changes would be preferable to the conventional methods. With such a method it would be also possible to monitor the adaptive mechanism of a kidney in response to a narrowing of its artery.

In theory, the $^{81}Rb/^{81m}Kr$ ratio method would meet these exacting demands. The development of this novel technique through animal experiments and the final evaluation in a number of human studies is described in chapters 6 and 7. The method answered the theoretical

expectations since the monitoring of renal blood flow changes appeared feasible during at least half an hour after an intravenous injection of the ^{81}Rb tracer. The results of the $^{81}Rb/^{81m}Kr$ ratio method in a patient with a unilateral renal artery stenosis and nephroptosis demonstrated the distinct advantages of this method over conventional methods of renal blood flow measurement. In addition, we could visualize the possible effects of a mobile kidney on its blood supply: the blood flow of the stenotic and ptotic kidney appeared drastically reduced in upright position, in contrast to the contralateral, non-ptotic kidney. Moreover, an adaptation of the involved kidney to the fall in filtration pressure could be observed in this unique experiment.

8.2 Conclusions

The results of the studies presented in this thesis have demonstrated the existence and elucidated the possible mechanisms of nephroptotic hypertension. Apparently the causal relation between nephroptosis and hypertension is not exclusively determined by the degree of renal mobility, but also by the artery 'length' of the mobile kidney. The latter can only be assessed with renal angiography, which should then be complemented with an upright angiogram in order to determine the orthostatic effect of the mobile kidney on its artery diameter. This procedure however, is invasive and hence some pre-screening examination will be mandatory. Serial IVU and radionuclide renography performed both in supine and upright position are the preferable methods, particularly after administration of a prostaglandin-synthesis inhibitor like indomethacin. The rather high prevalence of nephroptosis in female patients with essential hypertension may render such a screening worthwhile. On the other hand it might be preferable to use other techniques for this screening, since both mentioned methods already have shown to be of limited use for the detection of a renal artery *stenosis*. Probably the $^{81}Rb/^{81m}Kr$ ratio method with its continuous and non-invasive character, will be the method of choice to detect a nephroptotic hypertension in the future.

8.3 A look toward the future

The rehabilitation and recognition of nephroptosis as a concomitant cause of hypertension should stimulate a more profound research on the subject. A few suggestions have emerged from the results of our investigations.

Experimental studies on the relation between nephroptosis and fibromuscular dysplasia of the renal artery should be carried out in animals. In doing so it will be important to study not only the irritating effect of intermittent artery stretching but also the arterial haemodynamics, since a number of investigators attributed the fibromuscular and atherosclerotic lesions of an artery to haemodynamic stress[1-6].

Hormonal factors may play a role in the development of nephroptosis, as suggested by our results presented in chapter 2. Secondly, they might have an additional effect on the evolution of FMD[7], and thirdly, hypertension could be the result of a combination of nephroptosis and hormonal factors (see chapter 2). Both animal experiments and human studies should be performed to reach a deeper understanding of these relations.

Studies on nephroptotic hypertension should be further performed with a more *prospective* character. The $^{81}Rb/^{81m}Kr$ method might be a useful tool for this purpose. However, this method will need some practical improvements before it could be applied on a larger scale. First of all the interference of tissue background activity could be minimized if the ^{81}Rb tracer would concentrate and remain exclusively within the organ-of-interest, e.g. the kidney. This would enable an easier positioning of the detectors over the kidney and a longer time available for monitoring. Furthermore, the amount of pure ^{81}Rb needed for intravenous injection would be less than at present, with rubidium diffusing out of the kidney.

In conclusion, the studies suggested above may eventually confirm the role of nephroptosis in the onset of hypertension. This in turn would warrant performing preventive nephropexy.

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Samenvatting

In dit proefschrift worden de resultaten beschreven van een onderzoek naar het verband tussen wandelnieren (nefroptose) en hoge bloeddruk.

Afgezien van hoge bloeddruk zijn in het verleden vele klachten en symptomen, zoals pijn en urinewegontstekingen, toegeschreven aan wandelnieren. Het wisselend succes van het grote aantal verrichte operaties, waarbij de nieren van deze patiënten werden "vastgezet", was later aanleiding voor het ontstaan van een meer gereserveerde houding ten aanzien van de oorzakelijke rol van nefroptose. Nefroptose kon blijkbaar zowel met als zonder klachten of symptomen voorkomen.

Deze "geschiedenis van nefroptose" wordt beschreven in het eerste hoofdstuk. Hierin blijkt mede het gemis aan een uitgebreid onderzoek naar de rol van nefroptose als oorzaak van een verhoogde bloeddruk. Het belang van het bestuderen van dit verband wordt versterkt door het feit dat zowel wandelnieren als hoge bloeddruk veel voorkomen in onze samenleving. Opmerkelijk is het daarom dat uit het onderzoek, beschreven in hoofdstuk 2, bleek dat *driekwart* van de vrouwen met hoge bloeddruk een wandelnier had.

Van de mogelijke oorzaken die aan het gebleken verband tussen verhoogde bloeddruk en wandelnieren ten grondslag kunnen liggen, treden er twee op de voorgrond. De wandelnier zou in staande houding aan zijn vaatsteel kunnen trekken en daarmee de eigen doorbloeding kunnen belemmeren. Deze vernauwing in staande houding zou, analoog aan de "Goldblatt hypertensie", kunnen leiden tot verhoogde bloeddruk. Tevens zou het herhaald optreden van dit trekken en de daarmee gepaard gaande prikkeling van de vaatwand, op den duur kunnen leiden tot een fibromuskulaire dysplasie van de nierslagader (FMD), welke aandoening algemeen bekend is als een oorzaak voor verhoogde bloeddruk. De waarschijnlijkheid van deze laatste theorie wordt versterkt door het feit dat wij bij patiënten met een FMD vonden dat de aangedane nieren vrijwel alle uitermate beweeglijk waren in vergelijking met een controle groep.

In de hoofdstukken 3 en 4 wordt ingegaan op de eerstgenoemde mogelijkheid, dat de wandelnier zijn eigen bloedvoorziening belemmert in staande houding. De totale nierdoorbloeding (ERPF) bleek inderdaad bij patiënten met een wandelnier in staande houding sterker af te nemen naarmate de nieren meer zakten. In hoofdstuk 4 wordt aangetoond dat deze doorbloedingsafname mede het gevolg is van een afname van de doorsnede

van de slagader in staande houding. Deze diameterafname blijkt gecorreleerd met de mate van beweeglijkheid van de nier. Hierbij spelen echter de lengte en de mate van kronkeling van het vat ook een belangrijke rol: een lange, gekronkelde slagader laat de nier meer beweegruimte dan een korte, rechte nierarterie, alvorens er sprake zal zijn van trek en diameterafname.

De mogelijkheden van het opsporen van hoge bloeddruk door wandelnieren met behulp van bestaande, betrekkelijk eenvoudige methoden zoals het minuten IVU en de renografie, worden besproken in hoofdstuk 5. Beide methoden lijken geschikt om in staande houding optredende doorbloedingsafname van zeer beweeglijke nieren aan te tonen. In het verleden was echter gevonden dat de gevoeligheid van deze methoden beperkt is en dat hiermee slechts ernstige vernauwingen in de nierslagader kunnen worden aangetoond. De verklaring hiervoor lijkt te liggen in het aanpassingsmechanisme van de nier achter de vernauwing. Met medikamenteus ingrijpen in dit aanpassings-mechanisme met behulp van een prostaglandine-synthese remmer (indometacine) konden wij inderdaad de gevoeligheid van de renografie vergroten.

Ondanks deze mogelijke verbetering van de gebruikelijke technieken zou een methode die *direkt* de doorbloedingsverandering van een wandelnier zou kunnen vastleggen, de voorkeur genieten boven de bovengenoemde *indirekte* methoden. In de hoofdstukken 6 en 7 wordt de ontwikkeling besproken van een dergelijke methode, de "Rb/Kr verhouding methode". Met de ^{81}Rb speurstof bleek het mogelijk om, eerst in dierproeven en later ook bij de mens, de nierdoorbloeding gescheiden, uitwendig te vervolgen en de daarin aangebrachte veranderingen te meten. Bij een patiënte met een vernauwde nierslagader en een éénzijdige wandelnier kon worden aangetoond dat de doorbloeding in staande houding onmiddellijk sterk afnam in de gezakte nier, terwijl de andere niet-zakkende nier vrijwel geen doorbloedingsafname toonde. Een opmerkelijke bevinding hierbij was dat het met de Rb/Kr methode tevens mogelijk bleek om een langzaam herstel in doorbloeding van de gezakte nier waar te nemen. Dit zou goed kunnen passen bij het eerder genoemde, en bij dierproeven waargenomen, aanpassings-mechanisme van de nier achter de vernauwing.

In hoofdstuk 8 tenslotte worden de mogelijke gevolgen van deze bevindingen besproken, en wordt een toekomstbeeld geschetst van de Rb/Kr methode en van het onderzoek naar hoge bloeddruk veroorzaakt door wandelnieren.