The Kidney and the Elderly

Assessment of renal function
Prognosis following acute renal failure

Nele Van Den Noortgate

GHENT
UNIVERSITY

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De nier en de oudere:

Bepalen van de nierfunctie

Prognose van acuut nierfalen

Photograph on cover : my grandmother, Julienne De Vuyst, 90 years old

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door

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Manuscripts based on the studies described in this thesis

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N Van Den Noortgate, W Janssens, N Lameire, M Afschrift. Renal function in the oldest-old on an acute geriatric ward. Int Urol Nephrol. 2001;32:531-537.

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Part 1

Introduction

Chapter 1

Aims

Studies in an ageing population are often based on classification by chronological age, divided into young elderly (65 - 75 years old), elderly (75 - 85 years old) and old old (aged 85 years and older). Because of variations in genetic, environmental, social and economic factors, however, human beings age at different rates and even within individuals, organs and systems age differently. Therefore the elderly population is highly heterogeneous and, in addition to chronological age, is often classified according to health status. "Usual agers" are independently living elderly persons who have a variety of medical conditions. "Successful agers" are elderly persons with little or no loss in functioning and "accelerated agers" or frail elderly persons carry a heavy burden of chronic diseases and disabilities.

Although this work concentrates on the frail elderly persons, it provide an opportunity by way of introduction, to give in the *first part of this work* an estimation of the prevalence of decreased glomerular filtration rate in the elderly population in Belgium for the years 2000 and 2050 (chapter 2). In addition the functional and structural alterations of the ageing kidney (chapter 3) and the assessment of renal function (chapter 4) in the usual and successful ageing people are reviewed.

The *second part of this work* evaluates the usefulness of some new methods to assess glomerular filtration rate (GFR) in the old old, often frail elderly. The underlying somatic diseases induce a marked heterogeneity, making this population difficult to study compared to the young, healthy elderly. However, we focused on the old old because the clinician is often confronted with therapeutic decisions especially in this population segment.

In chapter 5, the studied population is characterised, by giving a description of renal function and risk factors for renal failure in the elderly, admitted to an acute geriatric ward. Chapter 6 evaluates in a medically stable elderly population admitted to the geriatric ward, the value of cystatin C in the assessment of GFR and the usefulness of the Modification of Diet in Renal Disease (MDRD) formula. Finally this chapter explores the correlation between the Cockcroft-Gault formula and an exogenous marker for GFR (^{51}Cr-EDTA). In Chapter 7, the impact of modifications in the methods to determine serum creatinine values on the creatinine clearance as GFR estimate, are studied. The validity of formulas estimating creatinine clearance without urine collection such as the Cockcroft-Gault formula is re-examined. Chapter 8 evaluates the place of ultrasonography, as a non-invasive and widely available technique, in the detection of renal impairment in the old old.

The *third part of this work* explores the influence of age on the prognosis of acute renal failure (ARF). For the clinician, dealing with the care of critically ill elderly patients, it is important to know the risks on adverse outcome of ARF in this elderly population.

By way of introduction chapter 9 and chapter 10 give a review of the pathophysiology, causes, the management and dialytic strategies of acute renal failure in an elderly population. In chapter 11 the prognosis and risk factors such as ARF for in-hospital mortality in the old old admitted to an intensive care unit, are evaluated. Chapter 12 investigates the prognosis and risk factors for mortality in the elderly patient developing ARF requiring dialysis, following cardiac surgery.

Chapter 2

Prevalence of decreased glomerular filtration rate in the elderly

Longitudinal studies suggest that usual ageing is considerably more varied and often associated with less dramatic alterations in renal function and structure than initially reported [1]. The results of the Baltimore longitudinal Study showed that an age-dependent fall in glomerular filtration rate (GFR) is not inevitable. About 30% of elderly individuals show no decrease in creatinine clearance [2].

Given the important implication of renal disease on health care and given the growing segment of the elderly population, an estimation of the prevalence of decrease in GFR in the year 2000 and 2050 is made for the elderly population (70 years and older) in Belgium.

The elderly population in Belgium is expected to expand from 1 220 882 in the year 2000 to 2 278 179 in the year 2050. Especially the old old (80 years and older) will be the fastest growing segment of the population with 376 786 old old people in the year 2000 and an expected threefold increase of 1 134 677 old old in the year 2050 [3].

To make an estimation of the prevalence of decrease in glomerular filtration rate (GFR) and the presence of chronic kidney disease (CKD), data from different organisations and epidemiological studies were used. To define the difference between decrease in GFR and CKD, the definition of the National Kidney Foundation was used [4](Table 1). CKD is defined as either kidney damage or GFR<60ml/min/1.73 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests and/or imaging studies.

Table 1: Stages of chronic kidney disease

Stage	**Description**	**GFR** (ml/min/1.73 m²)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60 – 89
3	Moderate ↓ GFR	30 – 59
4	Severe ↓ GFR	15 - 29
5	Kidney Failure	< 15 (or dialysis)

Together with the data from the third National Health and Nutrition Examination Survey (NHANES III), giving an estimation of the prevalence of the different stages of CKD, it is possible to make an estimation of the prevalence of CKD in Belgian adults ≥ 20 years [5] (Table 2).

Table 2: Prevalence of CKD in Belgian Adults ≥ 20 years for the year 2000 and 2050

Stage	Description	Prevalence		
		%	N in 2000 (N=7 864 523)	N in 2050 (N=8 723 938)
1	Kidney damage with normal or ↑ GFR	3.3	259,529	287,889
2	Kidney damage with mild ↓ GFR	3.0	235,935	261,718
3	Moderate ↓ GFR	4.3	338,174	375,129
4	Severe ↓ GFR	0.2	15,729	17,447
5	Kidney Failure	0.15	11,796	13,085

Data from the NHANES III make it also possible to estimate the prevalence of GFR categories in different age groups [4]. Using these data it is possible to make an estimation of the number of Belgian elderly people (aged 70 years and older) in the different GFR categories (Table 3). However, the fraction of elderly individuals with decreased GFR who really have CKD has not systematically been studied in NHANES III. Therefore, only an estimation of elderly people with moderate and severely chronic kidney disease (GFR < 60 mL/min/1.73 m² for ≥ 3 months) could be made for the years 2000 and 2050 (Table 3). As the NHANES III study has no data about kidney failure, the data of the Nederlandstalige Belgische Vereniging voor Nefrologie (NBVN) and the data of le registre des néphroloques Francophones de Belgique of the year 2000 were used to made an estimation of the elderly population who will have end stage renal disease (ESRD) in the year 2050 [6, 7] (Table 3). In the group of ESRD, elderly people with renal replacement therapy (haemodialysis and peritoneal dialysis) as well as elderly people with renal transplantation are included.

Table 3: Prevalence of decrease in GFR and moderate to severe kidney disease in the Belgian elderly population

GFR (ml/min/1.73 m²)	CKD stage	Prevalence		
		%	N in 2000	N in 2050
≥ 90	NA	25.5	311,325	580,936
60 – 89	NA	48.5	592,127	1,104,917
30 – 59	3	24.6	300,337	560,432
15 – 29	4	1.18	14,406	26,882
ESRD	5	0.22	2,686	5,011
		100	1,220,882	2,278,179

NA: Not applicable

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Chapter 3

The ageing kidney

Although many questions remain unanswered, adequate information is now available to provide a general understanding of the influence of usual ageing on renal function. Many of the current observations are supported by animal studies, specifically of the rat.

This review summarises the current knowledge of the anatomical and functional changes in the ageing kidney and some of the hypotheses that are currently investigated.

Anatomical changes

Advancing age is associated with progressive loss of renal mass. Renal weight decreases 20 to 30 per cent between the age of 30 and 90 years [1,2]. Also renal length diminishes by 2 cm between the age of 50 and 80 years [3]. The loss of renal mass is primarily cortical, with relative saving of the renal medulla. At the molecular level, progressive shortening of telomeres seems to occur in an age-dependent fashion in the renal cortex faster than in the medulla. Telomeres protect ends of chromosomes and shorten with increasing age in somatic cells [4]. Acting as a mitotic clock, telomeres reflect the replicative senescence of the cell [5]. These findings raise the possibility that telomere shortening becomes a limiting factor and contribute to some features seen in the senescent kidney [6].

The total number of identifiable glomeruli falls with age, roughly in accordance with the changes in renal weight [7,8]. The proportion of sclerotic glomeruli identified on light microscopy increases from 1-2% during the third to fifth decade, to 12% after age 70 and is as high as 30% in some apparently healthy 80-years-old people [9]. Glomerular basement membranes are patchily reduplicated and, in general, thicker than in the young [10]. However, despite these changes, studies of glomerular filtration characteristics show no differences in glomerular permeability with ageing.

The reasons for progressive glomerulosclerosis with age are not clear. Obviously, the marked vascular changes with age could partly play a role, but a primary involution of the glomeruli, as suggested by Oliver may also take place [3].

Usual ageing is associated with variable sclerotic changes in the walls of the larger renal vessels, which are enhanced in the presence of hypertension [9,11]. Smaller vessels are generally saved in usual ageing with fewer than 20% of the senescent kidneys from nonhypertensive subjects displaying arteriolar changes [11]. Microangiographic and histologic studies have identified two distinctive patterns of

changes in arteriolar-glomerular units with senescence [12-14] (Figure 1). In one type hyalinisation and collapse of the glomerular tuft are associated with obliteration of the lumen of the preglomerular arteriole with a resultant loss in glomerular blood flow. This type of change is seen primarily in the cortical area. The second pattern, observed primarily in the juxtamedullary area, is characterised by the development of an anatomic continuity between the afferent and efferent arterioles during glomerular sclerosis. The endpoint is thus loss of the glomerulus and shunting of blood flow directly from afferent to efferent arterioles. The arteriolar rectae verae, the primary vascular supply of the medulla are not decreased in number with age and their blood flow in the medulla is maintained.

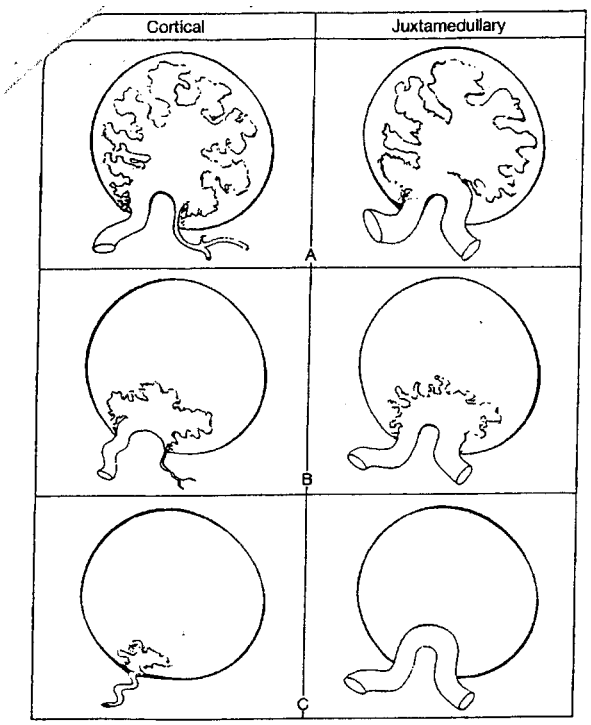

Figure 1: Progressive vascular simplification and glomerular degeneration of the cortical and juxtamedullary arteriolar-glomerular units; adapted from Takazakura et al [13]

Tubular cells undergo fatty degeneration with age, showing an irregular thickening of their basal membrane. The mean proximal tubular volume decreases with age, from 0.136 mm^3 to 0.061 mm^3 at the age of 84 [14]. In general, with progressive

age the reduction in proximal tubular volume parallels that of the glomerular volume, so that anatomical glomerulotubular balance is preserved into old age. Although the cells of the distal tubule are not affected, both the distal tubule and collecting system develop small diverticuli, the significance of which is unknown [3].

Interstitial changes consist mainly of increasing zones of tubular atrophy and fibrosis, which may relate to the defect in concentration and dilution as observed in usual ageing.

Functional changes

RENAL BLOOD FLOW

There is a progressive reduction in renal plasma flow of approximately 10% per decade. The decrease in renal blood flow is associated with significant increases in both the afferent and efferent arteriolar resistance [15]. Hollenberg et al. has shown that most changes occur in the cortex, with a relative increase in blood flow to the juxtamedullary region. These changes may account for the patchy cortical defects commonly seen in older adults [16]. Furthermore, as outer nephrons have a lower filtration fraction than juxtamedullary nephrons, the redistribution of blood flow toward the juxtamedullary region, together with the increase in the efferent arteriolar resistance may in part explain the age-related increase in filtration fraction [16,17].

Studies looking at the relationship between renal plasma flow and cardiac output, suggest that the major determinants of reduced renal blood flow with age are the primary anatomical and/or functional alterations in the renal vasculature and not the changes in cardiac output [18]. Studies in animals and humans have shown an age-related impairment in renal vasodilatory response, without difference in vasoconstrictory response. This blunted vasodilatory capacity in the face of appropriate vasoconstriction may indicate that the aged kidney is in a state of renal vasodilatation to compensate for the underlying sclerotic damage [15,17,19]. Tank et al. have shown in older rats a marked increase in the vasoconstrictive response to L-NAME with a significant increase in renal vascular resistance and a decrease in renal plasma flow. L-NAME is a competitive inhibitor of the formation of endothelial nitric oxide (NO) in older rats, suggesting a role for possible increased levels of endogenous NO to explain the decreasing vasodilatory reserve [20].

GLOMERULAR FILTRATION RATE

A progressive age-related decline in glomerular filtration rate (GFR) is well known to occur in men and women [17]. A cross-sectional study in 548 healthy volunteers in the Baltimore Longitudinal Study of Aging, demonstrates a progressive

linear decline in creatinine clearance of 0.9 ml/min/1.73m²/year [21] (Table 1). The longitudinal study of 254 normal subjects also revealed a main decrease of 0.75 ml/min/1.73m²/year. Of interest is that 36% of the subjects did not show an absolute decrease in creatinine clearance [22] (Figure 2). This study suggests that age-related loss of glomerular function is not a universal phenomenon, and that dietary, metabolic, hormonal or haemodynamic factors may play a major role in modulating the age-related decrease in renal function [22,23].

Table 1: Longitudinal analysis of age-related changes in creatinine clearance; adapted from Rowe et al [21]

Age years	**No. subjects**	**Creatine clearance** ml/min/1.73m²	**Creatinine clearance slope** ml/min/1.73m²/yr
17-24	1	125.3	-1.75
25-34	20	140.4 ±4.6	-1.09 ±0.70
35-44	64	132.7 ±2.0	-0.11 ±0.36
45-54	95	128.1 ±1.6	-0.73 ±0.30
55-64	60	121.8 ±1.9	-1.64 ±0.41
65-74	36	110.0 ±2.6	-1.30 ±0.57
75-84	17	97.0 ±3.4	-1.07 ±0.77
17-84	293	124.7 ±1.1	-0.90 ±0.18

The decrease in GFR with ageing is usually not accompanied with an elevation in serum creatinine concentration [24]. Since muscle mass, from which creatinine is derived, falls with age at approximately the same rate as GFR, the rather striking age-related loss of renal function is not reflected by an increase in the serum creatinine [25]. Thus, the serum creatinine level usually underestimates the decline in GFR in the elderly [26] (Figure 3). The assessment of GFR will be discussed further in detail.

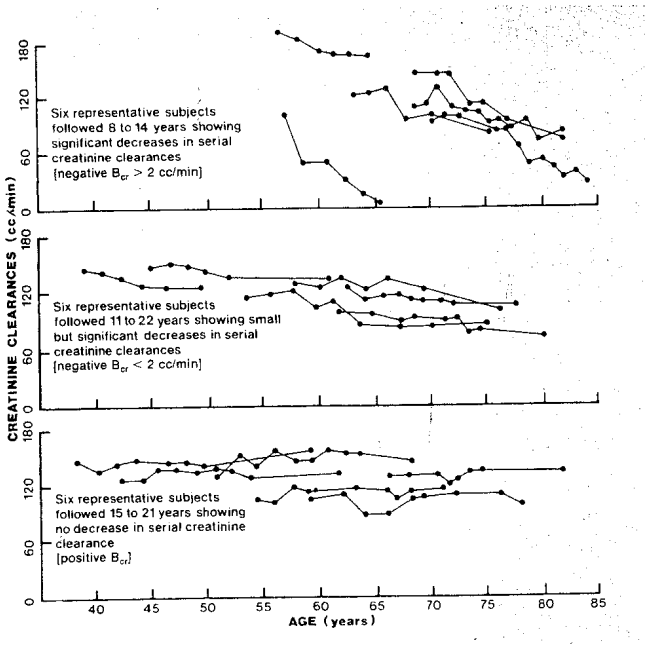

Figure 2: Individual plots of serial creatinine clearance vs. age in years for representative subjects; adapted from Lindeman et al [22]

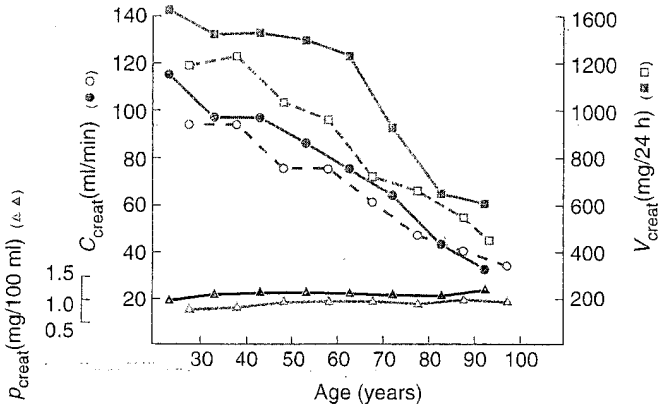

Figure 3: Changes in excretion of creatinine, plasma creatinine and creatinine clearance in healthy elderly individuals at different ages. Males are represented by closed, and females by open, symbols; adapted from Cameron J et al [26]

FLUID AND ELECTROLYTE BALANCE

Sodium-Conserving Ability

The ability of the aged kidney to conserve sodium in response to sodium restriction is impaired; it takes nearly twice as long for the aged individual to decrease urinary sodium excretion compared to younger persons [27] (Figure 4).

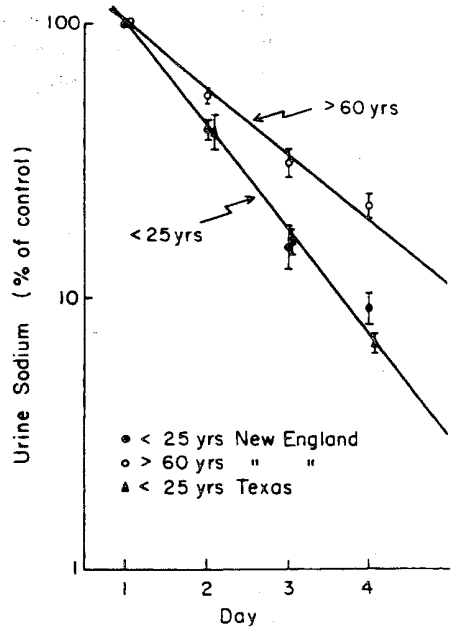

Figure 4: Response of urinary sodium excretion to restriction of sodium intake in normal humans. The mean half time ($t_{1/2}$) for eight subjects older than 60 years of age was -30.9 ±2.8 hours, exceeding the mean half-time of -17.6 ±0.7 hours for subjects younger than 25 years of age ($p<0.01$); adapted from Choudhury et al [6]

Clearance studies in young and elderly subjects have shown a decreased "distal nephron" capacity for sodium absorption in the elderly [28] (Table 2 and Figure 5). The ascending limb of Henle's loop and other tubular segments where aldosterone exerts its effects are primarily responsible for the impairment in tubular renal sodium handling by the ageing kidney [26]. Also anatomic changes in the ageing kidney such as interstitial fibrosis and decreased nephron number or functional and hormonal changes, including a relatively increased medullary blood flow or decreased Na,K-ATPase activity could cause an impaired tubular reabsorption of sodium. However the importance of these changes in the salt-loosing defect in the elderly human is less clear [26].

Studies in rats showed a decrease in juxtamedullary single nephron renin content [29] and intrarenal downregulation of mRNA and angiotensin-converting enzyme (ACE) [30]. Sodium-deprived aged rats showed a blunted increase in plasma renin activity with delayed decline in urinary sodium excretion, despite a decrease in mean arterial pressure [31]. Plasma renin release is also blunted in older individuals. Weidmann et al found only slightly lower baseline supine renin levels in elderly individuals versus younger ones [32]. However, with sodium depletion and upright posture, the increase in renin in the elderly group was well below that in the younger group. Failure to increase renin adequately results directly in an inadequate aldosterone response, resulting in a decreased renal tubular absorption of sodium in the elderly [32-34].

Table 2: Segmental handling of sodium in different parts of the nephron in young and elderly individuals; adapted from Macias-Nunez et al [28]

	Sodium clearance (ml/100ml)	**Proximal nephron reab.** (ml/100ml)	**Distal nephrion reabsorption** (ml/100ml)
Young (n=10)	3.20 ±2.12 (P<0.05)	18.3 ±7.2 (NS)	83.0 ±6.3 (P<0.05)
Elderly (n=12)	6.52 ±2.35	18.9 ±5.9	59.1 ±7.9

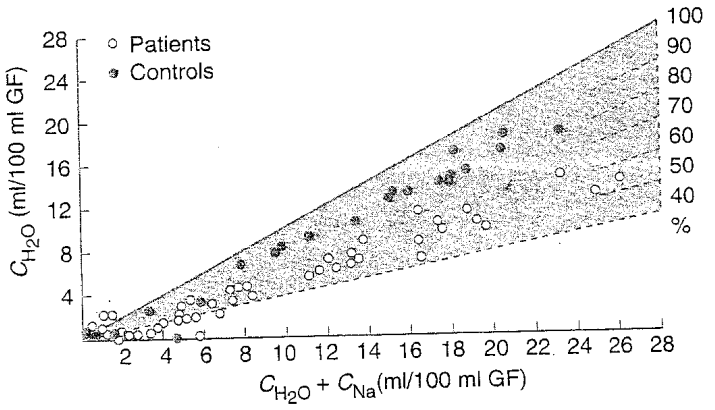

Figure 5: Graphical representation of the calculated segmental capacity to reabsorb sodium by the 'proximal' and 'distal' nephron. The healthy elderly individuals are indicated by open, the younger by closed circles; adapted from Macias-Nunez et al [28]

Sodium-Excreting Ability

Excessive sodium retention and volume overload are commonly encountered problems in older patients [34] (Figure 6). Short-term sodium loading studies show that both, the excretory capacity for sodium and the circadian variation in excretion are influenced by age [35]. The age-related decline in GFR is probably the major factor, which limits the ability of the aged kidney to excrete an acute sodium load. In addition, emergent studies have investigated the possible role of alterations in atrial natriuretic peptide (ANP) secretion in mediating the age-related impairment in natriuresis [36]. Baseline plasma ANP concentration was found to be generally increased in older subjects with a further increase following intravenous saline loading [36]. Thus, an impaired response in ANP secretion in mediating the age-related decline in natriuresis seems unlikely. However, since there is a report of an age-related decrease in the natriuretic and hypotensive properties of rat atrial extracts [37], Pollack et al. were able to show that the renal natriuretic response to an ANP infusion is blunted in the aged kidney despite a normal increase in cGMP (ANP second messenger) after ANP infusion [38]. Despite the increase in cGMP levels after ANP-infusion, an increase in Na excretion is not seen [38]. These results suggest an altered post-cGMP effector mechanism.

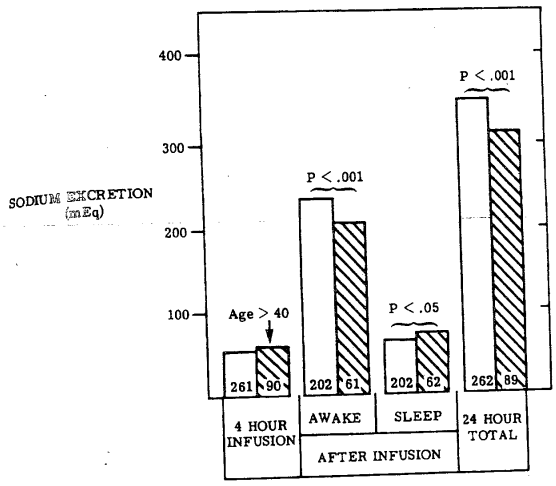

Figure 6: Comparisons of urinary sodium excretion in younger (clear bars) and older (hatched bars) subjects after 2L intravenous normal saline. Numbers at the base represent the number of subjects in each group; adapted from Choudhury et al [6]

Renal Concentrating Ability

The renal concentrating ability is well known to decline with age in humans [39,40] (Figure 7). These studies show that the age-related decline in the concentrating defect does not correlate with the decline in GFR. It has been suggested that an impaired solute transport by the ascending branch of the loop of Henle, may be responsible for the impairment in urine concentrating ability in elderly subjects [28]. This defect could diminish the inner medullary hypertonicity and thus impair the urinary concentrating ability. A relative increase in medullary blood flow could also enhance the removal of solutes from the medullary interstitium and thereby contribute to the decreased maximal urinary osmolality [16,28,40]. Studies examining the secretion and effectiveness of antidiuretic hormone (ADH) release show conflicting results. The available data suggest increased osmoreceptor sensitivity and a decreased renal responsiveness with ageing, resulting in partial nephrogenic diabetes insipidus [41,42]. Data in ageing rats are suggestive of an ADH resistance in the collecting tubules. The maximal urinary concentration despite 40 hours of dehydration and exogenous ADH was impaired in aged rats. Although solute-free water formation was normal, solute-free water reabsorption was impaired. The inner medullary solute content in both the old and young rats was identical; therefore, the ascending limb solute transport appears to be intact, whereas the collecting tubule water transport was diminished [43]. A postreceptor mechanism of ADH may play a role in this process. Studies in older rats confirmed this hypothesis [44,45]. These studies suggest that decreased expression of the collecting duct water channel aquaporin-2 in older rats is independent of changes in circulating ADH and intracellular cAMP [45].

Renal Diluting Ability

Also the ability of the kidney to dilute the urine is diminished with ageing. After water loading, the minimal urine osmolality is significantly higher in elderly subjects than in younger ones [46,47]. This impairment seems to be due to the decline in GFR. Additional studies however show that this is not the only mechanism [46]. Inadequate suppression of ADH or impaired solute transport in the ascending loop of Henle may also play a role. However, these factors have not been well been studied until now.

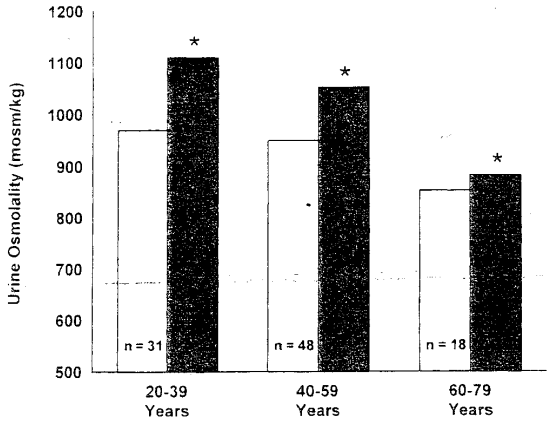

Figure 7: The effect of age on urine osmolality in response to 12 hours of water deprivation. Pre-treatment values (white bars), post treatment values (dark bars). The number of subjects in each group is noted at the base of each bar. Urine osmolality decreases significantly with age after water deprivation (*P<0.05); adapted from Choudhury et al [6]

Acid-Base Balance

Elderly subjects have an impaired ability to increase the urinary acid excretion in response to an acute acid load. An age-related decline in renal mass and GFR has been associated with this change [48]. When endogenous acid production was held constant, the changes in GFR with age correlated significantly with decrease in blood pH and plasma $HC0_3$ [49] (Figure 8).

However, Agarwal et al found that ammonium loading in older patients resulted in reduced ammonium excretion even after correction for GFR. These results suggest rather an intrinsic tubular defect in ammonium excretion [50]. Whether this defect is due to an anatomic or functional defect, such as impairment in the renin-angiotensin-aldosterone axis, frequently encountered in the aged, is not clear. Studies in senescent rats that orally received equivalent amounts of NH4Cl confirmed findings of a deficiency in the absolute amount of ammonium excreted after an acid load. This accounted for a more severe acidaemia in the older rats compared with the younger controls. Studies on the renal proximal tubular apical brush-border membrane (BBM) vesicle transport revealed that the sodium-hydrogen exchange activity, a major regulator of proximal tubular acidification, was similarly enhanced by the acid load in adult and aged rats. Phosphate transport was reduced to the same extent in both adult and aged rats. This suggests that impaired ammonium excretion also may mediate the age-related

impairment in renal adaptation to metabolic acidosis, even when compensating mechanisms appear to be intact [51].

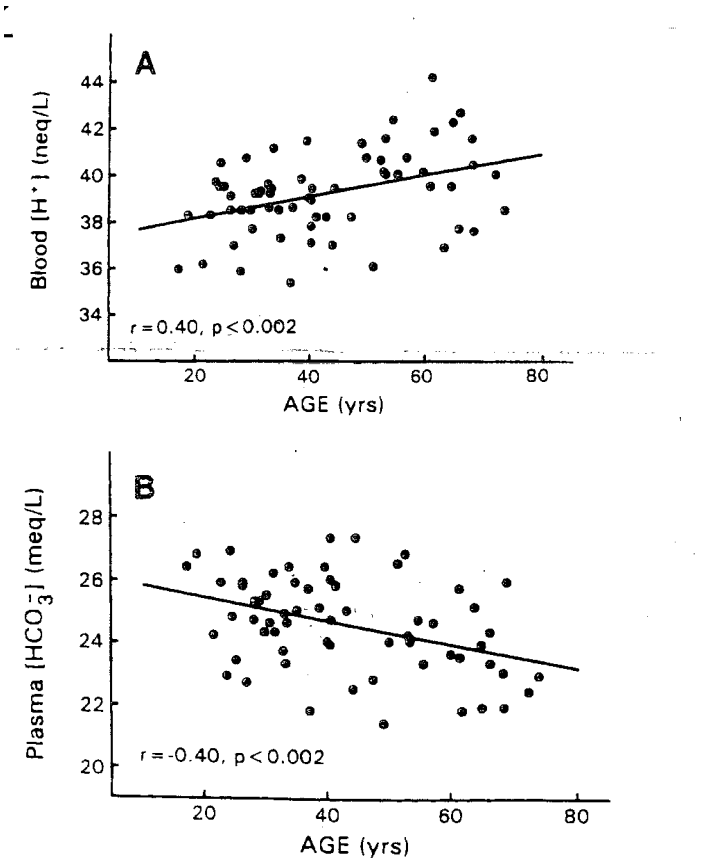

Figure 8: Relation between blood H + and age (A) and between plasma HCO3- and age (B) in normal humans (n=64). Each data point represents the mean steady state value in a subject eating a constant diet; adapted from Frassetto et al [49]

Potassium Balance

Total body potassium and total exchangeable potassium decrease with age in both sexes. This decrease may relate to the decrease in muscle mass and is more pronounced in women than in men [52]. Because potassium excretion in the distal tubule is enhanced by the presence of aldosterone, the relative hypoaldosteronism frequently present in the elderly predisposes to hyperkalaemia. Healthy elderly individuals, aged 65 to 85 years, had lower basal plasma aldosterone and blunted

aldosterone response to potassium infusion compared with younger subjects [53](Figure 9).

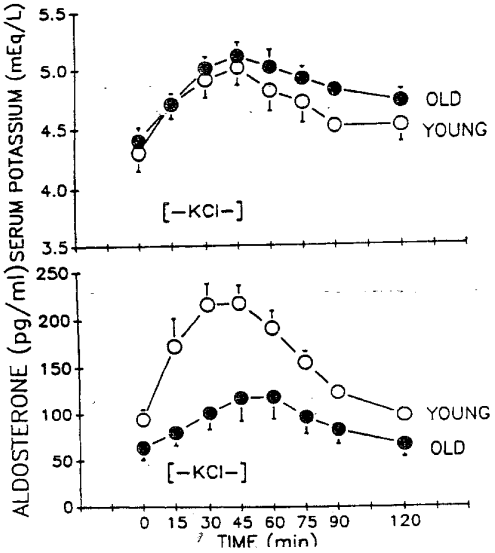

Figure 9: Serum potassium and aldosteron levels before, during and after infusion of potassium chloride in six healthy young and six healthy elderly men. Changes in potassium levels were similar, but elderly subjects had lower aldosterone responses (P< 0.005); adapted from Mulkerin et al [53]

In aged rats a tendency to develop hyperkalaemia when exposed to an acute potassium load, was seen in rats on a high potassium diet [54]. Also after bilateral nephrectomy older rats were unable to decrease serum potassium compared with younger rats after KCl infusion. The finding that the Na,K-ATPase activity was markedly reduced in the medulla of older rats suggests that both the renal and extrarenal potassium adaptations may be blunted [54]. Whether these findings apply to humans remains to be determined. However, exercise-induced elevation of plasma potassium in both healthy young and elderly suggests that there may be an impaired response of the beta-adrenergic adenylate cyclase system linked to the Na,K-ATPase exchange pump in skeletal muscle [55]. These results at least suggest that the intracellular uptake of potassium is be disturbed in the elderly.

CONTROL OF THE RENAL VASCULAR RESISTANCE

Intrarenal vascular tone is increased with age. Baseline and stimulated plasma norepinephrine levels rise with ageing and have been interpreted as indicating that there is a constant hyperadrenergic state in the elderly [56]. Other vasoactive factors may also contribute to this increased tone although the data describing these changes are complex and contradictory. For example, high basal levels of renal nerve activity, angiotensin II and endogenous endothelin contribute to vasopressor activity. The inhibition of endothelium nitric oxide by NO-synthase blockers (L-NAME and L-NMMA) produce an exaggerated vasopressor response in aged rats, indicating that the aged kidney may be in a state of renal vasodilatation to compensate for the underlying slerotic damage [19]. The data for basal renin and angiotensin levels remain confusing. A consistently observed blunted renin response to stimulation with artificial stressors, upright position or sodium depletion suggests that age does affect the vascular reactivity under physiological condition [57]. However other data show that vasodilators, including angiotensin converting enzyme inhibitors and angiotensin II blockers have similar effects regardless of age [58,59]. NO plays a major physiologic role in the maintenance of peripheral and renal vascular tone [60]. There appears to be a decreased intrarenal NO generation in older animals compared to younger ones [61]. However, functional studies suggest that NO is still very important in the control of renal vascular tone, because both acute and chronic NO inhibition cause exaggerated renal vasoconstriction in old rats. This may mean that NO that is present has an increased role as a counter-regulatory influence of the activated intrarenal vasoconstrictor system.

An important role in the preservation of renal function in presence of increased systemic vasoconstrictors and enhanced sympathetic tone is played by the intrarenal generation of vasodilating products of arachidonic acid (i.e. PGI2). Angiotensin stimulates synthesis of PGI2 and PGE2 within the kidney and the prostaglandin's act to preserve glomerular filtration in situations as sodium depletion, surgical stress and reduced cardiac output. With advancing age there is a widespread decrease in prostaglandin synthesis (PGI2) throughout the vascular endothelium, leading to a decrease in the PGI2/thromboxane A2 (TXA2) ratio, a maladaptation which is atherogenic. The ratio of urinary PGI2 to TXA2 also decreases in older subjects and in vitro studies in the rat have been shown that the TXA2 to PGI2 ratio is increased in glomeruli and inner and outer medulla of older kidneys [62].

Although no formal studies of autoregulation of GFR and RBF in otherwise healthy ageing human kidneys have been performed, there is enough circumstantial evidence to suggest that circulatory and neuroendocrine alterations with ageing make the kidneys of aged individuals more vulnerable to reductions of renal perfusion pressure compared with kidneys of younger individuals. Atherosclerotic involvement of

afferent arterioles caused by age, hypertension or diabetes is known to be associated with an impaired autoregulation of RBF and GFR.

RENAL FUNCTIONAL RESERVE

Renal functional reserve (RFR) is a measure of the ability of the kidney to increase GFR above baseline values. Baylis et al. documented that in the male senescent rat the normal renal haemodynamic response to aminoacid infusion is impaired [19]. In contrast, studies in healthy independent elderly individuals are showing that the RFR is not decreased [63,64] (Figure 10).

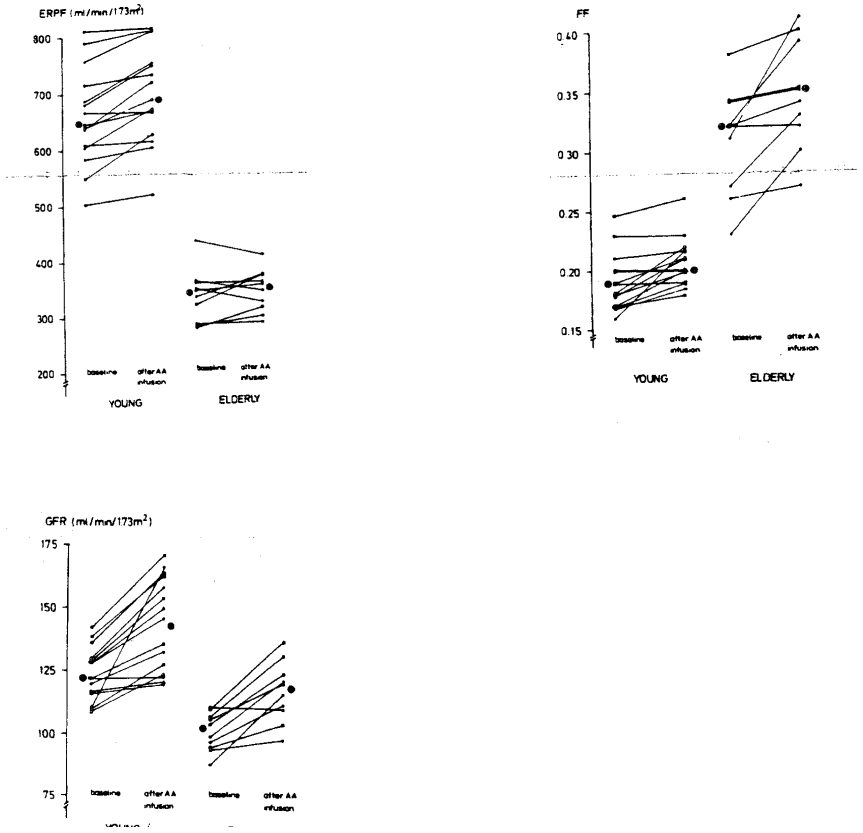

Figure 10: effective renal plasma flow (ERPF), glomerular filtration rate (GFR), and filtration fraction (FF) in young and elderly subjects at baseline and after amino acid (AA) infusion. ERPF remains unchanged, whereas GFR and FF increase

• Median; adapted from Fliser et al [63]

Mechanisms of age-dependent injury

The mechanisms of age-dependent injury in the kidney are closely related to the biological mechanisms of ageing. Species-specific lifespans and the complex phenotype of senescence appear to be modulated by a large number of genes. Alleles at such loci, acting in concert with numerous environmental agents, could differentially influence numerous independent and pathogenically overlapping biological mechanisms of ageing [65,66]. The hypotheses proposed for cellular and organism senescence include either damage to intra- or extracellular molecules or programmed or epigenetic changes in gene expression [65]. Also genetic factors, intrinsic stresses and extrinsic environmental factors regulate renal ageing [67].

GENETIC AND MOLECULAR EVENTS

Shortening of telomeres is critical to replicative senescence. Telomeres are DNA repeats (TTAGGG) at the ends of chromosomes that shorten in dividing normal cells. Melk et al. have shown that there is progressive shortening of telomeres in kidneys with age and that the rate of loss is greater in cortex than in medulla [4]. These results are in accordance with the greater loss of mass in cortex than in medulla. The relevance of these phenomena in renal senescence remains unclear.

Senescence-associated growth arrest is mediated by expression of cell cycle inhibitory genes and by downregulation of positive acting cell cycle regulation. Also cell cycle regulators as $p21^{WAF1/CIP1}$ and $p16^{INK4a}$ may have a place in cellular senescence of the kidney. Melk et al showed that $p16^{INK4a}$ can be induced in some individuals by ageing [68].

A marker of cellular senescence, senescence associated beta-galactosidase (SA-GAL), is present in ageing kidney and is inversely correlated with the recovery of kidney function after ischaemia/reperfusion injury. These results validate the direct correlation between the amount of senescent cells in the organ and its susceptibility to ischaemic injury [69].

Thus, at some point a senescent nephron is irreversibly shut down. It seems possible that this shutdown mechanism is triggered by molecular changes of senescence.

INTRINSIC STRESSES

One of the two most favoured hypotheses is an imbalance between synthesis and degradation of matrix proteins, due to oxidative injury and accumulation of oxidative end products and advanced glycation end products, causing the features of

glomerulosclerosis (Figure 11). The second hypothesis is one of glomerular haemodynamics due to the hyperfiltration theory and reduced nephron mass.

Especially rat studies have shown that mesangial cell expansion and extracellular matrix accumulation play a primary pathogenic role in some forms of glomerular injury and precede the appearance of focal sclerosis [60]. However, it appears that mesangial expansion is not necessarily associated with glomerulosclerosis. The development of glomerulosclerosis is usually preceded by mesangial expansion, especially in males. The greater susceptibility of the old male may be related to androgens, which can increase the synthesis of extracellular matrix material. In addition to increased synthesis, reduced rates of degradation will also cause accumulation of mesangial matrix products. One study shows that activity of a glomerular metalloprotease responsible for degradation of mesangial products is low in old male Munich Wistar rats with glomerular injury. This enzyme is elevated in females and castrated rats of both sexes and is associated with protection from renal damage [60].

Another proposed cause of renal lesions in the ageing rats has been the accumulation of advanced glycation end (AGE) products within the glomeruli [70]. AGE accumulate in the kidney of senescent rats, increase the synthesis of extracellular matrix and expand the glomerular mesangium. Chronic administration of the AGE inhibitor, aminoguanidine reduces the accumulation of AGE in the kidney. However, aminoguanidine has a number of other actions, including a preferential inhibition of inducible nitric oxide synthase, so that the mechanism by which aminoguanidine protects the ageing kidney from injury is still unclear.

The hyperfiltration hypothesis proposes that in a kidney with reduced number of nephrons an increased capillary blood flow through each glomerular capillary bed is generated leading to a high intracapillary pressure. Hill et al have shown that non-obstructive hyaline arteriosclerosis of the afferent arteriole is strongly associated with dilatation of the afferent arteriole, increase in glomerular capillary size and subsequent segmental glomerulosclerosis as seen in experimental models in which glomerular hypertension has been confirmed [71]. High intraglomerular pressure results in local endothelial cell damage, platelet aggregation and thrombin production [72]. Activation of platelets leads to release of growth factors, including platelet derived growth factor (PDGF), fibroblast growth factor (FGF) and transforming growt factor (TGF-β) all of which are associated with increased collagen production by fibroblast and mesangial cell sclerosis [73]. At the same time, alterations in the endothelium derived relaxing factor/endothelin axis increase the angiotensin II secretion. As glomeruli scleroses, the amount of blood flow directed to each of the remaining nephron increase, further potentiating the damage. Recently Keller et al have shown that the number of nephrons is reduced in patients with primary hypertension. These data provide evidence for the

concept that the number of nephrons, which is determined during foetal development, is an important determinant of cardiovascular abnormalities during adult life. Whether the reduced number of nephrons is caused by genetic or environmental factors is unclear [74]. Also in animal studies, glomerular capillary hypertension is a primary risk factor in age-dependent glomerular damage [60]. However, glomerular blood pressure does not invariably increase with ageing and structural injury may precede increased glomerular blood pressure, as evidenced in male Munich Wistar rats [60].

Drugs which reduce single nephron GFR (e.g. ACE inhibitors and angiotensin II blockers) reduce glomerular injury more than other drugs which control the systemic blood pressure to the same level [75]. Unfortunately it is still unclear if the protective effect of ACE inhibitors alters glomerular haemodynamics and thus prevents renal damage or if they act through altered signal pathways (angiotensin II as growth factor inducing mesangial sclerosis).

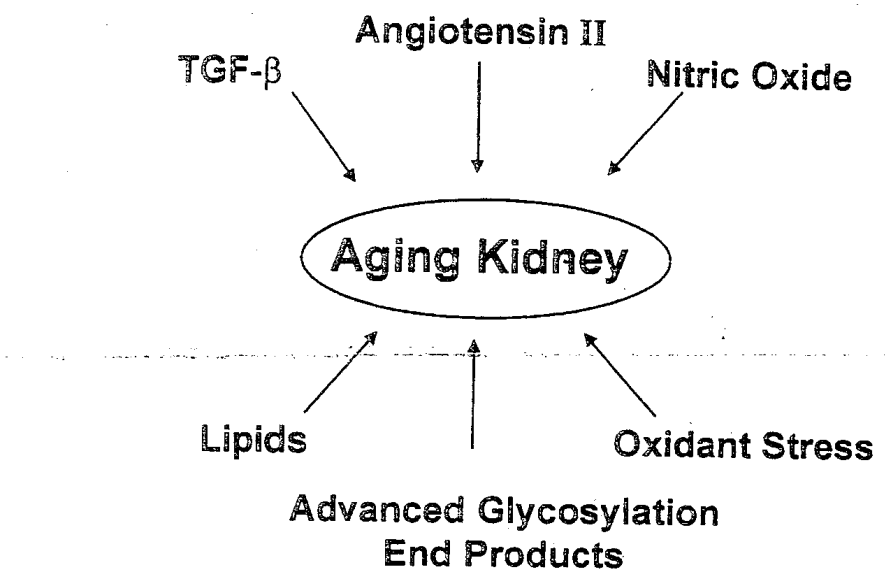

Figure 11: Factors associated with the pathogenesis of age-related glomerulosclerosis and decline in renal function; adapted from Choudhury et al [6]

The enhancement of longevity via caloric restriction (yet to be confirmed in primates) provides an argument for a major unification of apparently diverse mechanisms of ageing. Studies in rats showed that food restriction is associated with an increase in survival and a reduced incidence of diseases, including chronic progressive nephropathy [60]. Recent studies have shown that dietary restriction significantly reduce the age-related accumulation of levels of oxidantia in all tissues of rodents [76].

Several authors have also in humans shown the protective effect of low protein diets on chronic progressive kidney disease [77,78]. However, data of the MDRD study did not confirm the protective effect of low protein diet in moderate renal disease. The investigators concluded that for various reasons the data were not conclusive and that physicians must continue to make decisions based on the current balance of evidence for and against the efficacy and safety of dietary protein restriction [79].

EXTRINSIC (ENVIRONMENTAL AND LIFESTYLE) FACTORS

Interactions between specific extrinsic factors, intrinsic stresses and genetically determined individual susceptibility are possible and may explain why renal impairment is highly variable among elderly individuals. In an unselected population renal senescence may reflect the effect of ageing and age-related diseases. Age-related diseases accelerating renal senescence and influencing glomerular filtration rate are well known from studies in the young elderly and include hypertension, vascular disease, diabetes and heart failure [23,80-86]. End stage renal disease (ESRD) is not part of the ageing process. This propensity can be attributed in part to the high incidence of diseases that cause ESRD and the time dependency of their effects. Moreover, it is also possible that the interaction between disease stress and intrinsic senescence processes, i.e. a decrease in the ability to cope with disease stress, leads to acceleration of ageing of the kidney. Demographic criteria and single assessments of clinical and laboratory criteria have been identified which predict an increased incidence of chronic kidney disease (CKD). Longitudinal studies have demonstrated that lower income, diabetes, hypertension, haematuria and proteinuria are all independent risk factors for CKD in the elderly population [87]. Other variables as family history of kidney disease and use of non-steroidal anti-inflammatory drugs may also be useful for risk stratification.

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Chapter 4

Clinical implications of the ageing kidney

Under normal circumstances and without stresses, homeostasis is adequately controlled in the elderly. However, when stress or other diseases affecting kidney function are extant, the ageing kidney may be incapable to cope with acute changes, such as volume depletion and other circulatory disturbances. It is also possible that the interaction between disease stresses and intrinsic senescence processes lead to accelerate ageing of the kidney.

Renal blood flow and renal vascular resistance

An important consequence of the age-related decline in renal blood flow and GFR is the potential predisposition to enhanced ischaemic or toxic renal injury. In addition to the absolute decrease in renal blood flow, the autoregulatory capacity of the renal vasculature is probably impaired, thus increasing the risk of haemodynamically induced acute renal failure in the elderly (see acute renal failure).

Glomerular filtration rate (GFR)

As GFR declines with age in normal individuals, it can be difficult to distinguish age-related decrease in GFR from chronic kidney disease (CKD). The fraction of elderly individuals with decreased GFR who truly have CKD has not been systematically studied.

Detection of CKD in the elderly population should include an assessment of risk through assessment of sociodemographic characteristics, review of past medical history and family history. A clinical evaluation should include measurements of blood pressure, an estimation of GFR, testing for proteinuria and/or protein-to-creatinine ratio and examination of the urine sediment for red and white blood cells [1,2]. As most of age-related diseases are correlated with disabilities as age progresses, functional impairment of the elderly should always alert the physician to multi-organ dysfunction as ageing is a systemic process, influencing different organ systems.

Elderly with mild decreased GFR, low risk for progressive decline in GFR, and low risk for cardiovascular disease may require only adjustment of the dosage of drugs that are excreted directly by the kidney or whose active metabolites, formed in the liver, depend on urinary excretion.

ESTIMATION OF GFR

Adjustment of dosage of medications and diagnosis of CKD requires an estimation of the GFR.

GFR is traditionally measured as the renal clearance of a particular substance or marker from plasma. Under the right conditions, measuring the amount of an indicator in both plasma and urine allow the accurate calculation of GFR. Assuming that there is no extrarenal elimination, tubular reabsorption, or tubular secretion of the marker, then GFR = UV/P where U is the urinary marker concentration, V is the urine volume per unit of time and P is the average plasma concentration of the marker [3-5].

Whether endogenous or exogenous, an ideal indicator should not bind to plasma proteins and should be freely filtered at the glomerulus. It should be not secreted nor reabsorpted in the tubules or urinary collecting system. Its elimination should be entirely dependent on glomerular filtration. In addition, the marker should be easy to measure in plasma and urine without external interference of the assay.

The golden standard of measuring GFR is the determination of the clearance of exogenous markers such as inulin [6], isotopically labelled compounds such as iothalamate [7], chromium ethylenediamine tetracetic acid (^{51}Cr-EDTA) [8] and diethylenetriamine pentatic acid (^{99m}Tc-DTPA) [9]. Probably the most extensively investigated radionuclide-bound indicator of GFR has been ^{51}Cr-EDTA . The molecule is small, appears to have little binding to plasma proteins, and is freely filtered by the glomerulus. The clearance of the contrast medium iohexol, measured by high performance liquid chromatography, has recently been introduced [10,11]. These methods are however difficult to perform, expensive and not very practical for routine assessment of GFR, especially in a geriatric population.

GFR can also be assessed by measurement of the clearance of endogenous markers. Serum creatinine is the most widely used index of renal function. Creatinine is a small molecule, does not bind to plasma proteins and is freely filtered by the renal glomerulus. However, it has long been known that creatinine is also secreted by the renal tubule [3,4]. This secretion of creatinine varies substantially in the same individual over time and between different individuals. Moreover, the proportion of total renal creatinine excretion due to tubular secretion increases with decreasing renal function. Another problem, especially in the elderly, is that creatinine production is dependent on muscle mass, which is declining with ageing [12-15]. As a consequence, serum creatinine level may remain normal or become only minimally elevated in the old old, despite the fact that the clearance of creatinine is significantly reduced [13-16] (Figure 3, Chapter 3). It is also interesting and troublesome to note that the methods used by clinical laboratories to measure serum creatinine levels vary and have increasingly shifted in recent years from the picrate (Jaffé) method to modifications that are more

convenient for autoanalyzer techniques. Autoanalyzer methods use the Jaffé reaction but separate creatinine from noncreatinine chromogens by the rate of colour development and do not use deproteinisation as the original Jaffé method [15,17]. Therefore, more recent methods are affected by an important protein error. As a consequence, 'uncompensated' Jaffé methods have higher reference values for serum creatinine than 'compensated' or enzymatic Jaffé methods [18].

Measuring urinary creatinine clearance obviates some of the problems of using serum creatinine as a marker of GFR. However, the reliability of creatinine clearance is greatly diminished by the variability in tubular secretion of creatinine and by the problem of incomplete urine collections especially in elderly people [19]. Therefore, many attempts have been made to mathematically transform or correct the serum creatinine so that it may more accurately reflect GFR. Under ideal conditions, GFR should be equal to the inverse of the serum creatinine multiplied by a constant representing the creatinine production. Variations in creatinine production due to age and sex-related differences in muscle mass have been measured and have been incorporated in formulas to improve the ability of serum creatinine to estimate GFR. The most widely used formula is that of Cockcroft and Gault [20] (Table 1). This equation is based upon 24-hour urine collections for creatinine clearance. Studies in an ambulatory elderly population have shown a rather good correlation between measured and estimated creatinine clearance by the Cockcroft-Gault formula [20-23]. However, the Cockcroft-Gault formula underestimates true GFR in the healthy young elderly [19,23]. More recently the Modification of Diet in Renal Disease (MDRD) formula (Table 1) was developed to predict GFR from serum creatinine in patients with chronic renal disease [24]. This formula was derived from a comparison with the renal clearance of ^{125}I-iothalamate.

Table 1: GFR prediction equations

Cockcroft-Gault formula[a]	{((140 - age) x weight) / (72x S_{cr}) }x (0.85 if female)
MDRD- formula[b]	170 x $S_{cr}^{-0.999}$ x $age^{-0.176}$ x (0.762 if female) x $(SUN)^{-0.170}$ x $Alb^{+0.318}$

S_{cr}, Serum creatinine level (mg/dl); SUN, serum urea level (mg/dl); Alb, serum albumin level (g/dl)
[a] creatinine clearance measurement (ml/min)
[b] Modification of Diet in Renal Disease formula: GFR measurement (ml/min/1.73 m²)

A recent analysis of the predictive performance of renal function equations for a chronic kidney disease population with normal serum creatinine levels revealed that the most accurate results were obtained with the Cockcroft-Gault equation, whereas the most precise formula was the MDRD Study equation. Unfortunately, the predictive power of these formulas was suboptimal for ideal patient care. These results suggest that

direct measurements of renal function, using either exogenous or endogenous filtration markers may be the best way to consistently obtain accurate assessment of renal function in these patients (Table 2) [25]. It cannot be assumed that formulas to predict renal function in one population of patients will be valid when applied to another population.

Table 2: Bias, precision, and accuracy of renal function equation. Adapted from Bostom et al [25]

Renal function equations*	**Precision**†	**Bias**‡	**Accuracy** (% within specified range of iohexol GFR)	
			30%	50%
Cockroft-Gault	0.17	-26.5	59	88
MDRD 1	0.31	-46.0	24	71
MDRD 2	0.29	-41.7	28	82
Jelliffe 1	0.28	-43.3	30	77
Jelliffe 2	0.26	-39.8	36	82
Mawer	0.04	-15.2	53	80
Bjornsson	0.17	-23.9	62	89
Gates	0.24	-38.6	35	86

†As assessed with the R^2 statistic
‡As assessed with the mean prediction error.
*ml/min/1.73 m^2

One of the recently studied endogenous markers to assess GFR is serum cystatin C [26,27]. Cystatin C is a low-molecular-weight protein produced by all nucleated cells, with a stable production rate (housekeeping gene product) and does not appear to be affected by lean body mass, fever or gender [28]. Cystatin C is freely filtered by the glomerulus, reabsorbed and then rapidly metabolised by proximal tubular cell [29]. The renal plasma clearances of cystatin C and ^{51}Cr-EDTA are virtually identical [30]. Because cystatin C is metabolised and not excreted, its urinary excretion rate cannot been used to measure clearance. Recent studies have suggested that cystatin C may be superior to creatinine as an endogenous marker for GFR [4,30,31]. Especially mild reductions in GFR were more readily detected by a change in cystatin C than creatinine [4,31-34]. However, the clinical relevance for cystatin C remains unclear in identifying impaired renal function in some patient groups [32,33]. Oddoze et al. showed in steady-state diabetes with early renal impairment that cystatin C is not better than serum creatinine [35]. Moreover, the housekeeping capacity from serum cystatin C is more and

more discussed as recent reports have shown ectopic production of cystatin C by carcinoma and the influence of pharmaca on the production of cystatin C [36,37]. Concerning the elderly population, Finney et al. [38] and Fliser et al. [39] found that cystatin C is a better marker for early changes in GFR than plasma creatinine concentration, at least in young elderly subjects (68 years old) with plasma creatinine concentrations within the normal range [39].

Recent guidelines of the National Kidney Foundation propose to use an estimation of GFR as the best index of the level of kidney function. The level of GFR should be estimated from prediction equations that take into account the serum creatinine concentration and some or all of the following variables: age, gender, race and body size. The MDRD study and Cockcroft-Gault equations seems to provide useful estimations of GFR in adults. Measurements of creatinine clearance using timed urine collections do not improve the estimate of GFR over that provided by prediction equations. Autoanalyzer manufacturers and clinical laboratories should calibrate serum creatinine assays using an international standard [40].

COST-BENEFIT OF DIFFERENT METHODS FOR THE MEASUREMENT OF GFR

The usefulness of a test to measure GFR is dictated not only by issues of accuracy and precision but also by cost, safety and convenience. No single test of GFR in the clinical setting is suitable for screening of renal impairment, follow-up of disease progression, estimating renal clearance of drugs to guide dosing and research on kidney diseases. The goal should be to select the most accurate test to answer the question in the most cost-effective and most convenient manner possible in the population under study. It is clear that a test used in clinical research should be more focusing on accuracy than on cost. On the other hand, a test for clinical screening has to be as accurate as possible at an acceptable cost.

A problem in estimating cost-effectiveness in our country is the problem of reimbursement for clinical biochemistry. Moreover, even when reimbursement is not taken into account, many factors determine the cost so that only an estimation of the cost can be given (Table 3).

Table 3: Estimation of cost-effectiveness

	Cost (€)	**Accuracy**
Measured creatinine clearance	3.5	±
Serum creatinine	1.7	+
Serum cystatin C	5	+
Cockcroft-Gault formula	1.7	++
$MDRD_1$-formula	2.6	++
MDRD abbreviated	1.7	++
Inulin clearance	20	Gold standard
^{51}Cr-EDTA	125	+++

Fluid and electrolyte balance

The age-related impairments in renal concentrating and sodium conserving abilities and the apparent deficit in thirst sensation [41] are associated with an increased incidence of volume depletion and hypernatraemia in the elderly [42]. Especially the frail elderly with systemic illness and dementia is at increased risk for severe water deficiency.

The age-related impairment in maximal diluting capacity and the enhanced osmotic release of ADH are associated with a high incidence of hyponatraemia in the elderly. Especially the combination of thiazide diuretics and hypotonic fluid administration is the major cause of hyponatraemia in geriatric patients [43].

The presence of a renal acidification defect in addition to a decreased activity of the renin-angiotensin-aldosterone system may lead to an increased incidence of type 4 renal tubular acidosis or syndrome of hyporeninemic hypoaldosteronism in the elderly [44]. Consequently, given the possible problems with chronic potassium adaptation with ageing, medications that inhibit the renin-angiotensin system may increase the risk of hyperkalaemia [45-47] (Figure 1).

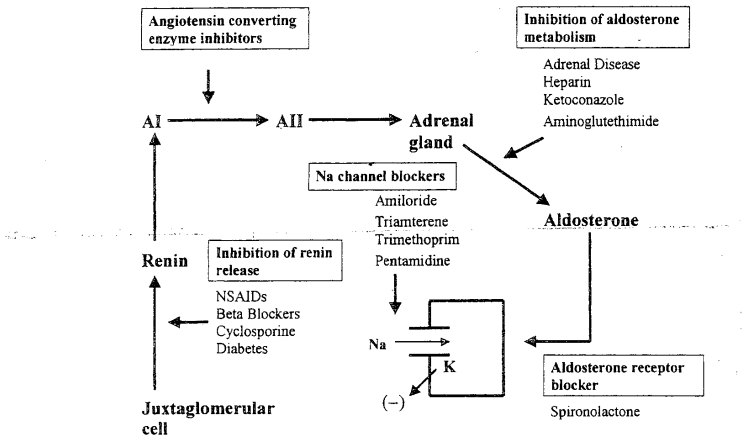

Figure 1 : Site of action of various pharmacological agents and disease states that can further impair activity of the renin-angiotensin-aldosterone axis and exacerbate hyperkalaemia in aged individuals with a progressive decline in renin and aldosterone levels; adapted from Choudhury et al [47]

AI, angiotensin; AII, angiotensin II; NSAIDs, nonsteroidal anti-inflammatory drugs

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Part 2

Assessment of GFR in the elderly

Chapter 5

Renal function in the oldest-old on an acute geriatric ward

Abstract

Aim: Evaluation of renal function and relation to risk factors for renal failure in very old patients admitted to an acute geriatric ward.

Methods: Retrospective chart review of patients aged 80 years and over, admitted to the acute geriatric ward from August 1998 till August 1999. Recorded data were: age, gender, previous medical history, primary diagnosis, medication use, weight, serum creatinine, BUN, sodium, potassium, cholesterol, urine and ultrasound of the kidney. The creatinine clearance was estimated by the Cockcroft-Gault formula, the glomerular filtration rate by the MDRD equation.

Results: 220 (60 males/160 females) patients were included. The mean serum creatinine on admission and discharge was 1.17 ± 0.45 mg/dl and 1.11 ± 0.48 mg/dl respectively. The mean estimated creatinine clearance in the very old was 38.11 ± 12.04 ml/min on admission and 39.00 ± 11.01 ml/min on discharge. Renal failure arbitrarily defined as an estimated creatinine clearance on admission of less than 30 ml/min was found in 26.4% of the patients. Only a significant correlation between failure to thrive and renal failure was found ($P<0.0001$).

The correlation coefficient between the Cockcroft-Gault and the MDRD formula was $r=0.66$ ($P<0.0001$); between the Cockcroft-Gult and the reciprocal serum creatinine was $r=0.60$ ($P<0.0001$) and between the MDRD and the reciprocal serum creatinine was $r=0.87$ ($P<0.0001$).

Conclusion: The weak correlation between the Cockcroft-Gault and other estimations of GFR in the acutely ill elderly, confirms the need to have a reliable estimation of glomerular filtration rate in the elderly.

Renal failure defined as a Cockgroft-Gault <30ml/min is found in 26.4% of the old old admitted to an acute geriatric department. The elderly with renal failure is more often admitted for failure to thrive. No great differences were observed between renal function on admission and discharge.

Introduction

The number of people aged 80 years and over (oldest-old) is expected to increase almost 6-fold by the year 2050. Moreover, the proportion of oldest-old will be 10 per cent or higher in most Western countries [1]. Geriatric departments will thus be faced with a higher incidence of health care problems in this segment of the population. Cross-sectional and longitudinal studies of healthy adults suggest a progressive decline in glomerular filtration rate with about 1 ml/min/year [2-4]. These studies included only a few oldest-old subjects and they showed also a great variability in renal function in the group of healthy elderly. Interestingly, about 30% of the elderly individuals showed no decrease in creatinine clearance [2-5]. Compared to younger patients, renal function plays an even more important role in drug clearance with an increasing risk of adverse drug reactions in very old patients. In addition the decrease in renal function probably decreases their fitness and wellbeing [6].

As kidney function plays an important role in drug clearance [5], the clinician wants a reliable estimation of the glomerular filtration rate as soon as the elderly is admitted to a geriatric ward. In addition, as far as we know, data on renal function in this segment of acutely ill very old patients are lacking. This paper is an attempt to estimate the prevalence of significant renal dysfunction and to determine some factors associated with renal insufficiency in patients admitted to an acute geriatric ward in a tertiary university hospital.

Materials and methods

All charts of patients aged 80 years and older, who were admitted between August 1998 and August 1999 to the acute geriatric ward of the University Hospital of Ghent were retrospectively reviewed. Clinical data including age, gender, previous medical history, primary diagnosis, date of admission to and discharge from the hospital or death, use of medication, body weight, biochemical markers on admission and discharge such as serum creatinine, BUN, sodium, potassium, cholesterol, C-reactive protein, urinalysis and results of the ultrasound of the kidneys were obtained from the charts. The creatinine clearance was estimated using the Cockcroft-Gault equation [7]. The glomerular filtration rate (GFR) was estimated using three different equations, as described by Levey et al (Table 1): a modified Cockcroft-Gault formula, a modified reciprocal serum creatinine and one recent described formula by the Modification of Diet in Renal Disease Study Group (MDRD-formula) [8].

Statistical methods. All results are presented as mean values ± SD. Two-tailed student's *t*-test and Mann-Whitney *U*-test were used for continuos variables. The

Bonferroni correction was applied for multiple testing effects. When appropriate the χ^2 test, Pearson or Fisher exact tests were used to compare categorical variables between patients with renal failure and normal renal function. Logistic regression analysis was used to identify variables predicting renal function. Linear regression formulas, correlation coefficients and Bland & Altman plot were used to compare the different methods of GFR estimation.

Table 1 : Equation to predict glomerular filtration rate

Cockcroft-Gault formula
GFR= 0.84 x (((140-age)xweight/72xserum creatinine) x0.85 if female)
Reciprocal serum creatinine
GFR= 0.69 x (100/serum creatinine)
MDRD formula
GFR= 170 x (serum creatinine)$^{-0.999}$ x (age)$^{-0.176}$ x (0.762 if female) x (SUN)$^{-0.170}$ x (Alb)$^{+0.318}$

serum creatinine (mg/dL); SUN=serum urea nitrogen (mg/dL); Alb=serum albumin (g/dL)

Results

A total of 220 patients (60 males and 160 females) older than 80 years were studied. Their mean age was 86.3 ± 3.9 years. The median hospitalisation duration was 14 days (range from 3 to 77 days). The in-hospital mortality was 7.5%.

The reasons for admission to the geriatric ward and the previous medical history are listed in Table 2.

The values for serum creatinine on admission and discharge in these very old patients (n=152) are represented in figure 1. The mean serum creatinine on admission was 1.17 ± 0.45 mg/dl, at discharge 1.11 ± 0.48 mg/dl. The creatinine clearance was calculated using the Cockcroft-Gault equation (n=114). The distribution of the estimated creatinine clearance on admission and discharge is shown in Figure 2. The mean creatinine clearance on admission was 38.11 ± 12.04 ml/min while at discharge a mean value of 39.00 ± 11.01 ml/min was calculated. This small difference is not significant.

Table 2 : Mortality, reason for admission, previous medical history and their correlation with renal failure

	Cockgroft-Gault < 30 ml/min (total n =42)	**Cockgroft-Gault ≥ 30 ml/min** (total n = 117)	*P*
Mortality	1	3	NS
Reason for admission			
Failure to thrive*	30	42	0.00008
Falls-locomotoric disorders	2	16	NS
Infectious diseases	7	13	NS
Dementia –behavioural	2	8	NS
Heart failure	3	8	NS
Previous medical history			
Cardiovascular diseases	21	31	NS
Arterial Hypertension	28	83	NS
Diabetes mellitus	6	16	NS
Nephrolithisasis ; UTI	5	16	NS

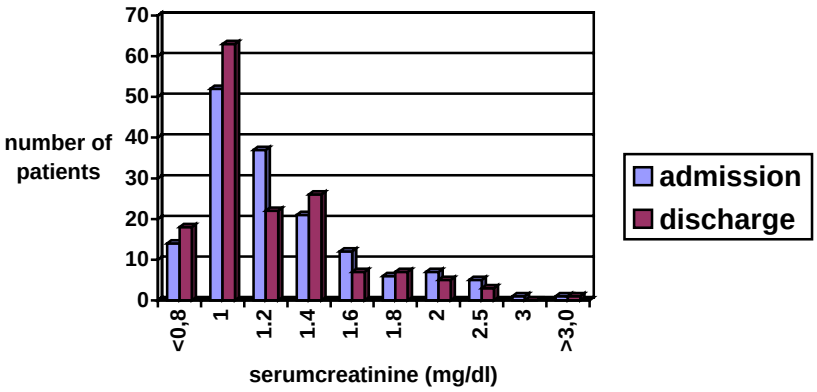


Figure 1: Distribution of serumcreatinine on admission and at discharge from the hospital

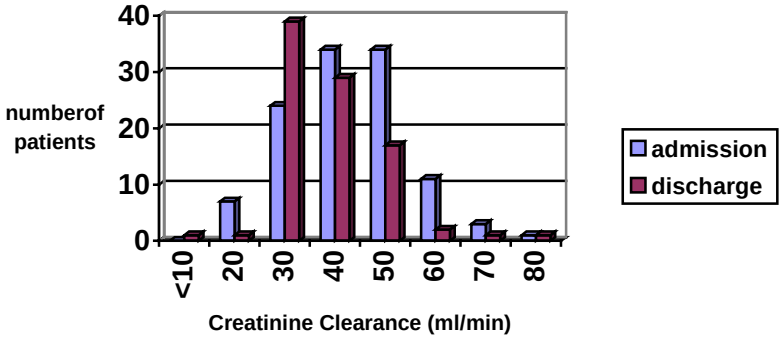


Figure 2: Distribution of the estimated creatinine clearance by the Cockgroft-Gault formula on admission and at discharge from the hospital

Renal failure was arbitrarily defined as a calculated creatinine clearance lower than 30 ml/min. Using this definition 26.4% of the patients had renal failure on admission. Age, gender, length of hospital stay and in-hospital mortality were not correlated with renal failure. From the reasons for admission, only failure to thrive was significantly correlated with renal function (P=0.01) and renal failure (P<0.0001), independent of other comorbidities leading to failure to thrive (Table 3).

Table 3: Comorbid diseases in patients with failure to thrive

	Cockcroft-Gault <30 ml/min (n=30)	**Cockcroft-Gault ≥ 30 ml/min** (n=42)	*P*
Heart failure	0	21	NS
Chronic ischemic heart disease	11	13	NS
Cerebrovascular accident	3	5	NS
Dementia	8	13	NS
Diabetes mellitus	5	6	NS
Infectious diseases	16	24	NS

Arterial hypertension was defined, according to the WHO criteria as a systolic blood pressure ≥140mmHg and/or a diastolic tension ≥90mmHg or a mean arterial pressure (MAP) ≥107mmHg and as treated hypertension. There was no significant

correlation between the presence of renal failure and treated arterial hypertension. In the patients with a calculated creatinine clearance >50ml/min (n=19), none had diastolic hypertension, while 42% (n=8) had systolic hypertension. No correlation was found between the use of ACE inhibitors (n=35), NSAID (n=17), diuretics (n=96) and renal failure. A plasma BUN/creatinine ratio on admission greater than 20 was found in 119 patients (54.3%). The mean plasma BUN/creatinine ratio was statistically not different on admission (23.13 ± 8.52) and at discharge (21.76 ± 8.65). There was a significant correlation (r=0.529; P<0.0001) between this ratio and renal function. However no significant correlation was found between the presence of a plasma BUN/creatinine ratio > 20 and the presence of renal failure or the use of diuretics.

Electrolyte disorders such as hypokalemia (potassium <3.5mmol/l), hyperkalemia (potassium >5.5mmol/l), hyponatremia (sodium <135mmol/l) and hypernatremia (sodium >145mmol/l) were found in 26, 9, 46 and 4 patients, respectively. There was no difference in frequency of electrolyte disorders in patients with renal failure.

Urine microscopy was obtained in 153 patients. Neither leucocyturia, defined as > 5 white blood cells/high power field (n=102), erythrocyturia, defined as >5 red blood cells/high power field (n=93), proteinuria, defined as >0.2g/l protein (n=53), glucosuria, defined as >0.05g/l glucose (n=20) nor a positive urine culture, defined as > 1 10^5 organisms/ml (n=31) were associated with renal failure.

Renal ultrasound was performed in 124 patients. A significant correlation (P=0.04) was found between abnormal ultrasound findings (especially differences in kidney size, although no exact data on kidney size is available) and renal function. This correlation was not longer significant when restricted to elderly with renal failure.

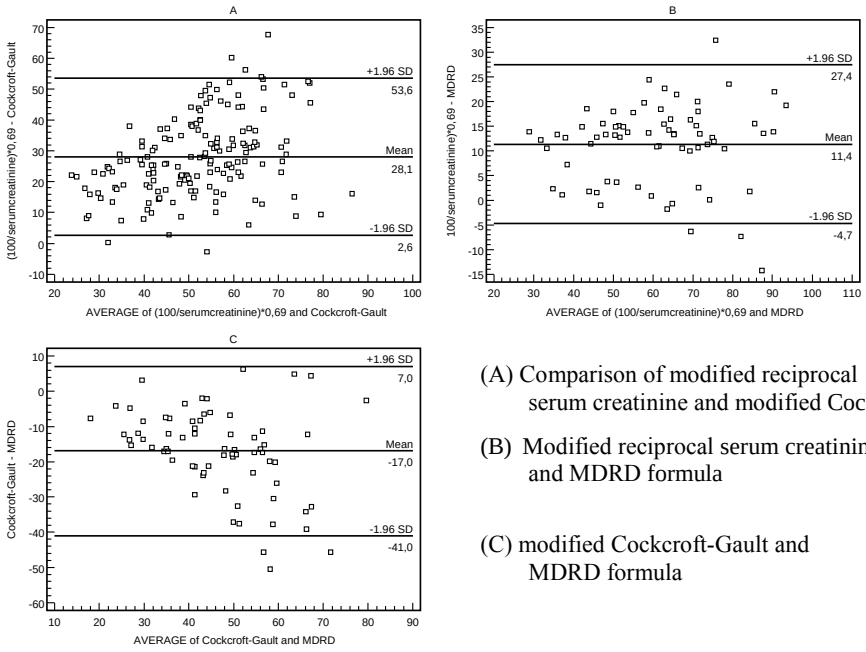
The estimated glomerular filtration rate by the MDRD-formula and the reciprocal for serumcreatinine was obtained in 69 patients, as serum albumin was not available for the other patients on admission.

Table 4 shows the correlation coefficients and regression lines between the different methods of estimation of GFR. Comparison between the different methods by Bland & Altman plot shows only a weak correlation between the modified Cockcroft-Gault, the MDRD formula and the modified reciprocal of serumcreatinine (Figure 3).

Table 4 : Correlation coefficients and regression lines for the different methods of GFR estimation

	1/creatinine	MDRD formula	Cockcroft-Gault formula
1/creatinine		*r* = 0.87*	*r* = 0.60*
		Y = -1,67 + 58,94*X	Y = 21.72* + 17.54 **X
MDRD formula	*r* = 0.87*		*r* = 0.66*
	Y = 0.24* + 0.01*X		Y = 10.79*** + 0.49*X
Cockcroft-Gault formula	*r* = 0.60*	*r* = 0.66*	
	Y = 0.77* + 0.004**X	Y = 21.49* + 0.88*X	

r = correlation coefficient ; * $P < 0.0001$; ** $P = 0.0002$; ***$P = 0.008$; Regression line with Y= parameter in heading of the column and X= parameter in heading of the row



(A) Comparison of modified reciprocal serum creatinine and modified Cockcroft Gault

(B) Modified reciprocal serum creatinine and MDRD formula

(C) modified Cockcroft-Gault and MDRD formula

Figure 3 : Comparison of different methods of GFR estimation by Bland & Altman plot

Discussion

Serum creatinine concentration remains the most widely used index of renal function in clinical practice [9]. In the very old this measure is not useful as a marker of renal function because creatinine production is low as muscle mass decreases with aging [10,11]. Another measurement used in many clinical studies is the creatinine clearance, calculated from the 24-hour renal excretion of creatinine [9,12]. Goldberg et al. found more variations in 24-hour creatinine clearance in the elderly than physiologically possible [13]. Larsson et al. found no correlation between EDTA clearance and 24h urinary creatinine clearance [5].

In clinical practice the glomerular filtration rate is often estimated by using the Cockgroft-Gault equation. It is remarkable to note that in the original report where the Cockcroft -Gault equation was validated, only 17 patients out of a total of 249, over the age of 80 years were included [7]. Goldberg et al. found that the correlation between 24h urinary creatinine clearance and the estimated value of creatinine clearance, using the Cockcroft-Gault equation was better for the elderly than for younger patients [13]. These findings were confirmed in a similar study of Friedman et al. [14]. Goldberg et al. also found that the Cockcroft-Gault formula tends to overestimate creatinine clearance at low levels and tends to underestimate the clearance at normal glomerular filtration rate [13]. This underestimation was confirmed by Fliser et al [5].

The creatinine clearance in the present study was estimated by the most widely used formula, namely the Cockcroft-Gault equation. To compare with methods of GFR estimation (as GFR is lower than creatinine clearance by tubular secretion of creatinine), a correction factor of 0.84 was added as described by Levey [8].

One could argument that these values were calculated in acutely ill people on admission, where the presence of extrarenal comorbidities may have influenced renal function. We especially wanted to focus on this population since it is this type of elderly people that is seen on an acute geriatric ward by the clinician at the moment decisions on therapy has to be taken. Moreover in our population, renal function seems not to change during hospital stay.

The mean calculated creatinine clearance in our study was 38.11 ± 12.04ml/min. These results are similar to the results obtained in the study of Cockcroft-Gault and Friedman [7,14].The mean serum creatinine (1.17 ± 0.45mg/dl) was relatively low probably due to a greater proportion of women in our study. As expected, a wide scatter was found in these very old and acutely ill people. In other studies, creatinine clearances of more than 80 ml/min were observed in healthy elderly [3,4]. We did not find these “normal values” probably because we did not study healthy elderly. Moreover the Cockcroft-Gault formula may underestimate the creatinine clearance in elderly patients with low lean body mass or normal renal function [6,13].

The MDRD formula seems to provide a more accurate estimate of glomerular filtration rate in chronic renal disease [8]. However this formula has as yet not been validated in the very old. The weak correlation between the Cockcroft-Gault formula and the MDRD formula in the present study can be due to the accumulation of errors in both calculated estimations. Further prospective studies looking for the equation which is most useful in an acutely ill elderly population seem warranted.

The finding that patients with renal failure, as defined in this study, have significantly more problems with well-being, expressed as more admissions for failure to thrive, independent of other comorbidities, is interesting. This result has to be confirmed in further prospective studies.

There was no indication that very old patients with renal failure had more arterial hypertension, peripheral arterial diseases, heart failure and diabetes. However, the present studied population is probably too small to allow definite conclusions. Furthermore we did not study a reference population. Studies in patients with an age ranging from 65 to 80 years old (young elderly) have indeed shown a significant correlation between hypertension, vascular disease, diabetes, heart failure and renal failure [15-22]. Further prospective and longitudinal studies in the very old are necessary to look for the influence and treatment of these diseases on the progression of renal failure.

In our hands, patients with renal failure have no higher mortality rates on the geriatric ward compared with those with “normal” renal function. This is probably due to the fact that much attention was paid to the hydration status, the presence of electrolyte disorders and to the nutritional status of the patients.

In conclusion, a great variation in creatinine clearance, even in the presence of a low serum creatinine was observed in very old patients who were admitted to an acute geriatric ward. Correct interpretation of the renal function remains difficult in this population since accurate measurement of GFR with inulin clearance or isotopes is not feasible on a routine basis. Moreover, the different formula's developed to estimate GFR seem to be of little value in the acutely ill elderly population. In view of the frequent problems with drug overdose in these patients with impaired renal function, we recommend regular monitoring of serum concentrations especially of drugs with a narrow therapeutic range.

Renal failure has a significant influence on the level of functioning and the nutritional status in the very old. As the ultimate goal of medical intervention, particularly in geriatrics, is to maintain the independency of the elderly, we should be aware of the importance of avoiding renal failure especially in the oldest-old.

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Chapter 6

Serum cystatin C concentration compared with other markers of glomerular filtration rate in the old old

Abstract

Objectives: To assess serum cystatin C, compared with other markers of renal function as a marker of renal function in the old old (aged 85 and older).

Design: A cross-sectional analysis of data obtained in medically stable people, aged 70 years and older in a geriatric ward at a university hospital.

Setting: University hospital in Belgium.

Participants: Forty-eight patients (17 men, 31 women) mean age ± standard deviation 84.4 ± 6.3 without acute illness or overt malignancy 7 days after admission were included. Twenty-five patients were aged 85 and older.

Measurements: Blood samples and 24-hour urine collections were obtained from each patient to determine serum creatinine, serum cystatin C levels, serum albumin and creatinine clearance. Glomerular filtration rate (GFR) was estimated using the Cockcroft-Gault formula and the Modification of Diet in Renal Study Group (MDRD) formula. On the same day, clearance of ^{51}Chromium ethylenediamine tetraacetic acid was performed in all patients as the criterion standard of GFR.

Results: Serum creatinine (r = 0.68), serum cystatin C (r = 0.62), urinary creatinine clearance (r = 0.57), the Cockcroft-Gault formula (r = 0.82) and the MDRD-formula (r = 0.65) correlated significantly with GFR (P < .0001). Regression analysis showed that serum cystatin C and serum creatinine were comparable markers of renal function (Y=0.442+0.007*GFR and Y=0.494+0.01*GFR respectively). Receiver operating characteristic analysis showed a similar area under the curve for serum cystatin C and serum creatinine (P = 0.5) in detecting renal impairment (GFR <80ml/min). The Cockcroft-Gault formula provides a good estimation of GFR when the GFR is less than 60 ml/min (Y=1.11+1.04*GFR). When the GFR is greater than 60ml/min, the Cockcroft-Gault formula underestimates GFR (Y=11.01+0.66*GFR). In patients aged 85 years and older, a slight decrease in GFR (51.8±21.3ml/min vs. 65.2±34.3ml/min in patients aged 70-84; P = .10) is observed. This is reflected by a non-significant increase in serum cystatin C (P = .06); whereas serum creatinine is identical in both groups (P = .88).

Conclusion: Serum cystatin C, serum creatinine, the Cockcroft-Gault formula, the MDRD-formula and urinary creatinine clearance are comparable markers of renal function in the overall older population. The Cockcroft-Gault formula underestimates renal function in older people with GFR greater than 60 ml/min. In our study, serum cystatin C was not superior to serum creatinine in the detection of renal impairment.

Introduction

The effect of aging on the glomerular filtration rate (GFR) is well documented. Cross-sectional and longitudinal studies suggest a progressive decline in GFR of approximately 1mL per minute per year, but the rate of decline is variable with usual aging. In some studies, 30% of the older individuals showed no decrease in creatinine clearance over time [1-3]. Because many drugs undergo renal clearance, a quick and accurate estimation of GFR is important as soon as an older patient is admitted [4].

The measurement of the clearance of a substance is one of the most convenient methods for the assessment of GFR [5,6]. The criterion standard method of measuring GFR is the determination of the clearance of exogenous markers such as inulin, isotopically labelled compounds such as iothalamate, chromium ethylenediamine tetraacetic acid (^{51}Cr-EDTA), diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) and the contrast medium iohexol [6]. These methods are impractical for use in a hospitalized geriatric population. GFR can also be assessed by measurement of the clearance of endogenous markers such as creatinine and urea, or by determination of their plasma concentration or their reciprocal, mainly of serum creatinine, [7] and serum cystatin C [6-17]. These markers are rapidly and easily assayed in the clinical laboratory. Cystatin C is a non-glycosylated, low molecular weight protein, containing 120 amino acids. Because the human cystatin C gene is a house-keeping type, serum cystatin C is steadily produced by all human nucleated cells, even in the presence of inflammation, and is not dependent on muscle mass, body mass index (BMI), or gender, as shown by previous studies performed in healthy older people [9,13-15]. This is in contrast to serum creatinine, the most widely used index of renal function in clinical practice, which is not very accurate in the very old because creatinine production decreases as muscle mass decreases with age. The accuracy of urinary creatinine clearance is affected by the problem of incomplete urine collections, especially in older people [18-20]. Several equations as the Cockcroft-Gault and more recently the Modification of Diet in Renal Study Group (MDRD) formula are available to estimate creatinine clearance from a patient's age, body weight, and serum creatinine [21,22].

This study attempts to explore the correlation between and usefulness of different methods of assessment of GFR, especially serum cystatin C against a reference

procedure employing an exogenous clearance marker in a convenience sample of very old hospitalized patients.

Patients and methods

Forty-eight patients (17 men, 31 women) admitted to the acute geriatric ward of the University Hospital of Ghent were included. The mean age ± standard deviation was 84.4 ± 6.3, 25 patients were aged 85 years and older (old old), 23 patients were aged between 70 to 84 (young old). The ethical committee of the University Hospital approved this study and all patients gave written informed consent. Patients were eligible for inclusion in the study if they were without urinary incontinence, dementia, or malignancy and were fully recovered from acute illness and dehydration by Day 7. All patients were on a standard diet containing 0.8 gram proteins/kg body weight.

At the day of the study, blood samples and 24-hour timed urine collections, carefully supervised by a nurse, were obtained from each patient to determine serum creatinine, serum cystatin C levels, serum albumin, and creatinine clearance. On the same day, clearance of ^{51}Cr-EDTA was performed in all patients as a reference for GFR assessment.

An estimation of creatinine clearance was made using the Cockcroft-Gault formula, GFR was also estimated using the MDRD-formula.

Serum and urinary creatinine levels were measured using a compensated calibrator for the Jaffé method, rate-blanked on a Roche/Hitachi 747 analyzer (Boehringer Mannheim, Germany). Serum cystatin C and serum albumin levels were analysed with the Dade-Behrings method using the Behring Nephelometer II (Marberg, Germany).

The plasma clearance of the radionucleotide marker was performed after intravenous injection of a standard dose of 3.7 MBq of commercially available ^{51}Cr-EDTA (Dupont Fleurus, Belgium) in 5mL physiological saline. The precise value of the dose injected was obtained by weighing the syringe before and after injection. Four blood samples were obtained 120, 180, 300 and 420 minutes after injection and the GFR was determined using the slope-intercept method as previously described [23].

Creatinine clearance, ^{51}Cr-EDTA clearance and calculated clearance using Cockcroft-Gault, and MDRD-formulas were adjusted to body surface area (BSA). The formula of Du Bois and Du Bois was used to calculate BSA ($BSA_{(m^2)}=0.007184*(\text{height}_{(cm)})^{0.725}*(\text{weight}_{(kg)})^{0.425}$) [24].

STATISTICAL ANALYSIS

The Medcalc package (Medcalc, Mariakerke, Belgium) was used for statistical analysis. Data are presented as mean ± standard deviation. A *P*-value < 0.05 was

considered to be statistically significant. The relationship between different methods of GFR assessment was explored using linear regression models and Passing and Bablok regression. Multiple linear regression analysis was used to examine the relationship between height, weight, BMI, gender, and serum creatinine and serum cystatin C. If the F-test in the analysis of variance is small (P <0.05) the hypothesis that there is no relationship is rejected and the multiple correlation coefficient is statistically significant. To assess the diagnostic accuracy of serum cystatin C and serum creatinine, the receiver operating characteristic (ROC) plots were performed.

Results

CORRELATION AMONG MARKERS OF GFR

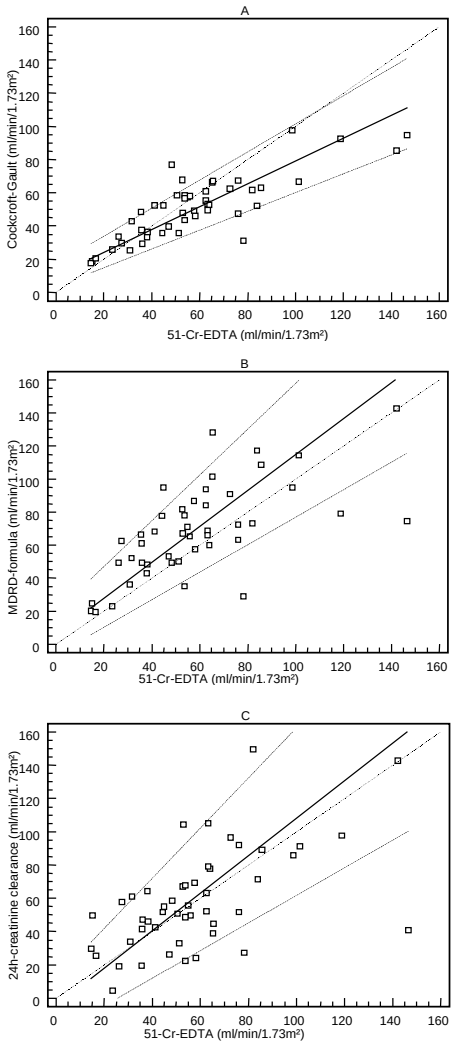
Table 1: Comparison between chromium ethylenediamine tertaacetic acid (^{51}Cr-EDTA) and different methods of glomerular filtration rate (GFR) estimation

Parameter	Mean ± SD	$r^{\dagger}$	Regression analysis[§]
^{51}CR-EDTA, ml/min[*]	58.2± 28.8		
1/Serum cystatin C, l/mg	0.92± 0.31	0.62	Y = 0.442 + 0.007*X
1/Serum creatinine, dl/mg	1.00± 0.48	0.68	Y = 0.494 + 0.01*X
Cockcroft-Gault, ml/min[*]	51.5± 19.2	0.82	Y = 10.09 + 0.69*X
MDRD, ml/min[*]	68.7± 28.2	0.65	Y = 5.57 + 1.09*X
Ur Creat clear, ml/min[*‡]	58.9± 30.5	0.57	Y = -4.81 + 1.13*X

[*] standardised for body surface area
[†] P<0.0001
[‡] On 24-hour urine sample
[§] Passing and Bablok regression analysis : Y = method of GFR estimation, X= ^{51}Cr-EDTA clearance, standardised for body surface area, ml/min

Results for the different methods of estimation of GFR and correlation with ^{51}Cr-EDTA using the correlation coefficient and linear regression are shown in Table 1. All markers of GFR were significantly correlated with ^{51}Cr-EDTA as a reference method of GFR. No significant difference was found between the different methods of GFR assessment. Interestingly, the Passing and Bablok regression (Figure 1) shows that the formula of Cockcroft-Gault provides a good estimation of GFR in older patients when GFR is less than 60 ml/min (Y=1.11+1.04*GFR). When the GFR is greater than 60ml/min, the Cockcroft-Gault formula underestimates GFR (Y=11.01+0.66*GFR). Considering the regression lines, the MDRD formula and the 24h creatinine clearance related better to the ^{51}Cr-EDTA even if the correlation coefficient (r = 0.66 and r = 0.57

respectively; $P < 0.0001$) are lower than for the Cockcroft-Gault formula (r=0.82; P<0.0001).



$r = 0.82$

$P < 0.0001$

$r = 0.65$

$P < 0.0001$

$r = 0.57$

$P < 0.0001$

Figure 1: Regression formula between ^{51}Cr-EDTA and (A) Cockcroft-Gault formula, (B) Modification of Diet in Renal Study Group (MDRD) formula and (C) 24h-creatinine-clearance

Regression line (_____) ; confidence interval (__ __ __) and identity line (-----).

SERUMCYSTATIN C AS MARKER OF RENAL FUNCTION

The mean serum cystatin C in our study population was 1.22 ± 0.42mg/l (range 0.53-2.51mg/l). The rise in serum cystatin C with age, although not statistically significant, was comparable with the decrease in GFR as measured with ^{51}Cr-EDTA. Multiple regression analysis shows that serum cystatin C is not dependent on BMI (P = 0.31) or gender as an estimator of GFR but that serum creatinine is dependent on these parameters (P = 0.03 and P = 0.02, respectively).

The regression analysis and the correlation coefficient between ^{51}Cr-EDTA clearance (X) and the reciprocal of serum cystatin C or the reciprocal of serum creatinine are comparable (Y=0.442+0.007*X; r = 0.62 and Y=0.494+0.01*X; r = 0.68, respectively). Diagnostic sensitivity in predicting decline in renal function (using a cut-off for GFR of 80mL/min) of serum cystatin C has been assessed using ROC analysis. Serum cystatin C (cut-off of 1.09mg/L) detects renal impairment (GFR<80 ml/min) with a sensitivity of 73 %. Alternatively, serum creatinine (cut-off of 0.85mg/dl) detects the same impairment with a sensitivity of 57% (specificity of 100% for both). Nevertheless, this difference is not statistically significant because the area under the curve (AUC) for serum cystatin C and serum creatinine is not different (AUCs were 0.931 and 0.896 respectively) (P = 0.5). Moreover, the correlation coefficient between serum cystatin C and GFR for patients with a GFR greater than 80 ml/min (r = 0.06) and for those with a GFR less than 80ml/min (r = 0.38) is not significantly different (P = 0.52).

RENAL FUNCTION IN THE OLD OLD

The overall mean ^{51}Cr-EDTA was 58.2 ± 28.8ml/min (range 14.6-146.5ml/min). Eight people had a GFR greater than 80 ml/min. There was a slight difference in GFR between the young old (65.2 ± 34.3mL/min) and the old old (51.8 ± 21.3mL/min), although not statistically significant (P = 0.10). This decrease is reflected by the rise in serum cystatin C (1.07 ± 0.31mg/l and 1.28 ± 0.39mg/l respectively; P = .06). No significant difference in serum creatinine was observed (0.99 ± 0.54mg/dL and 1.02 ± 0.43mg/dl respectively; P = 0.88). Only the Cockcroft-Gault formula shows significant decline in GFR (58.5 ± 21.9ml/min and 45.1 ± 13.8ml/min, respectively; P = 0.03).

Discussion

In this study of very old hospitalized patients, the widely used Cockcroft-Gault formula underestimates renal function in the elderly with GFR greater than 60ml/min, or 40% of the study population. This was also demonstrated in previous studies with healthy older people [15,18-20]. Because this segment of the population is growing, the problem of underestimation of renal function becomes more pertinent. As clinicians we

should be aware of this problem, especially in dosing renally excreted drugs such as antibiotics where doses that are too low may induce resistance.

The development of an accurate and rapid automated analytical method to measure cystatin C within 6 minutes (N-latex cystatin C assay on a Dade Behring Nephelometer II system), allows its routine use. This method demonstrates good analytical performance with satisfactory reproducibility (coefficient of variation = 1.71%-3.77%) [6]. Serum cystatin C is steadily produced by all human nucleated cells and is not dependent on muscle mass, BMI or gender, as confirmed by this and previous studies [9,14,16]. There is some controversy about cystatin C levels in patients with malignancy, so no patients with overt malignancy were included in our study [10,11]. Several studies found an increase in serum cystatin C with aging, comparable with a decrease in GFR [13-15]. In our study, the slight decrease in mean GFR for the old old, although not statistically significant, was confirmed by an increase in mean serum cystatin C.

There was no difference between serum cystatin C and serum creatinine in the overall estimation of GFR. Recently Fliser et al. showed a considerably better correlation for serum cystatin C in the older people [15]. In this study, only subjects with normal serum creatinine and GFR within the lower normal range were examined. In addition, other studies found that serum cystatin C is more sensitive in detecting an early decrease in GFR [9,11-15]. Our study could not confirm the superiority of serum cystatin C in detecting early renal impairment. Also, Bökenkamp et al. and Randers et al. found no significant difference between serum cystatin C and serum creatinine as marker of renal function [16,17]. Coll et al. confirmed our finding that there is no difference in area under the curve for serum cystatin C and serum creatinine in detecting renal impairment [12]. A possible explanation for the different results between the studies is that there is a difference in the study population. Our population was an older population with a wide range of renal function. Only a few patients had GFR within the normal or lower normal range. This can explain the different results of Fliser et al. [15]. Moreover, Coll et al. also found differences between serum creatinine and serum cystatin C only in the population with lower normal to normal GFR [12]. There are also large differences in the correlation coefficient between GFR and serum creatinine. Newman et al. and Fliser et al. found a lower correlation coefficient between GFR and serum creatinine than we did [9,15]. The differences between serum creatinine and GFR suggest that the methods used in some studies are less sensitive for pseudochromogens in serum. Because the cost for the determination of serum cystatin C is 100-times that of the cost for serum creatinine, the use of serum cystatin C is not recommended in an overall older population on a geriatric ward. Therefore, other methods and formulas still have a place in the assessment of GFR in the older people. No significant difference

could be found between the studied formulas. The Cockcroft-Gault formula underestimates renal function in older people with GFR greater than 60mL/min, because of too strong an effect of age in the formula. The MDRD formula was developed for use in patients with impaired renal function [22]. Interestingly, regression analysis shows only a slight overestimation of GFR in the older people with this formula, but more research should be conducted before using this formula in the old old.

In conclusion, serum cystatin C is comparable with serum creatinine as a marker of renal impairment in older people on a geriatric ward. The superiority of serum cystatin C in detecting early renal impairment could not be confirmed by our data. In the studied population of medical stable older people after admission to the hospital for an acute illness, there is no clear evidence of a clinical benefit of serum cystatin C. In the group of older people with moderate to severe renal impairment, the Cockroft-Gault formula is very useful for the assessment of GFR.

The clinician taking care for an older population must be aware of the advantages and limits of the different methods of estimating GFR. For routine clinical practice and when there is a clinical indication, estimation of GFR should be made by using at least two different methods; in the case of discrepancy, a more sophisticated method such as the plasma clearance of ^{51}Cr-EDTA should be applied.

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Chapter 7

Reevaluation in adults and children of formulas for predicting creatinine clearance using compensated creatinine methods

In clinical practice, glomerular filtration rate (GFR) is the most important parameter for the evaluation of renal function [1]. Dosages of drugs that are eliminated by glomerular filtration, are often based on GFR. At present, the most reliable methods that allow accurate assessment of overall GFR require intravenous administration of exogenous compounds and are both cumbersome and expensive. In clinical practice, creatinine clearance (CrCl) is widely accepted as a simple measure of GFR. However, CrCl systematically overestimates GFR because creatinine is freely filtered by the glomerulus and is also secreted by the proximal tubule. In the earliest methods, serum creatinine was assayed by the Jaffé reaction after deproteinization, eliminating the pseudo-chromogen effect of proteins [2]. Similarly, the first automated methods used dialysis membranes to prevent interference from plasma proteins. Today, however, analyzers use undiluted serum and plasma, making them subject to the so-called "protein error" [3]. This produces a positive difference of ~27 μmol/L creatinine compared with HPLC methods [4-7]. Because urine contains relatively little or no protein, the protein error affects only creatinine determinations in serum. Therefore, CrCl is underestimated when creatinine methods affected by protein error are used. This underestimation has been stated to be compensated by the overestimation attributable to tubular secretion of creatinine. However, studies confirming this statement are lacking.

In compensated Jaffé methods, the values assigned to the calibrator set point are adjusted to minimize the pseudo-creatinine contribution of proteins. The result is that compensated methods produce lower creatinine values. Alternatively, the protein error can be avoided by use of enzymatic creatinine methods. Collection of timed urine for CrCl is often a major source of error; therefore, simple formulas have been introduced to estimate GFR based on serum creatinine concentration, age, gender, body weight, and body length [8-13]; these formulas thus do not require urine collections. However, it is not always clear which creatinine method was used when applying these formulas.

We examined 80 patients (33 males (age range, 51-74 years) and 47 females (age range, 56-81 years)), referred for nuclear medicine clearance (^{51}Cr-EDTA clearance) before chemotherapy because of renal insufficiency or for nephrologic evaluation (geriatric patients). We also examined 27 pediatric patients [15 males (7-17 years) and

12 females (6-17 years)], in whom inulin clearance has been determined for nephrologic evaluation of a nephroblastoma or because they had received nephrotoxic drugs. Clearance determinations succeeded in 23 children. In 4 children, urine collections were inadequate.

The elimination rate of ^{51}Cr EDTA was measured according to the methods of Chantler and co-workers [14,15] and Van de Wiele et al. [16]. Inulin clearance was determined by an enzymatic assay [17]. Serum creatinine was measured by a standard HPLC method [18]. Serum and urinary creatinine were measured on a Modular P analyzer with commercial reagents (Roche): (a) a kinetic rate-blanked Jaffé assay based on the modified kinetic alkaline picrate method [19]; (b) a kinetic rate-blanked Jaffé compensated assay for reactive proteins according to manufacturer's instructions; (c) an enzymatic assay using the Creatinine Plus method [20-22]. Serum total protein, albumin, urea nitrogen, uric acid and total bilirubin levels were measured with the use of commercial reagents (Roche).

CrCls were calculated according to the formula: *UV/Pt*, where *U* represents the urinary creatinine concentration (µmol/L), *V* is urinary collection volume (mL), *P* is serum creatinine concentration (µmol/L), and *t* is urinary collection time (1440 min). In children, CrCl values were corrected for body surface. CrCls were also calculated according to the Cockroft-Gault method [8] and the abbreviated Modification of Diet in Renal Disease Study (MDRD) method [9,10] in adults and the method of Schwartz and co-workers [11-13] in children.

Values are expressed as the median (interquartile range). Methods were compared using the Pearson correlation coefficient. Correlation studies were performed according to Bland and Altman [23].

Median serum creatinine concentrations in adults were 183,2 (84,8–204,5) µmol/L by HPLC; 173,8 (72,3–207,7) µmol/L by the enzymatic assay, 178,2 (89,1–213,7) µmol/L by the uncompensated Jaffé method, and 174,7 (71,6–207,3) µmol/L by the compensated Jaffé method. Linear regression equations in adults were as follows :

Enzymatic method(y) vs HPLC(x):
y(µmol/L) = 0.96x (µmol/L) - 2.47µmol/L (r=0.98)

Compensated Jaffe(y) vs HPLC(x):
y(µmol/L) = 0.95x (µmol/L) + 0.44µmol/L (r=0.98)

Uncompensated Jaffe method(y) vs HPLC(x):
y(µmol/L) = 0.84x (µmol/L) + 24.94µmol/L (r=0.98)

The equations demonstrate an overestimation of serum creatinine by the uncompensated Jaffé method in the range <155 µmol/L and an underestimation in the

higher range compared with the HPLC serum creatinine results. (Additional tables and figures are available as a Data Supplement accompanying the online version of this Technical Brief at http://www.clinchem.org/content/vol49/issue6/).

Effects of patient variables (gender, age, body mass index) and concentrations of uric acid, bilirubin, total protein, albumin, and creatinine on the differences between creatinine methods were studied in detail. In a multivariate regression model, we found a highly significant correlation ($P<0.0001$) only between the serum uncompensated Jaffé creatinine concentration and the difference between uncompensated Jaffé and enzymatic serum creatinine concentrations (Figure 1A). This difference between the uncompensated Jaffé and enzymatic creatinine methods was agedependent when children and adults are examined together (Fig. 1B). In the overall group of adults, we observed no impact of the patient variables, including age, or of the concentrations of other substances on the difference between the creatinine methods. However, in a subgroup of nephrotic patients (n=9) presenting with extremely low serum protein levels (< 50 g/L), we observed a smaller positive difference attributable to pseudo-chromogens (median, 15 µmol/L; interquartile range, 12–19 µmol/L; $P<0.05$).

The median (interquartile range) CrCls values in adults (n=80) were 43,4 (15,3–74,2) µmol/L for the HPLC, 49,6 (15,3–76,7)µmol/L for the enzymatic, 37,5 (14,9–56,8) µmol/L for the uncompensated Jaffé and 48,0 (15,8–74,6) µmol/L for the compensated Jaffé creatinine methods. The linear regression statistics are shown in Table 1.

Cockroft-Gault estimates of clearance in adults (n=80) produced median (interquartile range) values of 48.3 (24.5–69.5) µmol/L for the HPLC, 55.0 (24.4–78.7) µmol/L for the enzymatic, 46.0 (23.2–64.5) µmol/L for the uncompensated Jaffé and 53.2 (24.5–75.5) µmol/L for the compensated Jaffé methods. The linear regression statistics are shown in Table 1. Abbreviated MDRD estimated clearance in adults (n=80) produced median (interquartile range) values of 50.3 (25.9–74.8) µmol/L for the HPLC, 58.7 (26.1–92.4) µmol/L for the enzymatic, 47.1 (26.0–71.8) µmol/L for the uncompensated Jaffé and 56.3 (25.7–88.7) µmol/L for the compensated Jaffé methods. The linear regression equations are shown in Table 1.

Schwartz estimated clearance in children (n=23) produced median (interquartile range) values of 173,8 (127,8–193,7) µmol/L for the enzymatic, 108,4 (87,1–114,8) µmol/L for the uncompensated Jaffé and 169,5 (116,3–179,9) µmol/L for the compensated Jaffé methods. For the inulin clearance, the median (interquartile range) was 123.1 (97.3–152.8)mL/min (n=23). Linear regression equations are shown in Table 1 (n=23).

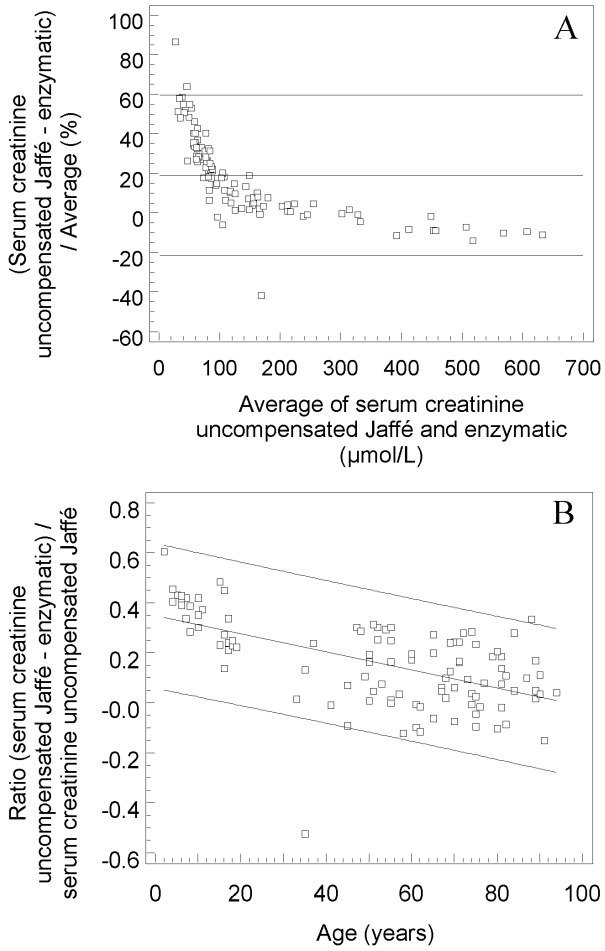

Figure 1: Variables affecting the difference between creatinine methods
(A) Bland-Altman plot comparing the two methods; (B) correlation between the relative difference between the results obtained with the two methods and patient age

Median GFRs estimated by the Cockroft-Gault equation varied by as much as 18% depending on the creatinine method used. Similarly, median GFRs estimated by the MDRD equation varied as much as 20%. In adults, the use of the enzymatic method produced the highest estimated GFR and the uncompensated Jaffé the lowest regardless of the equation used.

We observed marked differences between the various methods for serum creatinine. Because they were affected by the protein error, uncompensated Jaffé methods produced higher serum creatinine results, whereas the results obtained with the

compensated Jaffé, enzymatic and HPLC creatinine methods were comparable. The difference between the uncompensated Jaffé and the enzymatic method depended mainly on the underlying concentration of serum creatinine. We observed no impact of patient variables or other substances. Because of their lower serum creatinine concentrations, we observed a relatively higher difference between the uncompensated Jaffé and enzymatic serum creatinine methods in children. In infants, who generally present with a higher protein error and even lower serum creatinine concentrations, a larger difference between these two creatinine methods is to be expected.

Table 1: Linear regression statistics for the various creatinine methods

y[a]	**x**	**slope**	**Intercept,** mL/min	***r***
Creatinine[b]				
HPLC	^{51}Cr EDTA	0.88	9.77	0.87
enzymatic	^{51}Cr EDTA	1.06	-1.99	0.87
compensated Jaffé	^{51}Cr EDTA	1.00	-0.88	0.88
uncompensated Jaffé	^{51}Cr EDTA	0.69	3.96	0.82
Cockcroft-Gault algorithm[b]				
HPLC	^{51}Cr EDTA	0.96	1.93	0.90
enzymatic	^{51}Cr EDTA	1.06	2.77	0.90
compensated Jaffé	^{51}Cr EDTA	0.99	4.61	0.90
uncompensated Jaffé	^{51}Cr EDTA	0.74	9.75	0.87
Abbreviated MDRD[b]				
HPLC	^{51}Cr EDTA	0.92	5.32	0.81
enzymatic	^{51}Cr EDTA	1.21	-0.45	0.86
compensated Jaffé	^{51}Cr EDTA	1.12	1.67	0.86
uncompensated Jaffé	^{51}Cr EDTA	0.80	7.99	0.85
Schwartz algorithm[c]				
enzymatic	inulin	1.14	18.89	0.76
compensated Jaffé	inulin	1.11	18.73	0.65
uncompensated Jaffé	inulin	0.46	46.62	0.64

[a] y = clearance based on the method specified in the column (mL/min)
[b] In adults (n=80)
[c] In children (n=23)

In adults, the uncompensated Jaffé CrCl was lower than the ^{51}Cr EDTA clearance. In contrast, enzymatic and compensated Jaffé CrCl values were slightly higher, which is attributable to a relatively small tubular secretion of creatinine [24, 25]. The Cockroft-Gault and abbreviated MDRD algorithms for calculating GFR correlated closely with ^{51}Cr EDTA clearance when calculated with the creatine results from the HPLC, enzymatic, and rate-blanked compensated Jaffé methods. However, the results obtained with the same algorithms were lower than the ^{51}Cr EDTA clearance when based on uncompensated Jaffé test results. The abbreviated MDRD and Cockroft-Gault equations correlated well.

The median GFRs obtained with the Schwartz equation varied by 39%, depending on the creatinine method used. In children, the use of the enzymatic method produced the highest estimated GFR and the uncompensated Jaffé the lowest.

In children, practical problems in timed urine collection have contributed largely to the widespread use of calculated CrCl values based on serum or plasma creatinine concentration and body length. In contrast to the results for adults, the results obtained with Schwartz CrCl values in children and infants are significantly higher (in our series up to twofold higher in 4 of 23 cases) than inulin clearances when the compensated Jaffé or enzymatic creatinine methods is used. If the noncompensated Jaffé test is used, the negative analytical effect of the protein error on CrCl is countered by the positive physiologic effect of the relatively more important tubular secretion of creatinine. Because serum creatinine values are lower in children, especially between ages 1 and 3 years, relative differences between compensated and noncompensated creatinine methods are very important.

Care should be taken when using estimated GFRs based on CrCl algorithms for drug administration, in particular for drugs such as cis-platinum and aminoglycoside antibiotics. In the example of the cytostatic drug cis-platinum, it is recommended to administer one-half the dose when CrCl decreases to <60 mL/min.

In conclusion, because collection of timed urine is cumbersome and susceptible to errors, calculated GFRs (Cockroft-Gault and MDRD algorithms in adults and Schwartz algorithm in children) are often used. However, care should be taken in the choice of the serum creatinine method when applying these formulas.

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Chapter 8

Place of ultrasonography in the assessment of renal function in the old old

Abstract

Background: Ageing is associated with progressive loss of renal mass and kidney length as well as a decline in glomerular filtration rate (GFR). This study wants to evaluate if there is a correlation between renal function and kidney size measured by ultrasonography (US) and if US kidney size can help to estimate GFR in the old old.

Methods: Twenty-five medically stable older people (mean age 85 ± 5 years) were examined in a geriatric ward at a university hospital. Blood samples were obtained to determine serum creatinine level. On the same day clearance of ^{51}chromium ethylenediamine tetraacetic acid (^{51}Cr-EDTA) was performed as the gold standard of GFR. Kidney length, transverse and anteroposterior dimensions were measured by ultrasonography.

Results: Serum creatinine (r=-0.67; P=0.0002), Cockcroft-Gault formula (r=0.82; P<0.0001), absolute length (r=0.51; P=0.008) and volume of the kidney (r=0.46; P=0.02) correlated significantly with GFR. After ROC analysis, length showed a lower specificity than sensitivity in detecting renal impairment. Adding length to the Cockcroft-Gault formula did not improve the estimation of GFR (P=0.44). In contrast adding length to serum creatinine level could improve the estimation of GFR (P=0.015).

Conclusion: In the old old, kidney length and volume are significantly correlated with GFR. However, length has a low specificity in predicting renal impairment. Therefore, in clinical practice, serum creatinine level and calculated creatinine clearance are more useful in predicting renal impairment. However, normal kidney length can help to exclude renal impairment in the old old at risk for underestimation of GFR by a calculated creatinine clearance.

Introduction

The effect of ageing on the kidney is well documented. Ageing is associated with progressive loss of renal mass. Renal weight decreases 20 to 30 per cent between the age of 30 and 90 years [1,2]. Also renal length diminishes by 2 cm between the age of 50 and 80 years [3]. The loss of renal mass is primarily cortical, with relative sparing of the renal medulla. The total number of identifiable glomeruli decreases with age, in

accordance with the changes in renal weight [4,5]. Cross-sectional and longitudinal studies suggest a progressive decline in GFR of approximately 1 mL per minute per year, but the rate of decline shows a large individual variation with usual ageing. In some studies 30% of the older individuals showed no decrease in creatinine clearance over time [6,7]. Because many drugs undergo renal clearance, a quick and accurate estimation of GFR is important as soon as an older patient is admitted [8]. Many methods are available to assess GFR in the elderly, each with its advantages and limits [9-11]. In clinical practice serum creatinine level remains the most widely used index of renal function [11-13]. Predictive formulas using serum creatinine levels should be used with caution, only to get an approximate idea of the renal function [14]. The Cockcroft-Gault formula [15] is very useful in the assessment of the elderly patient with moderate to severe renal impairment. On the other hand, it underestimates GFR in the elderly person with normal renal function [9,13,14,16]. The most convenient method is the measurement of the clearance of an exogenous substance such as inulin or isotopically labelled compounds as iothalamate, ^{51}chromium ethylenediamine tetraacetic acid (^{51}Cr-EDTA), diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) and the contrast medium iohexol [17]. These methods are impractical for use in a hospitalized geriatric population.

Ultrasonography of the kidney is ideally suited for imaging kidneys. The best measure of renal mass is volume, which correlates well with GFR in children [18]. However, calculation of volume is prone to significant error [19]. Therefore maximal length has become the standard parameter because it is easily determined and correlates well with renal volume [20].

The first purpose of this study was to evaluate if kidney size (i.e. length and volume) correlates with GFR in the old old. Secondly, we evaluate if kidney size, measured by ultrasonography, can be used in estimating GFR or added to clinically used estimations of GFR, as serum creatinine and Cockcroft-Gault formula, can improve the accuracy of these estimations.

Subjects and Methods

Twenty-five patients (17 women, 8 men) admitted to the acute geriatric ward of Ghent University Hospital were included. The mean age ± standard deviation was 85 ± 5 years. The ethical committee of the Hospital approved this study. Patients were eligible for this study when fully recovered from acute illness and dehydration by day 7. Eligible patients were recruited consecutively and included after an informed consent was given by the patient. All patients were on standard diet containing 0.8g proteins/kg body weight.

On the day of the study, blood samples were obtained from each patient to determine serum creatinine level and clearance of ^{51}Cr-EDTA was performed in all patients as a reference for GFR assessment. On the same day, ultrasound of both kidneys was performed in order to measure length (L), transverse (W) and anteroposterior diameters (T). The volume (V) was calculated using the prolate ellipse formula ($V=LxWxTx(\pi/6)$) [21]. Relative length of the kidney was calculated using absolute kidney length and body height ratio (KBR) [22]. A mean absolute and relative kidney length was calculated using the sum of the right and left kidney length divided by two.

Ultrasonography measurements were performed using an ATL scanner equipped with a curved array 3.5 MHz transducer. The longitudinal and maximal laterolateral diameters were measured on the largest section through the long axis of the kidney with the transducer placed on the lateral part of the abdomen. The anteroposterior diameter was measured on the largest coronal cross section with the same position of the transducer. All examinations were performed by the same physician.

An estimation of creatinine clearance was made using the inversed ratio of serum creatinine and the Cockcroft-Gault formula as well.

Serum creatinine level was measured using a compensated calibrator for the Jaffé method, rate-blanked on a Roche/Hitachi 747 analyzer (Boehringer, Mannheim, Germany).

The plasma clearance of the radionucleotide marker was performed after intravenous injection of a standard dose of 3.7 MBq of commercially available ^{51}Cr-EDTA (Dupont Fleurus, Belgium) in 5 mL physiological saline. The precise value of the dose injected was obtained by weighing the syringe before and after injection. Four blood samples were obtaine 120, 180, 300, and 420 minutes after injection. The GFR was determined using the slope-intercept method as previously described [23].

STATISTICAL ANALYSIS

The Medcalc package (Medcalc, Mariakerke, Belgium) was used for statistical analysis. Data are presented as mean ± standard deviation. Student t-test was used for continous variables. A *P*-value <0.05 was considered to be statistically significant. The relationship between different methods of GFR assessment, kidney measurements and ^{51}Cr-EDTA was assessed using Pearson correlation coefficient and linear regression models. Multiple linear regression was used to evaluate if absolute length and serum creatinine levels or Cockcroft-Gault formula are independent variables for the estimation of GFR. If the *P*-value for the different regression coefficients is less than the conventional 0.05, then these coefficients are statistically significant and the corresponding independent variables exert independent effect on the estimation of GFR.

Receiver operating curve (ROC) analysis were used to evaluate sensitivity and specificity of kidney length in estimating GFR.

Results

RENAL FUNCTION AND KIDNEY SIZE

The overall mean ^{51}Cr-EDTA , the estimated clearance by the Cockcroft-Gault formula, the mean serum creatinine and the mean kidney measurements are shown in Table 1. No significant difference was found in absolute and relative length between the left (101 ± 9 mm; 0.616 ± 0.054 respectively) and the right kidney (102 ± 10 mm; 0.623 ± 0.055 mm respectively). Also no significant difference was found in renal mass between left (116 ±34 mm³) and right kidney (107 ± 33mm³). Mean absolute length of the kidney was significantly greater in men (106 ± 10 mm) than in women (99 ± 6 mm) (*P*=0.02). This difference between men and women disappeared for relative length (0.617 ± 0.056 and 0.621 ±0.046 respectively). No significant correlation was found between body height and kidney length in the old old (*r*= 0.36; *P*= 0.07).

Table 1: Measurements of kidney function and kidney size in the old old

	Mean (SD)	**Range**
^{51}Cr-EDTA (ml/min)*	50 (23)	11 – 102
Cockcroft-Gault (ml/min)*	48 (20)	15 – 85
Serum creatinine (mg/dL)	1.08 (0.64)	0.48 - 3.50
Absolute kidney length (mm)	101 (8)	89 – 122
Relative kidney length (mm)	0.62 (0.05)	0.50 - 0.70
Kidney volume (cm³)	116 (26)	75 – 196

* standardized for body surface area

Correlation coefficients and regression lines for serum creatinine levels, Cockcroft-Gault formula and kidney sizes with the gold standard for GFR, ^{51}Cr-EDTA, are shown in Table 2. The best correlation with GFR was found for the Cockcroft-Gault formula followed by the inversed serum creatinine level. Also the absolute kidney length and renal volume were significantly correlated with ^{51}Cr-EDTA clearance. No correlation was found with the relative length of the kidney. In clinical practice a wide variation of kidney length was found for comparable GFR in the old old (Figure 1).

Table 2: Comparison of measurements of renal function and kidney size with ^{51}Cr-EDTA

	r	*P*-value	Regression analysis
1/Serum creatinine (dl/mg)	0.70	0.0001	Y=0.46+0.01X
Cockcroft- Gault* (ml/min)	0.82	<0.0001	Y=14.9+0.66X
Absolute length (mm)	0.51	0.008	Y=91.4+0.19X
Relative length	0.31	0.14	Y=0.58+0.0007X
Volume (cm³)	0.46	0.02	Y=91+0.44X

r = correlation coefficient *Standardized for body surface area

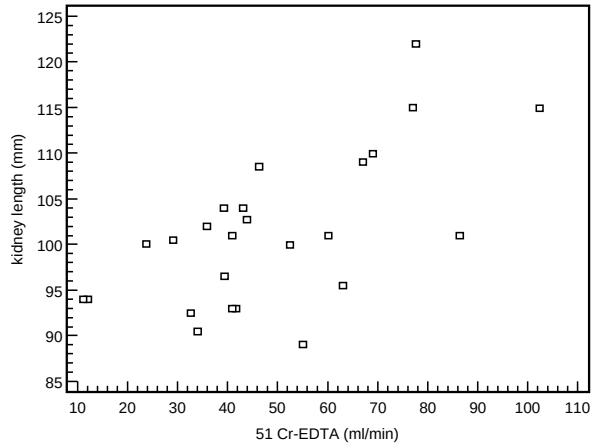

Figure 1: Correlation between kidney length and GFR

KIDNEY SIZE AND ESTIMATION OF GFR

After ROC analysis, absolute kidney length was found to be less specific than sensitive in detecting renal impairment. Data of kidney length with 100% sensitivity and respective specificity in predicting impaired GFR are shown in Table 3. The positive predictive value of kidney length in detecting renal impairment was only between 50 à 60 %. A high negative predictive value could be observed in detecting impairment of GFR. This suggest that kidney length can be useful to exclude renal impairment.

Table 3: Length of the kidney predicting the impairment of GFR with 100% sensitivity (ROC analysis)

	Renal length (mm)	**Specificity** (%)
^{51}Cr-EDTA < 60 ml/min	≤ 108.5	55.6
^{51}Cr-EDTA < 40 ml/min	≤ 104	35.3
^{51}Cr-EDTA < 30 ml/min	≤ 100.5	59.1

Table 4 shows that adding kidney length to the Cockcroft-Gault formula is not very useful in predicting GFR. For serum creatinine level on the other hand, there may be statistically a better estimation of GFR after adding kidney length (Table 5).

Table 4 : Multiple Regression Analysis for absolute length and Cockcroft-Gault formula

	β-coefficient	***P*-value**	**Multiple correlation coefficient**
^{51}Cr-EDTA	48.35		
Cockcroft-Gault	1.06	0.0003	0.77
Absolute length	- 0.47	0.44	0.78

Table 5: Multiple Regression analysis for absolute length and serum creatinine

	β-coefficient	***P*-value**	**Multiple correlation coefficient**
^{51}Cr EDTA	-83.35		
Serum creatinine	31.51	0.0002	0.70
Absolute length	0.97	0.015	0.78

Discussion

In the old old a significant correlation was found between renal mass and GFR, isotopically measured. Similar findings were previously described in children [18]. This correlation is greater for absolute kidney length than for kidney volume in the old old and is absent for relative kidney length. The absence of correlation for relative kidney length can be explained by the finding that body height is not anymore correlated with kidney length in older people. This finding was also previously demonstrated by Emamian et al. [24]. Other studies confirmed that volume measurements are not more accurate than renal length [25], but this remains a point of discussion [24,26]. Although

a significant correlation was found between renal length and GFR, the usefulness of renal length in estimating GFR in clinical practice remains a problem due to low specificity in detecting renal impairment. In contrast, a high negative predictive value was found in detecting different degrees of renal impairment. Consequently, it was possible to detect a cut-off for kidney length above which all the old old had a GFR greater than the limit of impairment. This suggests that kidney length can be used to exclude renal impairment.

As kidney length itself has no high positive predictive value for renal impairment, the question raised if adding kidney length to frequently used indices of renal impairment (i.e. serum creatinine level and Cockcroft-Gault) could help in estimating GFR. Compared with kidney length the correlation between serum creatinine level and the Cockcroft-Gault formula at one side and GFR at another was much stronger. Statistically there was a little benefit of adding kidney length to serum creatinine level. Although in clinical practice, the usefulness of this act is limited by the wide variation and low specificity of kidney length in predicting GFR as previously discussed. A good correlation of Cockcroft-Gault and GFR was not influenced by adding kidney length.

Our data concerning GFR, mean Cockcroft-Gault formula, mean serum creatinine, kidney length and kidney volume are consistent with the findings of previous studies looking at a comparable old old population [9,13-16,24]. Also for the correlation coefficients and regression analysis comparable data were found with previous studies [9,13-16]. Although a limited population was studied, this population can be called representative for the old old population on an acute geriatric ward.

In conclusion, in the old old, kidney length and kidney volume are significantly correlated with glomerular filtration rate. Kidney length has a low specificity in predicting renal impairment. Therefore, in clinical practice, serum creatinine level and certainly Cockcroft-Gault formula are more useful in estimating glomerular filtration rate in the old old on an acute geriatric ward. However, normal kidney length can help to exclude renal impairment in the old old at risk for underestimation of GFR by a calculated creatinine clearance.

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Part 3

Prognosis and risk factors of mortality following acute renal failure : does age make a difference ?

Chapter 9

Acute renal failure in the elderly

Introduction

Between 1999 and 2050, demographic projections predict a major increase in the population above 65 and more particularly in the portion older than 80 years. Global life expectancy at any age has progressed in the developed world and at age of 70 years a European man can expect to live another 12,5 years and a woman another 16 years. It is thus evident that in the next years the practice of medicine in the Western world will be profoundly influenced by the health care needs of the rapidly enlarging elderly population.

Renal services must therefore be prepared for an increasing number of elderly patients with both acute and chronic renal failure.

The term "elderly" changes with time and chronological age is not really important. It is the biological age which determines functional capability, although until now it cannot be accurately measured. It is likely that in the near future 75 or even 80 years of age will be the definition of "elderly"[1]. Until there is an agreed definition of "biological age" and chronological age, the cut- off point of 65 years will be used in this chapter as the definition of elderly.

There are medical reasons to expect an increasing number of elderly patients with ARF. First, the ageing kidney, due to structural and functional alterations, is less able to cope with rapid haemodynamic changes and with changes in water and salt balance. In particular, the glomerular reserve and capacity of renal autoregulation are diminished in the elderly kidney [2,3]. These structural and functional alterations are described in detail elsewhere in this book. The most important anatomic and functional alterations are summarized. Second, an increasing number of individuals will have chronic systemic diseases, such as hypertension, diabetes mellitus, atherosclerosis, heart disease, and malignancies. Some of these diseases result in diminished renal reserve. A much more aggressive diagnostic and therapeutic approach to illness in the elderly population carries with it the risk for ARF from complications of these procedures or the subsequent therapeutic interventions.

Thirdly, the elderly population consumes twice as many medications, including nephrotoxic agents, as all other age groups combined. The marked and progressive decrease in renal function, associated with increasing age, implies that the dosage of

drugs that are predominantly renally excreted should be reduced; a fact that is sometimes forgotten.

These three factors all contribute to the additional risks for the development of ARF in the elderly population and nephrologists are already now facing an increasing demand to provide renal intensive care, including acute dialysis, to very old patients.

Structural and functional alterations in the aged kidney.

The main characteristic of the physiological aging of the kidney is the limitation of the adaptive renal response to different situations that threaten to disturb the homeostasis of the organism. Under normal circumstances, the structural and functional alterations may have no major clinical impact since the renal functional reserve is sufficient to meet the excretory demands. However, aging can adversely affect the course of a superimposed renal disease, and the pre-existent reduction in functional reserve in the aging kidney may magnify the excretory defect, caused by any new insult. That such a reduction in the functional reserve exists has been suggested by an age-related impairment in renal vasodilatory response to intravenous glycine [4], and in postprandial hyperfiltration, following a meal in older compared to younger animals [5]. However, it is possible that in many studies of the functional renal reserve in the elderly, confounding factors such as inadequate control of blood pressure and/ or moderate cardiac dysfunction have not been excluded. In fact, healthy independent elderly individuals in good nutritional state and with regular physical activity do not show a decrease in renal functional reserve [2,6].

HAEMODYNAMIC AND NEUROENDOCRINE FACTORS

One of the major protective adaptations of the kidney to hypotension, volume depletion or reductions in cardiac output is the ability to autoregulate renal blood flow (RBF) and glomerular filtration rate (GFR) to a relatively constant level over a wide variety of renal perfusion pressures. It appears that in experimental states of low cardiac output or extracellular volume depletion, two situations frequently encountered in the elderly, there is a loss of autoregulation following reduction in renal perfusion pressure [7]. The fall in GFR is primarily due to a failure to increase the postglomerular resistance. In addition, a displacement of the autoregulation curve of both RBF and GFR to the right has been observed in the presence of an increased sympathetic tone, present in clinical situations such as heart failure or shock. In these situations a modest reduction in arterial blood pressure can threaten the preservation of renal haemodynamics and GFR.

Baseline and stimulated plasma norepinephrine levels rise with advancing age and these have been interpreted as indicating that there is a “constant hyperadrenergic

state in the elderly" for review see [8]. Intrarenal vascular tone increases with age. Vasoactive factors may contribute to this increased tone although the data describing this change are complex and contradictory. For example, high basal levels of renal nerve activity, angiotensin II , and endogenous endothelin contribute to vasopressor activity but endothelin, endothelium-derived relaxing factor blockers L-NAME and L-NMMA and angiotensin II all produce an exaggerated vasopressor response in aged rats [9-11]. There appears to be a decreased somatic production of nitric oxide (NO) in older animals compared to younger ones [12]. The data for basal renin and angiotensin levels remain confusing, e.g. studies report both normal and low levels of renin and angiotensin in unstressed aged rats compared to younger controls [13-17]. A consistently observed blunted renin response to stimulation with artificial stressors, upright posture or sodium depletion, suggests that age does affect vascular reactivity under physiological conditions. However other data show that vasodilators, including angiotensin converting-enzyme inhibitors and angiotensin II blockers, have similar effects regardless of age [17]. Consequently, one may surmise that a relative increase in endogenous NO activity preserves renal blood flow and GFR but reduces the vasodilatory reserve and adaptation to superimposed haemodynamic insults.

An important role in the preservation of renal function in the presence of increased systemic vasoconstrictors and enhanced sympathetic tone is played by the intrarenal generation of vasodilating products of arachidonic acid (i.e. PGI2). Angiotensin stimulates synthesis of PGI2 and PGE2 within the kidney and prostaglandin's act to preserve glomerular filtration in situations such as sodium depletion, surgical stress, and reduced cardiac output. Cyclooxygenase-inhibition with non-steroidal anti-inflammatory drugs (NSAIDs) reduces the GFR and RBF in these conditions. With advancing age there is a widespread decrease in prostacyclin (PGI_2) synthesis throughout the vascular endothelium, leading to a decrease in the PGI_2/ thromboxane A_2 (TXA_2) ratio, a maladaptation which is atherogenic. The ratio of urinary PGI_2 to TXA_2 also decreases in older subjects [18] and in vitro studies in the rat have been shown that the TXA_2 to PGI_2 ratio is increased in glomeruli and inner and outer medulla of older kidneys [19].

How these circulatory and neuroendocrine alterations affect the autoregulatory defence and contribute to an enhanced risk for acute renal dysfunction in elderly people is not clear. Although no formal studies of autoregulation of GFR and RBF in otherwise healthy aging human kidneys have been performed, there is enough circumstantial evidence to suggest that the kidneys of aged individuals are more vulnerable to reductions of renal perfusion pressure than younger kidneys. A disease state where autoregulation of RBF and GFR is likely to be impaired, is atherosclerotic involvement of afferent arterioles caused by age, hypertension, or diabetes mellitus. It is conceivable

that in this situation the responsiveness of these arterioles to changes in their wall tension is decreased, making renal perfusion and function vulnerable to even small fluctuations in systemic blood pressure. A prototype of human disease, common at older age, and where the kidney is forced to autoregulate is atherosclerotic renal artery stenosis. However, every disease, characterized by enhanced sympathetic tone and/or elevated levels of angiotensin II, such as heart failure or hypovolaemia, will be associated with greater difficulty in autoregulating the GFR, in the presence of a decrease in renal perfusion pressure.

Direct interference with the protective autoregulatory mechanisms, either by disease or by pharmacological interventions may precipitate acute renal insufficiency. Drugs known to impair renal autoregulation or to interfere with the renal vasodilatory capacity include angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor antagonists, loop diuretics and prostaglandin synthesis inhibitors, like aspirin and the NSAIDs.

OTHER RENAL FUNCTIONAL ALTERATIONS IN THE ELDERLY.

Concentration and dilution of the urine.

The impairment of renal concentration, together with the well-known deficit in thirst perception, makes the elderly particularly liable to develop dehydration and hypernatraemia [20,21].

Maximal diluting ability also decreases with age [22] and together with the enhanced osmotic release of AVP leads to a high incidence of hyponatraemia.

Urinary sodium excretion.

The ability of the aged kidney to conserve sodium in response to sodium deprivation is decreased [23] and, when sodium restriction is imposed, it takes nearly twice as long for the aged kidney to decrease urinary sodium excretion compared with younger individuals. A decrease in distal tubular sodium reabsorption [24] may be explained by aging-induced renal interstitial scarring and decreased nephron number, increased medullary flow and changes in hormonal levels regulating sodium excretion. Both basal and stimulated circulating plasma renin and aldosterone levels have been found to decrease with aging in healthy elderly subjects. Lower nephron renin content, intrarenal downregulation of renin mRNA, and ACE have been demonstrated. On the other hand, the natriuretic ability of the aged kidney appears to be blunted when faced with sodium loading or volume expansion for review see [22]. The slower natriuretic response to an acute saline load has important implications for the evaluation of the urinary parameters used in distinguishing acute prerenal and renal failure see below.

Elevated ANP levels have been found in healthy elderly to be 3 to 5 times those of the healthy young [25,26]. The metabolic clearance of ANP in elderly is decreased in comparison to that in the young at similar low ANP infusion rates. Also the renal natriuretic response to an ANP infusion is blunted in the aged kidney [27,28], despite a normal increase in cGMP after ANP infusion [29].

Acid-base balance

The decreased renin and aldosterone activity in the elderly contributes to an increased incidence of type 4 renal tubular acidosis hyporeninaemic hypoaldosteronism and may cause a greater propensity toward hyperkalaemia in a variety of clinical settings, such as the presence of gastro-intestinal bleeding or during potassium loading, e.g. potassium supplementation associated with diuretic therapy. Given possible problems with chronic potassium adaptation with aging, medications that inhibit the renin-angiotensin system such as ACEi, heparin, cyclosporine, tacrolimus, β-blockers, and NSAID may increase the risk of hyperkalaemia in the elderly. Similarly, sodium channnel-blocking agents such as trimethoprim, pentamidine, and potassium-sparing diuretics such as amiloride, triamterene, and spironolactone can add to underlying defects in potassium excretion in the elderly [30-32].

The evidence that all these structural and functional renal alterations represent an enhanced risk for ARF in the elderly is indirect. For example, the age-associated structural glomerular alterations might exacerbate post-ischaemic reductions in GFR. Aged kidneys may have fewer nephrons to recruit to support renal function, and may thereby magnify the deficit incurred by an ischaemic or nephrotoxic insult. Alternatively, aging tubular cells may be more vulnerable to ischaemic damage because cellular antioxidant defences decline with age and oxidant injury may be a critical determinant of ischaemic ARF.

Experimental studies in the aging rat have provided support for an enhanced risk of developing ischaemic and toxic ARF [33-37]. In all ischaemic models, the decline in renal function in the aged rat was significantly greater than in the young rat, and the rate of recovery was much slower. Despite the substantial differences in post-ischaemic renal function, evaluation of tubular injury surprisingly failed to reveal any difference among the different age groups. The lack of relationship between the severity of ARF and the extent of morphologic damage strongly suggests that the age-related changes had a glomerular/haemodynamic basis, rather than reflecting an intrinsic difference in tubular susceptibility to ischaemic damage. However, following graded periods of in vitro anoxia, renal function, as assessed by renal cortical slice uptake of PAH and tetraethylammonium, was impaired to a greater extent in old as compared to young rats [36]. This suggests that in addition to the changes in RBF and GFR, alterations in the

metabolism and biochemistry of aging tubular cells might play a role in mediating age-related enhancement of ischaemic renal cell injury.

NO is another mediator that could play a role in the propensity for more frequent ARF in the elderly. Studies have shown that NO synthesis blockade decreases renal blood flow, GFR, and Kf more in aging than in young rats, suggesting that NO may play a progressively increasing and important role in controlling renal function in advancing age than in the young [12,38]. NO production appears to be reduced with aging in isolated conduit arteries [39,40] and a 40% decrease in serum levels of the NOS substrate L-arginine has been found [41]. Similar findings have been noted in aging humans [42]. It may be that renal endothelial NO production is maximized in the normal elderly to maintain stable renal function. Measurements of NO production in the face of renal ischaemia still need to be done in human subjects.

In a rat model of ARF, an increase in glomerular NO production seems to play a protective role in renal function by counteracting the vasoconstrictor substances released during ARF [43]. When challenged with gentamicin, older animals showed a more severe renal failure compared to younger animals. In addition, a lower glomerular NO production in basal conditions, and a markedly blunted stimulation of NO synthesis by gentamicin were found in older animals [44]. In a renal artery clamp model [45] the basal renal dynamics were similar in old and young animals, but one day after ARF, the decrease in GFR was more severe in old than in young, due to a greater rise of renal vascular resistance in the old animals. However, the histological renal damage after ischaemia was comparable in the two groups with ARF. Five days after ARF, the recovery of renal function was slower in older rats. In two other groups of animals, two different scavengers of oxygen-free radicals, dimethylthiourea (DMTU) and superoxide dismutase (SOD), were administered at the time of arterial occlusion. DMTU had protective effects in the young but not in the old animals; in contrast, SOD was more effective in old than in young rats. To test the hypothesis that such a difference was related to the capacity of SOD to increase the levels of NO, four more groups of young and old rats were pre-treated with L-arginine, a precursor of NO. No difference in renal dynamics was detected in basal conditions, but when older rats were pre-treated with L-arginine in their feed 7 days before renal artery occlusion, there was marked improvement in GFR and RPF, and a decrease in renal vascular resistance. L-NAME, an NOS inhibitor, given to older L-arginine-fed rats abolished the renal haemodynamic response seen with L-arginine and superoxide dismutase [45].

Glomerulosclerosis may not be the primary factor leading to ischaemic renal failure in aging rats. In fact, when histologic variations between young and old rats were minimized by a low protein diet, renal artery clamping still led to a significant decrease in GFR and RPF and an increase in renal vascular resistance in older versus younger

rats [45]. Studies using blood oxygenation level-dependent magnetic resonance imaging in nine elderly female volunteers between 59 and 79 years of age showed a relative inability to improve medullary oxygenation with water diuresis compared with younger subjects, thus suggesting a possible predisposition to hypoxic renal injury also in older human individuals [46].

Incidence of ARF in the older population

The true incidence of ARF is difficult to estimate because the definition of ARF used in the published series is not uniform. Patients with either an acute but modest increase of serum creatinine or with severe dialysis-dependent ARF are included. Some papers include all forms of ARF while in others only acute tubular necrosis (ATN) is considered and different criteria for dividing the patients into "young" and "old" are applied. However, it is fair to state that the frequency of development of severe ARF is undoubtedly increased with advancing age.

In a prospective, 2-year study it was found that individuals over 70 years of age comprised more than 70% of all cases of ARF [47]. The frequency of severe ARF was 17 per million population in those under 50 years of age and was increased by 56-fold (949 per million population) in those aged 80 to 89 years. In a large series of 748 patients with ARF in the Madrid area, it was observed that 36% of these cases were older than 70 years, although this age category represented only 7% of the general population in that area [48]. In the years 1991 and 1992, a total number of all ARF patients attending 13 tertiary care hospitals in the Madrid area was 209 cases pmp per year, while in the patients aged over 80 years ARF was observed in 1129 cases pmp per year [49].

In France, the incidence of ARF in patients admitted in nephrology units was slightly higher than 100 pmp per year [50].

Several reports have observed a gradual increase in the mean or median age of the patients who develop ARF in different observation periods [51-55].

Figure 1 depicts a recent study from the Tenon Hospital in Paris [1]. Between October 1971 and September 1996, 381 patients older than 80 years in a total of 2111 patients suffering from ARF were admitted to the nephrology ICU. Whereas the percentage of ARF patients over 80 years of age out of the total number of patients with ARF was always less than 4% before 1978, this number has grown to about 40% in the period 1995-1996.

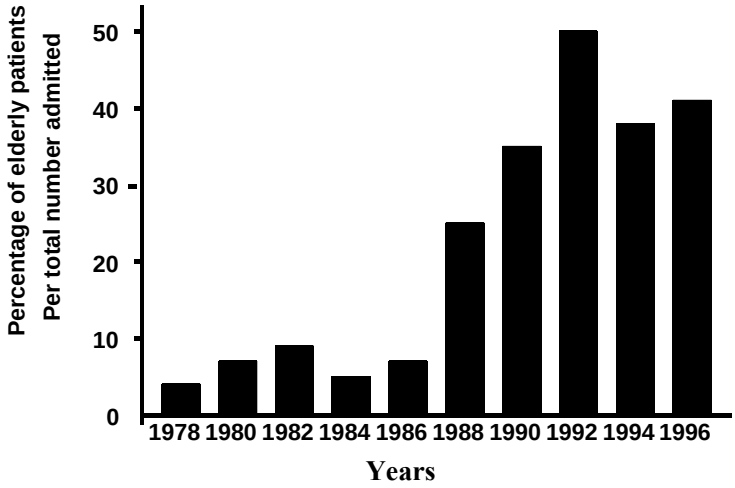

Figure 1: Percentage of ARF patients over 80 years of age out of the total number of patients with ARF admitted to the nephrology ICU from the Tenon Hospital (Paris) [1]

In those series in which ARF could be related to a specific causal factor, for example cardiopulmonary resuscitation, postcardiac surgery, aortic aneurysm surgery, the number of elderly patients also increased. [56-58]. In many studies, a reduced baseline renal function emerged as a strong independent risk factor [57,59,60].

Causes of acute renal failure in the elderly

The aetiology of ARF is frequently multifactorial, so that any classification of ARF poses problems of definition. In many reports, the cause of ARF is defined as the most likely factor, that was responsible for the deterioration in renal function.

Table 1 summarizes the distribution of all causes of ARF in elderly described in a recent series in which the aetiology was sufficiently detailed [1].

Table 1: Causes of ARF in patients older than 70 years in the Tenon Hospital (Paris) [1]

	Number N=381	%
Obstructive renal failure	**85**	**22.3**
Prostatic adenoma	22	5.8
Prostatic cancer	19	5.0
Bladder/ureter cancer	15	3.9
Uterus/ovaria cancer	9	2.4
Colo-rectal cancer	5	1.3
Nephrolithiasis	5	1.3
Retroperitoneal fibrosis	8	2.1
Ureteral stenosis	1	0.3
Fecaloma	1	0.3
Pre renal failure	**92**	**24.1**
Dehydration	55	14.4
Heart failure	14	3.7
Dysregulation of GFR	21	5.5
Hepato-renal syndrome	2	0.5
Intrinsic renal failure	**204**	**53.5**
Tubulopathy		
Shock	99	26.0
Cardiogenic shock	*21*	*5.5*
Septic shock	*54*	*14.2*
Hypovolaemic shock	*34*	*8.9*
Rhabdomyolysis	20	5.2
Multiple myeloma	14	3.7
Drugs (aminoglycosides; NSAID; ACEI; Iodinated contrast media)	23	6.0
Interstitial		
Pyelonephritis	8	2.1
Immunoallergic nephropathy	8	2.1
Glomerulopathies	8	2.1
-Goodpasture(‘s Syndrome)		
-Wegener		
-Post-infectious glomerulonephritis		
Vascular thrombosis	6	1.6
Cholesterol embolism	3	0.8
Blood incompatibility	1	0.3

PRERENAL CAUSES.

A major cause of an acute deterioration in renal function in the elderly is “prerenal failure”, a decreased perfusion of the kidney, e.g. from a decrease in cardiac

output; gastrointestinal losses caused by vomiting, diarrhoea, or bleeding; renal losses due to glycosuria and use of diuretics [61].

The incidence or acute prerenal failure in the aged is difficult to estimate (Table 2). In some series, these cases are deliberately excluded from analysis, and in series where they are included, the definition of ARF is not uniform.

For example, in community-acquired ARF, prerenal azotemia was found in 70% of the patients, who had a mean age of 62.5 years [62]. In 3 geriatric units, all records of patients admitted were analyzed. Of a total of 273 patients with raised urea or serum creatinine on admission, 53.3% suffered from prerenal failure. This incidence increased to 70% in the age group older than 85 years [63]. Forty-five of the 338 patients older than 70 years, hospitalized in an internal medicine unit over 1 year for a non-nephrological problem, presented with ARF. A prerenal cause was found in 20 patients (60%), and was due to diuretics in 12 patients (45%) [64]. Finally, in the Tenon study [1] 24,1% of ARF patients older than 80 years were categorized as prerenal.

Table 2: Frequency of prerenal ARF in elderly subjects

Age	> 85 yrs	>80 yrs	65-79 yrs	65-85 yrs	>70 yrs
McInnes [63]	70 %				
Gentric [64]					60 %
Klouche [65]				35 %	
Pascual [49]		30 %	28 %		
Akposso [1]		24 %			

Hypovolaemia.

Hypovolaemia is common in the elderly and may present as either prerenal failure or, if not corrected, may progress to post-ischaemic ATN.

Hypovolaemia is frequently caused by dehydration and is present in approximately 1% of all community hospital admissions of elderly patients [66]. Reduced renal water conserving capacity, reduced thirst and reduced water intake, all contribute to the genesis of dehydration in the elderly. Up to 25% of non-ambulatory geriatric patients are for these reasons mildly dehydrated [67]. Particular risk factors for dehydration in elderly nursing home residents include acute febrile illnesses, multipharmacy intake especially diuretics and laxatives, age over 85 years, and being bedridden [68]. During infections in nursing home residents, hypernatraemia, an

indicator of dehydration, is seen in 25% of all febrile patients. Untreated, the mortality of dehydration exceeds 50%. Nursing staff documentation of impaired oral intake, in combination with an elevated serum sodium and BUN/Cr ratio, provides early clinical and laboratory evidence of dehydration in this setting [69,70]. Hypovolaemia may also be caused by fluid redistribution from the intravascular to the interstitial space in states of cardiac failure, nephrotic syndrome, decompensated liver cirrhosis with ascites, pancreatitis, extensive burns, and malnutrition.

The diagnosis of hypovolaemic acute prerenal failure in the elderly is difficult because the clinical signs and symptoms of dehydration are often unreliable. They depend on the volume, the rate, and the nature of the fluid losses. Clinical examination will include attention to the jugular venous pressure, orthostatic changes in pulse and blood pressure, skin turgor, moisture in the axillae, and hydration of mucous membranes. Interstitial fluid loss can be detected by decreased elasticity of the skin, especially over the forehead, the sternum, and the anterior area of the thigh. These changes are difficult to interpret in the elderly in whom a loss of subcutaneous tissue elasticity is often observed. Dry mucous membranes of the tongue and oral mucosa are present with volume depletion, but also in patients breathing through their mouth. A rapid fall in body weight indicates the volume of body fluids lost. Although prerenal failure is usually associated with oliguria, prerenal failure with preserved diuresis has been observed [71].

The traditional urinary parameters used for differentiating prerenal from renal failure as low fractional urinary excretion of sodium and/or of urea must be interpreted with caution, because they may merely reflect age-related disturbances in tubular handling of sodium and water. In view of the chronic reduction in urinary concentrating ability, urinary sodium and osmolality may not achieve “prerenal” values during acute renal insults. An elevated urinary sodium concentration or FE Na obtained in an elderly patient may suggest an established parenchymal injury, but prerenal hypoperfusion may still be present and should anyway be corrected. It is known for some time that the FE Na is unreliable in sodium-retaining states such as chronic heart failure, decompensated cirrhosis, after diuretic therapy, after administration of contrast agents, and in pigment-induced nephropathy, and sepsis [72]. In one study in which the urinary parameters of elderly and younger patients with ARF were compared, prerenal failure indices were found in 21% of elderly with established ATN. The latter was defined by non-response to a trial of acute volume expansion [73].

Although the vast majority of patients with prerenal ARF may be identified by clinical and urinary evaluation, there are some elderly patients whose volume status cannot be confidently assessed. In this setting, a rising central venous pressure in response to fluid therapy is a valuable guide to therapy. “Blind” infusion of fluid should

not be undertaken without haemodynamic monitoring, especially in elderly azotaemic patients with impaired heart function. As explained earlier, older hypovolaemic patients often respond slower to a challenge of an acute volume load than younger patients.

Haemodynamically-mediated ARF.

Non-steroidal anti-inflammatory drugs (NSAIDs).

Since the introduction of the NSAIDs, a great number of cases of ARF has been observed in elderly individuals, not only because of their frequent use in this age (group) but because elderly kidneys are very sensitive to the renal vasoconstriction and the sodium retention associated with these drugs [74]. Population-based case-control studies demonstrated that the incidence of ARF is rare (2 per 100,000 person years) but is increased fourfold by NSAID usage [75].

In the age category over 60 years, these drugs were incriminated in more than 25% of drug-induced ARF [76]. In a large epidemiological study in a general internal medicine practice renal impairment was diagnosed in 18% of the patients, taking ibuprofen. However, serious renal dysfunction occurred in only 0.5% of the patients. If the renal effect of the NSAID is characterized in a first phase by a functional alteration which is rapidly reversible after stopping the treatment, this can lead to ATN in presence of prolonged renal ischaemia.

Well-known risk factors for NSAID induced nephrotoxicity include age above 60 with atherosclerotic cardiovascular disease, pre-existing chronic renal insufficiency (serum creatinine >180 μmol/L), and states of renal hypoperfusion such as sodium depletion, diuretic use, hypotension, and avid sodium states such as cirrhosis, nephrotic syndrome, and congestive heart failure [77]. There is, however, little evidence that NSAIDs impair the renal function in otherwise healthy elderly individuals. A particular characteristic of this cause of ARF is the hyperkalaemia which is sometimes out of proportion to the degree of renal impairment, especially when these patients are also treated with potassium-sparing diuretics or ACE-inhibitors. These risk factors are additive and patients with multiple risk factors are rarely included in clinical studies of these drugs.

It was originally hoped that agents with a more selective inhibition of COX-2 would not adversely affect renal function compared to nonselective NSAIDs. It appears however that selective COX-2 inhibitors probably have the same qualitative effects on renal function as non-selective NSAIDs [78]. It is therefore relevant that in elderly patients on a salt-restricted diet the COX2-selective inhibitor, rofecoxib, decreased GFR iothalamate clearance by approximately 15% [79]. In a cohort of elderly patients with decreased creatinine clearance on a low-salt diet and treated with rofecoxib or

indomethacin a similar decrease in the GFR (10–12%) and decreased excretion of sodium and water were noted with both agents [80].

A post-hoc analysis of the data from more than 50 clinical studies involving over 13000 study participants treated with celecoxib for an average period of 12 weeks documented a similar incidence of adverse renal effects using either celecoxib (4.3%) or the nonselective NSAIDs (4.1%) [81]. Although some studies have suggested that COX2 inhibitors may not cause as severe a decline in renal function as comparator non-selective NSAID [82], it is premature to take comfort in these reports, because the study subjects were not at high risk of renal insufficiency. Importantly, a few cases of acute renal insufficiency caused by COX2-selective NSAID have recently been reported [82,83] and the same precautions apply thus to both the nonselective NSAIDs and COX-2 selective NSAIDs. In addition most of the COX-2 selective drugs have rather long half-lives 11 hours for celecoxib and 17 hours for rofecoxib.

Rarely some patients may develop an acute oligo-anuric renal failure, associated with microscopic haematuria, significant proteinuria, and exceptionally eosinophilia reflecting an allergic acute tubulo-interstitial nephritis following NSAID treatment. Cure is obtained after stopping the medication. Even more exceptional is the development of a membranous nephropathy with these drugs.

Angiotensin converting enzyme inhibitors (ACEI) and angiotensin II (AII) receptor blockers

Several recent large clinical studies have drawn attention to the possibility of ACEI to cause ARF [84-86]. For example in the ELITE study, including patients over 65 years, a persistent but moderate elevation of creatinine has been noted in 10.5% of the patients, while the ACE medication had to be withdrawn because of ARF in less than 2% of the patient population [87].

Haemodynamic ARF caused by ACEI or by AII receptor blockers develops either in patients with a stenosis of the renal artery in a solitary kidney, or with bilateral renal artery stenosis. The diagnosis of renovascular disease is frequently overlooked and its increasing prevalence is associated with age and the vascular comorbidity in the population. Renovascular disease has been found in 34% of aged individuals suffering from heart failure [88], but patients with severe chronic heart failure, polycystic kidney disease, or intrarenal nephrosclerosis without renal artery stenosis are also at risk [89]. ACEI and/or AII antagonists are often indicated in these patients and the risk of haemodynamic ARF is thus not negligible. The pathophysiology of this syndrome has recently been described [90-92]. The frequency of ARF-induced by ACEI in the elderly has been estimated to vary between 6 to 23% in patients with bilateral renal artery stenosis and increases to 38% in patients with unilateral stenosis in a single kidney [93].

Besides functional ARF provoked by these drugs, a possible lethal association is the development of sometimes catastrophic hyperkalaemia. We have recently described a series of 25 patients (mean age 74 years) who presented with a hyperkalaemia (mean value 7.7 mmol/L) and a mean serum creatinine level of 3.8 mg/dL [32]. Fifty percent of these patients were dehydrated and all had been treated with a combination of spironolactone and ACEI, a regimen that was recently recommended for heart failure. Two of the patients died and two were successfully resuscitated.

RENAL CAUSES.

Renovascular diseases.

Acute obstruction of the renal vasculature by thrombosis of the renal artery or its intrarenal branches by cholesterol or non-cholesterol emboli are more common in the elderly.

One important risk for intrarenal emboli is the presence of atrial fibrillation, where the relative risk for peripheral embolisation aorta, renal, pelvic, and extremities has been calculated to be 4 in men, and 5.7 in women compared to the general population.[94]. ARF caused by complete renal artery thrombosis occurs when the occlusion is bilateral or in case of unilateral acute occlusion, with a non-functioning contralateral kidney. Flank pain with or without low-grade fever, and leukocytosis are the most common presenting symptoms. Macroscopic or microscopic haematuria are not always present. Whereas total occlusion of both renal arteries is usually manifested by anuria, minimal output of urine may be observed and the differential diagnosis with other forms of ARF may become difficult.

In patients with acute renal artery occlusion the urinary concentrations of sodium, urea, creatinine, and osmolality are similar to those found in the serum and the calculated FE Na is close to 100% [95]. The diagnostic work-up should include DTPA renal scanning, demonstrating markedly diminished or absent renal perfusion, followed by aortography with delayed pictures to define reconstitution of the distal renal artery and a nephrogram.

The management of ARF due to acute renal artery thrombosis is a challenge in these patients with often widespread vascular disease. Selective infusion of streptokinase or urokinase into the occluded renal artery is the first line therapy [96]. In some patients, fibrinolytic therapy may be followed by balloon catheter angioplasty to correct residual non-ostial renal artery stenosis. If thrombolytic therapy is ineffective, surgical revascularization should be promptly attempted. Surgery may offer a better chance for renal salvage in renal artery thrombosis complicating catheter angioplasty or occurring in association with acute aortic occlusion because of the risk of distal embolization. Recovery of renal function may be expected in only 30 to 40% of the

cases [96,97]. The optimal treatment for renal infarction is uncertain, but medical therapy is generally preferred. Although surgery can restore vascular patency, it is associated with a higher mortality rate and with no better renal functional recovery than that seen with anticoagulation or thrombolytic therapy alone [98]. Medical therapy will lead to improved renal function only if there is incomplete occlusion or if effective thrombolysis is initiated within 90 to 180 minutes, which represents the ischaemic tolerance of normal renal tissue [98]. Intravenous heparin followed by oral warfarin has been the standard anticoagulant regimen in this setting. Thrombolytic therapy with streptokinase or tissue-type plasminogen activator can in most cases effectively lysis the occluding thrombus. However, this modality should be considered only with early diagnosis when the ischaemic renal tissue is still viable. The risk of systemic bleeding can be minimized by local intraarterial infusion of the thrombolytic agent, rather than intravenous administration [98].

The one setting in which early surgery remains the treatment of choice is in patients with traumatic renal artery thrombosis, particularly if performed within the first few hours [99]. Surgical revascularization can be considered in patients with severe renal failure in whom there is no functional recovery within 4 to 6 weeks. Late embolectomy has led to improvement in renal function in selected patients, indicating that ischaemic atrophy can still be reversed [100].

The syndrome of multiple cholesterol emboli.

Recent studies suggest a much higher incidence of this syndrome than previously suspected and large series of patients suffering from multiple cholesterol emboli have been described. The clinical presentation and treatment of this disease has recently been summarized in an excellent review [101].

Cholesterol embolization can appear either spontaneously or following an intervention such as vascular bypass, angioplasty, or arteriography and is mainly observed in elderly males, suffering from generalized atheromatosis. Renal microembolisation is responsible for one third of the cases of ARF after emergency intervention for abdominal aorta aneurysm, explaining why some of these patients develop ARF without preceding hypotension. When ARF appears after an angiographic procedure, it usually presents after 2 to 4 weeks, which is in contrast with radiographic contrast ATN, that usually develops in a few days. In cases of cholesterol emboli, renal recovery is not observed in 30 to 40% of the cases. Treatment with anticoagulants or streptokinase and tissue plasminogen activator are often predisposing factors. These drugs apparently destabilize the cholesterol crystals in the atheromatous plaques [101].

Flank pain with or without moderate fever and leukocytosis are the initial symptoms. Micro- or macrohaematuria are not always present and accelerating

hypertension, rapid deterioration of renal function, neurologic symptoms, visual problems, digestive haemorrhages, or pancreatitis may be present. Ischaemic lesions at the legs or feet are frequent and present either as purpura, livedo reticularis, gangrene, or vascular ulcers. Laboratory results sometimes reveal eosinophilia, low complement and acute phase response. The clinical diagnosis of cholesterol emboli is confirmed by kidney biopsy in 30% of the cases, muscle biopsy in 21% of cases, skin biopsy in 17% of the cases or at post-mortem in 22% of the cases.

A recently described therapeutic protocol [102] includes complete stopping of anticoagulation drugs; forbidding any invasive intravascular procedure; prompt treatment of heart failure, and early initiation of haemodialysis associated with intense parenteral nutrition. Finally, patients who show signs of inflammation should receive corticosteroids. Peritoneal dialysis, by avoiding heparin, does not offer any advantage as was suggested in the past [103]. With this therapeutic regimen the authors have observed a considerable increase in the patient survival; nevertheless, still 32% of the patients needed permanent haemodialysis. The best results with corticosteroids have been reported by Boero et al [104]. Other authors have suggested that these patients should be treated with statins [105].

Acute tubular necrosis (ATN).

By far the most frequent cause of ARF in young as well as in older patients is post-ischaemic or post-nephrotoxic ATN [73].

In the Tenon hospital series [1], organic ARF was present in 53.5% of all cases and the most prominent causes of ATN were shock in 49.1%, nephrotoxic drugs in 6% , rhabdomyolysis in 9.8%, and multiple myeloma in 6.8% of the patients (Table 1).

Renal insults that characteristically cause this form of ATN include aminoglycoside nephrotoxicity, radiocontrast-induced ATN, rhabdomyolysis-induced ATN, and ATN complicating open heart surgery [106]. In two series of ARF in the elderly the incidence of the non-oliguric form was 19% and 24.5%, respectively [51, 73]. Clearly, any insult causing oliguric ATN can also result in the non-oliguric form of the disease.

Although for didactic reasons the distinction between ischaemic and toxic ATN is often made, ATN is frequently the result of combined risk factors in any age category [3,49]. Furthermore, the interaction between renal hypoperfusion and nephrotoxins is at least additive and probably synergistic. Particularly in older patients with ATN, several chronic premorbid conditions (i.e. congestive heart failure, hypertension, or diabetes mellitus) predispose to its development.

Post-ischaemic ATN.

Post-ischaemic ATN accounts in tertiary care hospitals for approximately 50% of all cases of ARF in the elderly [1,73, 107].

Post-operative ARF. Complications of major surgery, including hypotension during or after surgery, postoperative fluid loss due to gastrointestinal or fistula drainage, gastro-intestinal blood loss [108], arrhythmia's, and myocardial infarction, account for about 30% of all cases of post-ischaemic ATN [89]. Another important factor implicated in the aetiology of postoperative ATN is sepsis, particularly arising in the abdomen.

A systematic review of 28 studies that examined pre-operative risk factors for post-operative ATN found that a raised plasma creatinine or urea pre-operatively were strong predictors of post-operative worsening of renal function [109]. In some, but not all studies, advanced age and left ventricular dysfunction were also associated with a greater risk of postoperative ATN. Many of the other risk factors for ARF, including preoperative renal dysfunction, cardiac dysfunction, and vascular disease are all more common with advanced age. Since cardiac surgical interventions become more frequent in elderly patients numerous studies have defined the risks for developing ARF in these patients [57,60,110]. Following coronary artery surgery, the three major risk factors were: old age, pre-operative renal dysfunction, and post-operative haemodynamic instability, defined as the need of inotropic drugs. Although ARF occurred in 16% of the patients, only 1.2% required dialysis. In the latter category, the mortality was 44 % [111]. It was found that an abnormally low urine output during cardiopulmonary bypass was one of the earliest peri-operative clinical markers of patients at risk for post-operative ATN [112].

ATN after elective or emergency operation for abdominal aortic aneurysm is particularly frequent in aged people. In patients above 70 years of age, the incidence of ATN varies between 4% and 23%, depending on selection and pre-operative status of the patients. Emergency intervention for ruptured aneurysm has a mortality of 50 % [113] and this result has not changed over the years [114]. In contrast, elective surgery is now recommended in patients in their seventies and eighties and has a mortality of 5% (for review see [58]). The most common cause of transient renal ischaemia during aortic aneurysm operation is peroperative hypotension due to hypovolaemia. However, low arterial blood pressure is not always followed by ATN. Infrarenal aortic cross-clamping causes an increase in renal vascular resistance and a decrease in RBF that may persist for hours after unclamping. The aortic clamping time is thus a major determinant of the occurrence of post-operative ATN. An important cause of renal failure after aortic clamping and unclamping is renal microembolization.

Sepsis. Infection and in particular gram-negative septicaemia account for another 30% of cases of ARF in the elderly [1,49,65]. The elderly may deviate from the classic presentation of septic shock. Acute confusional states, general weakness or loss of appetite can be the presenting manifestations of infection and elderly patients with bacteraemia may be afebrile.

The low FENa in septic ATN, persisting during prolonged oliguria, suggesting persisting renal hypoperfusion, may give rise to confusion. It was found that the sequestration in the extracellular space of the fluid given during reanimation in older patients is longer compared to younger ones [115]. Volume replacement, even under Swan-Ganz monitoring, results in further fluid redistribution, with preferential sequestration of the fluid in the extracellular volume and the third space.

The multisystem organ failure syndrome (MOSF). The elderly have a characteristic MSOF syndrome [116], which differs somewhat from that in young patients because of pre-existing multiple (chronic) organ diseases. The syndrome is most often precipitated by, in descending order of frequency, infection, metastatic carcinoma, cardiac arrhythmia's, haemorrhagic shock, and acute myocardial infarction. The mortality ranges from 46% when two organs have failed, to 67% for three, to 80% for four. ARF carries a greater than 80% mortality rate in elderly patients with MSOF syndrome.

Nephrotoxic ATN

Radiocontrast ARF. Contrast nephropathy is the cause of 13% of all cases of ARF and ranks third of all hospital-acquired cases of ARF [117]. In general the acute deterioration of renal function appears within 24 to 48 hours after the contrast administration with a (peak) in the serum creatinine around day 3-5, followed by a return to the initial value within 7 to 10 days in the majority of cases [118]. A minority of patients develop (further) complications ranging from a prolongation of hospitalisation to the need for dialysis. The mortality in these cases can be as high as 29% [117]. In a prospective study, 183 patients aged 70 years or older underwent 199 cardiac catheterizations and angiography [119]. A clinically significant increase in serum creatinine levels developed in 11%. Multivariate analysis revealed that risk factors in these aged patients were: administration of >200 ml contrast material, a serum albumin level <35 g/L, diabetes mellitus, serum sodium <135 mmol/L, and baseline serum creatinine level >133 μmol/L. The most important risk factors for contrast nephropathy are a existing chronic renal failure, dehydration and the association of diabetes with chronic renal failure. Several studies have explored the efficacy of preventive hydration before exposure to contrast media [118,120]. Whereas most studies showed no differences in outcome in low-risk patients, intravenous hydration

with hypotonic saline, 0.45% at 1 ml/kg/hr during 12 hours before and after the contrast administration, significantly protects the high risk patients, including the elderly [120,121]. This protection is explained by a reduction of the renal concentration energy at the medullary level by the hydration and the salt loading decreasing the risk for hypoxic lesions in this vulnerable zone [122]. Up till now no study has been able to show that oral hydration is similarly effective as the parenteral route. Substances like furosemide, mannitol and dopamine are nowadays not longer recommended [118,120]. A recent placebo-controlled, prospective study has shown that the combination of hydration with the oral administration of acetylcysteine had an additional protective effect [123]. Although the nephrotoxicity of gadolinium is clearly lower than of the iodium containing media, cases of ARF have been observed with this agent [124].

Antibiotics. Aminoglycoside antibiotics are one of the most common causes of nephrotoxic ATN in the elderly. Erroneous estimate of GFR, based on the serum creatinine concentration may lead to inappropriate dosing. The other risk factors for aminoglycoside nephrotoxicity are the duration of the treatment, volume depletion, and concurrent cephalosporin use [125].

The elderly are also at significantly greater risk of the nephrotoxic effect of vancomycin. An incidence of 18.9% in patients older than 60 years compared to only 7.8% in younger patients was observed [126]. Using multivariate logistic regression models, concurrent use of loop diuretics was significantly associated with vancomycin nephrotoxicity.

Rhabdomyolysis.

Older people are very susceptible to rhabdomyolysis in different settings like acute immobilisation, trauma, infections, cerebrovascular accidents, and hypothermia. Surgery in which there is either prolonged muscle compression due to positioning during a long procedure, or in which there is vascular occlusion because of tourniquet use in orthopedic or vascular reconstructive surgery may lead to rhabdomyolysis [127,128]. Most of these patients develop mild ARF, mostly not needing dialysis, and have an uneventful recovery. This cause is frequently not recognised.

Acute interstitial nephritis (AIN)

The older patient may be more at risk of AIN because of the multitude of drugs that are often prescribed to this type of patient; AIN was diagnosed in 18.6% of all biopsies, performed in patients aged over 60 years [129]. This syndrome presents as ARF with histological features of interstitial oedema and inflammation and is caused by a variety of agents, especially NSAIDs. The AIN caused by NSAID's is clinically characterized by the combination of ARF and heavy proteinuria, especially when

minimal change nephropathy, another mechanism of NSAID induced nephropathy is associated [130]. Prompt recognition of AIN by renal biopsy may lead to early intervention with cortiosteroids and more rapid recovery of the renal function. Without treatment, renal failure may be prolonged and even permanent.

Glomerulonephritis.

Acute glomerulonephritis is quite a common cause of ARF in the elderly. Studies of renal biopsies [129-133] show a remarkably high incidence of crescentic glomerulonephritis. Haas et al. 2000 recently identified all native renal biopsy specimens from patients aged 60 years or older between 1991 through 1998. Twenty-five % of the 4,264 biopsy specimens were obtained from patients aged 60 years or older, and acute renal insufficiency was the indication for biopsy in 259 of these patients (24.3%). Close to 50% of the biopsies comprised glomerular diseases, 40 % revealed tubulointerstitial disease and the rest showed vascular diseases or multiple lesions. Among the conditions associated with rapidly progressive glomerulonephritis, both the idiopathic, and anti-GBM-associated glomerulonephritis are relatively common in older patients. Any form of crescentic glomerulonephritis in the elderly has a poor prognosis.

The same principles apply to treatment of older adults with crescentic glomerular disease but restraint should be exercised in the use of powerful immunosuppressive agents such as corticosteroids, immunosuppressive drugs and plasmapheresis. Aggressive immunosuppression in rapidly progressive glomerulonephritis in older (>60 years) patients is associated with a relative risk of death 5.3 times higher compared to younger patients [134].

Diffuse proliferative glomerulonephritis, commonly occurring in association with infections is another nephritic cause of ARF in the elderly. Clinical features of post-streptococcal glomerulonephritis in the elderly include hypertension in 82 %, oedema in 73 %, dyspnoea and pulmonary congestion in 41 %, and oliguria in 75 % of the cases [135]. Hence, post-infectious glomerulonephritis in the elderly is easily confused with congestive heart failure. The combination of ARF, a nephritic urine sediment and pulmonary oedema in an elderly patient must alert the clinician for this diagnosis. Post-streptococcal glomerulonephritis in the elderly seem(s) to have a favourable short-term prognosis [136].

The single most common diagnosis in elderly patients suffering from ARF due to glomerulonephritis was found to be focal/segmental glomerulonephritis which, in the absence of ANCA testing, may include patients with undiagnosed “vasculitis” [129,137]. Compared with patients younger than age 60, the elderly have also a higher incidence of vasculitis and Wegener’s granulomatosis, whereas the incidence of systemic lupus erythematosus is significantly lower [138].

Because of the potential for reversing ARF in some forms of glomerulonephritis, there should be no hesitation in performing a renal biopsy. Renal biopsy does not carry a greater risk in the older patient than in the younger age group and adequate renal tissue can be obtained in 80 to 95 %, with a complication rate of 2.2 to 9 % [139]. However, the interpretation of the histological findings may be more difficult because of complex changes in the aged kidney or intercurrent diseases as arteriosclerosis or global sclerosis.

POSTRENAL CAUSES.

Urinary obstruction is one of the important causes of ARF in the elderly. In two major series the incidence of postrenal ARF was 7.9 and 9 % in patients over 70 and 65 years, respectively [140]. Obstructive uropathy is most frequently encountered in community- and hospital ward-associated ARF and is less common in ICU-related ARF [141]. It is however more common in selected patient populations such as older men with prostatic disease and patients with a single kidney or intraabdominal cancer, particularly pelvic cancer [47,142,143]. Finally, the cause of obstructive uropathy is often amenable to therapy. Thus, obstructive uropathy should be considered in each case of ARF.

ARF develops only with bilateral obstruction or obstruction in a solitary functioning kidney. The obstruction, which may be either intrinsic or extrinsic, can occur at any level of the urinary tract in the elderly.

The most important causes and pathophysiology of urinary tract obstruction have recently been summarized [144,145]. Among the causes of lower urinary tract obstruction, prostatic enlargement due either to benign prostatic hyperplasia or prostatic adenocarcinoma is the most common. Benign prostatic hyperplasia affects 50 % of men aged 50 and increases to 90 % by the ninth decade of life [146]. A small fraction of these patients develop severe obstructive ARF, which in some progresses to irreversible renal failure. Some of them may present with symptoms of advanced renal failure, rather than with prostatism. In case of prostatic carcinoma it is usually the invasion of the uretero-vesical junctions that causes bilateral hydroureteronephrosis with progressive renal insufficiency. Rectal examination and serum prostate-specific antigen (PSA) determination are the most efficient means of excluding a prostatic malignancy. Urethral strictures, often secondary to iatrogenic causes and urethral trauma, are the second most common cause of urethral obstruction in males.

The most common cause of post-renal failure in females is ureteral obstruction due to pelvic malignancy — in particular invasive carcinoma of the cervix and its treatment with radiotherapy. From all causes of retroperitoneal fibrosis, the so-called inflammatory abdominal aortic aneurysm occurs mainly in elderly men and causes

radiographic demonstration of medial displacement of the ureter similar to that seen in idiopathic retroperitoneal fibrosis [147]. Severe ureteral obstruction may be seen even with small inflammatory aneurysms. These inflammatory aneurysms are of interest because there are several reports of successful corticosteroid treatment of the ureteral obstruction when surgery was not an option [148]. It is recommended that the ureters be placed anterior to the laterally directed iliac grafts at the time of aortoiliac aneurysm repair. If this is not done, ureteral obstruction is likely to result.

Deposition of uric acid crystals in the tubular lumen uric acid nephropathy may cause obstruction and its severity is directly related to the plasma levels of uric acid. Acute uric acid nephropathy is most often seen following chemotherapy for leukaemias and lymphomas [149]. In this setting, the liver converts the purine load generated by cytolysis into uric acid. The high filtered load of uric acid and tubular reabsorption combine to produce high tubular concentrations of soluble urate and uric acid. Acidification of tubular fluid converts urate to uric acid, which can occlude tubular lumina.

Other causes of intratubular crystalline precipitation have been recently summarized [150]. ARF associated with calcium oxalate crystalluria can accompany ethylene glycol ingestion, administration of the anaesthetic agent methoxyflurane, and small-bowel bypass operations [151]. High doses of methotrexate can lead to intratubular precipitation of the insoluble 7-hydroxy metabolite of methotrexate [150]. Other crystalline substances that can potentially precipitate within renal tubules and lead to ARF include acyclovir, triamterene, sulphonamides, and protease inhibitors such as indinavir [150].

In patients suffering from multiple myeloma intratubular precipitation of myeloma proteins and perhaps other proteins also can lead to ARF [152]. Dehydration with resultant high tubular water reabsorption and radiographic contrast material can facilitate myeloma protein deposition. These patients are at uniquely increased risk for ARF-associated with radiocontrast administration [153], use of NSAIDs [154], and angiotensin-converting enzyme (ACE) inhibitors [155]. Less commonly, hypercalcaemia and cryoglobulinaemia can precipitate ARF. Tumour lysis syndrome is most often seen after institution of chemotherapy but it can occur prior to any cancer treatment. Some series have documented spontaneous appearance of tumour lysis syndrome in 10 to 25% of all cases [156]. These spontaneous cases should be suspected in patients with massive tumour burden with rapid turnover, such as with high-grade lymphomas. Hallmark findings include a markedly elevated uric acid level, associated with oligoanuric ARF. In contrast with that occurring after chemotherapy, hyperphosphataemia may not be prominent [156]. Treatment prior to anuria consists of allopurinol, saline infusion, and loop diuretics to flush out uric acid crystals.

Recognition of intratubular obstruction as a potential cause of ARF has important therapeutic implications. For example, prophylactic therapy with the xanthine oxidase inhibitor allopurinol can prevent accumulation of uric acid in tumour lysis syndrome. Moreover, forced diuresis decreases tubular salt and water reabsorption, thereby diluting tubular fluid with decreases in crystal and protein concentrations. Finally, manipulations that increase urinary pH can increase solubility of crystalline substances such as methotrexate, uric acid, and sulfonamides [150].

Diagnosis of postrenal ARF

Clinical

It is imperative to exclude an obstructive cause in any patient presenting with ARF, because prompt intervention may result in improvement or complete recovery of renal function. Elderly males with unexplained ARF should undergo bladder catheterization.

The presence of alternating anuria and polyuria is an uncommon but classic manifestation of urinary tract obstruction and is usually caused by fluctuating accumulation and release of urine behind a stone that changes its position. In rare cases, unilateral obstruction can lead to anuria and ARF; vascular or ureteral spasm, mediated by autonomic activation, is thought to be responsible for the loss of function in the non-obstructed kidney [156].

The urinary parameters in obstructive ARF are similar to those found in ATN. However, some patients may have high urinary osmolality and low urinary sodium concentrations, simulating prerenal failure. Depending on the cause of the obstruction, crystalluria and haematuria may give clues to the presence of post-obstructive ARF.

Important clinical sequelae are the post-obstructive diuresis and the presence of hyperkalaemic renal tubular acidosis [148]. Post-obstructive diuresis, as the name implies, is the profuse diuresis (> 4L/day) that occurs after the release of the obstruction and never occurs unless both kidneys, or a single functioning kidney, are completely obstructed. The period of total obstruction is usually short, often a few days to a maximum of one week. Once the obstruction is relieved, the urine output generally ranges from 4 to 20 litres per day. In addition to the sometimes enormous losses of water and salt, patients may also become depleted of bicarbonate, calcium, magnesium and phosphate. The patient's volume and electrolyte status must be carefully monitored and appropriately adjusted during the diuretic phase. It is helpful to measure the total electrolyte losses in the urine. However, the phase of post-obstructive polyuria can be prolonged by excessive administration of fluids. Provided the patient does not develop

symptoms or signs of intravascular volume depletion, it is reasonable to infuse a daily volume somewhat less than the volume of urine passed in the preceding 24 hours.

The development of hyperkalaemic, hyperchloraemic tubular acidosis can be explained by the inability to lower the urinary pH below 5.5 during acid loading or by an inability to secrete renin during extracellular volume contraction hyporeninemic hypoaldosteronism [144]. Although this type of hyperkalaemic tubular acidosis usually presents indolently, it tends to persist after correction of the obstruction. Patients who fail to correct their hyperkalaemia as their ARF is reversed by dealing with the obstructive lesion, should be investigated for the presence of tubular acidosis [144,148].

Radiological

Ultrasonography is a safe and easily accessible initial investigation in the evaluation of patients with ARF. The diagnosis of obstruction is based on the finding of a dilated collecting system filled with urine. Ultrasonography exhibits a high degree of sensitivity (90 to 98 %) but a lower specificity (65 to 84 %) for detection of obstructive nephropathy [157]. Patients with highly distensible collecting systems or with pyelocaliectasis may be misdiagnosed as having hydronephrosis. False-negative studies have been reported in patients with very early (less than 8 hours) obstruction [158,159]. In many of these cases, the patients were of older age and the obstructing process, usually prostatic carcinoma or retroperitoneal fibrosis, encased the retroperitoneal ureters and renal pelvis, preventing their dilatation [160]. In the elderly, partial obstruction may be obscured by volume depletion. When there is strong suspicion of obstruction, the ultrasonograhic examination should be repeated after volume repletion.

Although intravenous pyelography and retrograde pyelography define the anatomical site and nature of the obstructive process much more accurately than renal ultrasonography, these techniques are no longer recommended as first step in the investigation of post-obstructive ARF. These examinations may however remain necessary in the preoperative evaluation because they allow visualization of the distal (point) of the ureteral obstruction. This may be important when ureterolysis is envisaged in case of retroperitoneal fibrosis. Antegrade pyelography has several advantages in patients with obstructive ARF. First, if there is dilation of the renal pelvis on ultrasound, the introduction of a fine needle into the renal pelvis under ultrasonographic guidance is almost always successful. Second, if a complete obstruction is found to involve the ureters, the operator can easily proceed to a therapeutic nephrostomy. Third, this examination will demonstrate the proximal border of the ureteral obstruction.

Studies have shown that obstruction of the kidneys produces changes in the Doppler-sonography waveform that result in an elevated resistive, or Pourcelot, index [161]. In pathologic hydronephrosis, arteriolar vasoconstriction secondary to

thromboxane production, increases the resistive index, distinguishing this disorder from kidneys that have dilated collecting systems, but are not obstructed.

Computed tomography can also be helpful in patients with an unidentified cause of obstruction in whom ultrasound has been unsatisfactory.

Although nuclear medicine imaging techniques are inferior to radiographic and ultrasonography studies in providing the diagnosis of urinary tract obstruction, they are useful for testing whether any significant degree of renal function is preserved in kidneys with severe anatomic hydronephrosis.

Treatment of the elderly patient with ARF.

In general the non-dialytic and dialytic treatment of ARF is the same in the elderly as in other adults. The non-dialytic treatment of ARF is discussed in other chapters. Also the drugs and other measures that might be employed to prevent ARF are the same in all age categories and have been discussed extensively in other chapters of this book. Since the selection of certain dialysis modalities may be different in the elderly compared to the younger patient population, this topic will be discussed here in greater detail.

THE DIALYTIC MANAGEMENT

The indications for dialysis in the elderly are the same as in the adult population. The selection of a given dialysis modality (haemodialysis, haemofiltration, or peritoneal dialysis) is not determined by the age of the patient itself but by a number of patient and/or disease- specific factors. These include the presence of haemodynamic instability, severe hypervolaemia, hypercatabolism, compromised pulmonary function, bleeding potential, vascular access problems and others that have been thoroughly discussed elsewhere.

Dialysis therapy of ARF patients is still the subject of a number of controversies, which include the role of peritoneal dialysis, the possible impact of the biocompatibility of the haemodialysis membranes and the choice between continuous renal replacement therapies (CRRT) and the intermittent forms of haemodialysis (IHD). These controversies have always been discussed related to the ARF population as a whole [91,162-167] and have not focused on the elderly ARF population. Since the possible impact of the biocompatibility of dialysis membranes has not yet been studied in an elderly ARF patient population, it will not further be discussed in this chapter.

PERITONEAL DIALYSIS

The many advantages of peritoneal dialysis as a continuous dialysis technique in critically ill patients have been described by Ash and Bever [168]. Despite these

theoretical advantages, there are several reasons why peritoneal dialysis is currently less frequently used in ARF patients:

1. There has been a change in the spectrum of patients developing ARF; the underlying disease[s] are much more serious than in the past, sepsis and hypercatabolism are often present, and ARF frequently develops quite late in the development of a multi- organ dysfunction syndrome. The lower efficiency of peritoneal dialysis in removing solute and fluid compared to extracorporeal dialysis limits its usage in patients with ARF who require significant volume and solute removal.

2. ARF often occurs in patients with intra-abdominal surgery where the insertion of an intra-peritoneal catheter may cause problems of leakage and can be considered as a source of infection.

3. By increasing the intra-abdominal pressure, peritoneal dialysis may compromise lung function and may therefore not be feasible in patients with the acute respiratory distress syndrome.

4. As dextrose in the dialysate provides the osmotic gradient to achieve fluid removal, frequent exchanges with dialysate containing high dextrose is occasionally used to achieve negative balance in fluid overloaded patients. Dextrose absorption from the peritoneal cavity is frequently significant. It has been shown in 5 patients with ARF that high dextrose-containing dialysate resulted in a respiratory quotient greater than 1.0 consistent with net lipogenesis. Four of these five patients absorbed more than 500 g of dextrose over 24 h. As overfeeding could lead to hepatic steatosis, increased CO_2 production with worsening of respiratory failure, and hyperglycaemia, the risks of using high dextrose-containing dialysate fluids should be weighed carefully against the potential benefits [169].

The principles of peritoneal dialysis, its application in ARF and the indications, contraindications and complications have recently been described in detail [170-172].

In 246 elderly patients with ARF, the survival between those treated with peritoneal dialysis and haemodialysis was not different [51].

CONTINUOUS VERSUS INTERMITTENT HEMODIALYSIS

A recent review of all clinical trials that have examined the effect of dialysis-related variables on clinical outcomes in patients with ARF requiring intermittent haemodialysis (IHD) has been published [173]. In particular, the role of biocompatibility of dialyzer membranes, and timing, intensity, and adequacy of dialysis were discussed.

Direct outcome comparative studies between CRRT and IHD in elderly ARF patients are not available; however, a large prospective study comparing these different dialysis strategies on outcome of patients of all ages with ARF was inconclusive [174].

Some recent papers have described the application of CRRT in elderly patients with ARF [175-178]. All findings support not only that aggressive renal replacement therapy is justified in critically ill elderly ARF patients but suggest that continuous haemodiafiltration may be well suited to their management; however, none of these studies help to discern between the different treatment modalities.

The last years "hybrid techniques" have emerged to provide alternative answers in the polarized discussion between IHD and CRRT. These "slow, extended daily dialysis" (SLEDD) techniques all combine the advantages of CRRT and IHD by using a dialysis monitor and water treatment module for on-line production of dialysate to do slow, but extended and daily, haemodialysis. Until now, no large scale studies are available on SLEDD; however, the technique is increasingly being used and the first report was positive [179].

These SLEDD modalities may be particularly indicated in elderly, critically ill ARF patients, although comparative studies between the different dialysis modalities in this particular segment of the patient population are not available.

It is our opinion that all dialysis strategies should be mastered and utilised in the appropriate indications in elderly ARF patients. So far, no hard evidence is available that one technique above the other is superior, if at least all techniques are used in the correct indications and applied by a skilled ICU and dialysis team. However, in the old patient with ARF, daily "slow" dialysis modalities such as peritoneal dialysis, CRRT, and SLEDD may be more appropriate than the "classical" 4-hours dialysis, even if the latter is performed on a daily basis.

Recovery and prognosis of ARF in the elderly

The recovery of renal function in elderly patients surviving ARF is usually assessed at discharge from the hospital . The cumulative results of 3 series, comprising a total of 296 patients [3], indicated that 198 patients or 67 % recovered renal function completely while only 8 or 2.7 % did not recover sufficiently to remain free of dialysis. At least in one study [73], the recovery of renal function was not different between older and younger patients.

In one study of long-term prognosis, 15 out of 35 elderly [43 %], surviving ARF had a normal serum creatinine at 39 months from discharge from the hospital [64].

Studies in mixed ARF populations indicate that some patients show a progressive and slow deterioration of the renal function, with age to be one determinant of long-term recovery [180-182].

An analysis of the long-term prognosis of elderly patients with ARF and surviving their stay in the ICU revealed that 18 months after discharge from the hospital, only 10 % were still alive. Preliminary data suggest that most of these patients died from a cause related to their original disease responsible for the ARF [3].

There is clearly no consensus whether age is an independent predictive prognostic factor. Some studies, however, concluded that it is in the elderly that outcome has improved over the years [183,184]. The most recent analysis of prognosis of ARF in very old patients (>80years old) showed that although there was a slight but significant increase in mortality when compared to an age-matched population, mortality in the elderly was no worse than the overall mortality of ARF in the literature [1]. However, almost half of the patients in this series suffered from either prerenal or obstructive diseases, both known to be associated with a relatively easier recovery of renal function than ATN.

Several risk models developed for critically ill patients have now been applied to patients with ARF, especially in the situation where ARF occurs as part of a multiple system organ failure (for review see [185]). Some individual renal units, like the Madrid scoring system, have developed their own prognostic equations that are simpler than the risk models and therefore can be applied easier at the bedside [186]. A recent comparative validation of several scoring systems in ARF patients revealed that the Madrid scoring system was the most accurate in predicting the prognosis of these patients [187].

Until a validated method of assessing the severity of disease and predicting the outcome in the individual patient with ARF is available, one can not conclude that old age is by itself an independent indicator of a poor prognosis.

It is certainly not sufficient to allow the nephrologist to deny elderly patients the full range of therapeutic options.

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Chapter 10

The dialytic management of acute renal failure in the elderly

Abstract

In this article the different dialysis strategies in the management of acute renal failure (ARF) in the elderly are discussed. Although peritoneal dialysis (PD) offers some theoretical advantages, there are several medical and technical reasons why it is currently less frequently used. The choice between intermittent hemodialysis (HD) and continuous renal replacement therapy (CRRT) is determined by a number of considerations, the most important ones being hemodynamic stability, the need for hyperalimentation and/or ultrafiltration, and the local experience with one or both techniques. Some recent studies with CRRT in elderly ARF patients describe favorable results. Slow extended daily dialysis (SLEDD) modalities may be particularly indicated in elderly, critically ill ARF patients because these techniques combine the advantages of both CRRT and HD. Finally, the importance of the biocompatibility of dialysis membranes is discussed. Although there are a number of theoretical arguments to use biocompatible membranes, this opinion is not always supported by the results of recent comparative studies. It is the opinion of the authors that all dialysis strategies should be mastered and utilized for appropriate indications in elderly ARF patients.

Introduction

The elderly, defined as the portion of the population more than 65 years of age, is the fastest growing sector of the general population in the Western world. In the United States, it has grown from 4% in 1900 to its current level of approximately 12.7%. The prediction for the year 2030 is that this proportion will reach 20%. In Europe the population more than 60 years old in 2025 is expected to be around 224 million people [1]. It can thus be expected that the incidence of acute renal failure (ARF) in the elderly population will increase. In view of the structural and functional alterations occurring in the aging kidney [2], it is not surprising that elderly individuals are more prone to the development of ARF in high-risk circumstances, because comorbidity increases with age, and the elderly are now frequently exposed to polypharmacy and more aggressive diagnostic and therapeutic interventions. Since most cases of ARF in older individuals occur in hospitalized patients and are associated with

multiorgan failure (MOF), both the general and dialytic management of these patients require specific knowledge and skills.

The true incidence of ARF in the elderly is difficult to estimate, because different diagnostic criteria of ARF are used in most published series. According to Groeneveld et al. [3], the age-related yearly incidence was only 17 per million population (pmp) in adults less than 50 years old, but 949 pmp in the 80±89 year old age group. In the years 1991 and 1992, the total number of all ARF patients attending 13 tertiary care hospitals in the Madrid area was 209 cases pmp/year, while in the patients more than 80 years old, ARF was observed in 1129 cases pmp/year [4]. In addition, in the nephrology intensive care unit (ICU) of the Tenon hospital in Paris, the percentage of patients more than 80 years of age admitted for ARF, always less than 4 % of the total number of ARF patients before 1978, has grown to a current proportion equalling approximately 40% [5].

Of the 8797 patients from the Quality Measurement and Management Initiative cohort who underwent coronary bypass surgery, 1.2% developed ARF. Of these patients, 5.2% were 80 years or older and the risk of ARF increased exponentially with increasing age [6]. In many studies, particularly those that have focused on ARF subsequent to cardiac surgery, a reduced baseline renal function emerged as a strong independent risk factor [6-9]. All these data suggest that ARF is more frequent in the elderly population.

The causes and prognosis of ARF in the elderly have been extensively discussed elsewhere [4,5,10-12] and are beyond the scope of this article. It is sufficient to note that many authors found that age per se is not an important determinant of survival in patients with ARF and that the prognosis has improved considerably during the last decades in spite of an increase in the severity of disease [10,13]. It should also be noted that in the series of Drüml et al. [13], of the 145 elderly ARF patients who fulfilled dialysis criteria, 66 were not dialyzed due to spontaneous remission (28 of 66) or because therapy was withheld (38 of 66).

In this article we focus on the dialytic management of elderly patients with ARF. Dialysis therapy of ARF patients is still the subject of a number of controversies, which include the role of peritoneal dialysis (PD), the possible impact of the biocompatibility of the hemodialysis (HD) membranes, and the choice between continuous renal replacement therapies (CRRTs) and the intermittent forms of HD. These controversies, always discussed for the ARF population as a whole [14-20], have not previously focused on the elderly ARF population.

The role of peritoneal dialysis

The many advantages of PD as a continuous dialysis technique in critically ill patients have been described by Ash and Bever [21]. Despite these theoretical advantages, there are several reasons why PD is currently less frequently used in ARF patients:

First, there has been a change in the spectrum of patients developing ARF; the underlying diseases are much more serious than in the past, sepsis and hypercatabolism are often present, and ARF frequently develops quite late in the development of a multiorgan dysfunction syndrome (MODS). The lower efficiency of PD in removing solute and fluid compared to extracorporeal dialysis limits its usage in patients with ARF who require significant volume and solute removal.

Second, ARF often occurs in patients with intra-abdominal surgery, where the insertion of an intraperitoneal catheter may cause problems of leakage and can be considered as a source of infection.

Third, by increasing the intra-abdominal pressure, PD may compromise lung function and may not be feasible in patients with the adult respiratory distress syndrome (ARDS).

Fourth, as dextrose in the dialysate provides the osmotic gradient to achieve fluid removal, frequent exchanges with dialysate containing high dextrose are occasionally used to achieve a negative balance in fluid overloaded patients. Dextrose absorption from the peritoneal cavity is frequently significant. It has been shown in five patients with ARF that high dextrose containing dialysate resulted in a respiratory quotient greater than 1.0, consistent with net lipogenesis. Four of these five patients absorbed more than 500 g of dextrose over 24 hours. As overfeeding could lead to hepatic steatosis, increased CO_2 production with worsening of respiratory failure, and hyperglycemia, the risks of using high dextrose-containing dialysate fluids should be weighed carefully against the potential benefits [22].

The principles of PD, its application in ARF, and the indications, contraindications, and complications in the critically ill have recently been described in detail [23,24]. In 246 elderly patients with ARF, the survival between those treated with PD and HD was not different [25]. The problems associated with acute PD experienced by Sonnenblick et al. [26] were peritonitis in 27%, sepsis in 13%, perforation of an organ in 8%, and hemorrhage in 6% of the patients. Some minor complications ranged from hypotension, catheter obstruction, hypokalemia, hyperglycemia, dehydration, and hypothermia.

Continuous versus intermittent hemodialysis

Several recent reviews have extensively covered the choice of either intermittent HD or CRRT in critically ill patients with ARF [15,17,27-30]. We have discussed in some detail the place of intermittent HD in patients with ARF [31] and Karsou et al. [32] have recently reviewed in depth all of the clinical trials that have examined the effect of dialysis-related variables on clinical outcomes in patients with ARF requiring intermittent HD. In particular, the role of biocompatibility of dialyzer membranes and timing, intensity, and adequacy of dialysis were discussed.

Swartz et al. [33] made an analysis of treatment modalities [continuous venovenous hemofiltration (CVVH) versus HD] in 349 adult patients with severe ARF based only on the first modality chosen in an intent-to-treat fashion to minimize the effect of patient assignment, of other uncontrolled biases, or of multiple switches in treatment. Initial univariate analysis showed the odds of death when receiving initial CVVH to be more than twice that when receiving initial HD. Progressive exclusion of patients in whom the modality of renal replacement therapy (RRT) might not be open to choice and/or in whom the risk of death was very high, left 227 patients for analysis. Their risk for death was 1.09 [confidence interval (CI) 0.67±1.8; P = NS] for initial CVVH, a value virtually equivalent to the risk value for initial HD. These results show that the high crude mortality rate of patients undergoing CVVH is related to the severity of illness and not to the therapeutic choice per se.

Direct outcome comparative studies between CRRT and intermittent HD in elderly ARF patients are not available; however, a large prospective study comparing these different dialysis strategies on the outcome of patients of all ages with ARF was inconclusive [34]. Furthermore, a meta-analysis, published in abstract form and comprising nine studies (692 patients with a mean age of 53.7 years) did not find a significant lower mortality risk between intermittent HD and CRRT, although there was a trend for better survival with CRRT [35].

Continuous extracorporeal therapies have assumed increasingly greater popularity in the management of critically ill ARF patients in the ICU. These continuous techniques include continuous arteriovenous hemofiltration (CAVH), continuous arteriovenous hemodialysis (CAVHD), continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). The different continuous techniques depend on the vascular access (arteriovenous, venovenous) and/or whether only convective or a combination of convective and diffusive removal is applied.

The major advantages of these continuous techniques over intermittent HD are considered to be 1) the gradual removal of uremic toxins and fluid without fluctuations, 2) the purely convective solute transport, 3) the high biocompatibility of the applied

materials, 4) the high sieving capacity of the membranes, 5) the isotonic ultrafiltration, 6) the good clinical tolerance and hemodynamic response, 7) the absence of rebound in solute concentrations, 8) the stability of the desired body hydration, and 9) the possibility for unlimited concomitant parenteral alimentation. It has, however, not yet been shown whether these advantages have a significant impact on patient outcome, the ultimate measure of treatment efficiency.

Many studies have suggested a greater hemodynamic stability in patients on CRRT, compared to intermittent HD [28,30,36]. Although the results were often statistically significant, the clinical relevance of the observed differences was low [30].

The only cross-over study performed to date did not find a difference in hemodynamic tolerance of CRRT compared to intermittent HD [37]. When certain guidelines are followed, such as use of biocompatible membranes, cool dialysate, a blood flow of less than 150 ml, a dialysis session of at least 4 hours, and slow or no ultrafiltration at the start of the session, acceptable cardiovascular stability can also be achieved in hemodynamically unstable patients treated with intermittent HD [38].

Although in recent years the problem of achieving adequate solute and fluid removal in ARF patients has received much attention, the targets for adequate solute clearance in ARF remain unknown and the importance of removing middle and large uremic toxins in the setting of ARF remains to be determined [32,39]. However, a recent prospective randomized study showed a clear impact of the amount of ultrafiltration by CVVH on the survival of critically ill ARF patients. The authors recommend that ultrafiltration should be prescribed according to the patient's body weight and should reach at least 35 ml/hr/kg [40].

Rigorous azotemic control obtained during CRRT can only be matched with very intensive intermittent HD regimens [41,42]. Based on computer-based models, critically ill patients with a greater than 80 kg body weight will almost always require daily intermittent HD to achieve the same azotemic control as with CRRT. However, although blood-based urea kinetics used to estimate the dose of dialysis provide consistent results in intermittent HD, they substantially overestimate the amount of solute removal when compared with dialysate-side kinetics in ARF [43].

Another theoretical advantage of CRRT modalities is that the highly permeable hemofilters used in these techniques allow the passage of small amounts of medium to large molecular weight substances, including cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β. An association between morbidity and mortality from sepsis and/or multiple organ failure and inflammatory cytokines has been suggested by several studies, although strategies aimed at abrogating the effects of pro inflammatory cytokines in human forms of sepsis have not shown unequivocal benefit [44]. There has been interest in examining the effect of CRRT on these cytokines. The removal of

cytokines with high volume hemofiltration or frequent filter changes of polyacrylonitrile hemofilter has been described [45-48]. CVVH with an AN-69 membrane, leads to a decrease in the concentration of TNF-α, IL-1, and IL-6. Most of the removal is due to adsorption to the AN-69 membrane, and the concentration remains low for only a few hours after a filter change [49,50]. However, a decrease in the concentrations of anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist was also observed. There was no demonstrable relationship between cytokines removal and improved hemodynamic stability.

A recent review compared a large number of studies with either CRRT or intermittent HD for treatment of patients with MOF and concluded that for MOF patients with ARF, there is compelling evidence that CRRT provides better survival than intermittent HD, with more improvement in pulmonary gas exchange, hemodynamic instability, azotemia control, fluid overload, and nutritional support. In patients with MOF and no renal failure, there is little evidence that CRRT enhances survival, oxygenation, and perfusion [51]. Also in a recent study by John et al. [36], CVVH did not improve parameters of splanchnic regional perfusion like pH_i, pCO_{2I}, or pCO_2 gap in septic shock ARF patients, despite more beneficial effects on the systemic hemodynamics of CVVH compared to intermittent HD.

Recently some articles have described the application of CRRT in elderly patients with ARF. Alarabi et al. [52] studied a total of 111 elderly patients (average age 70.4 years) from the cardiac surgery ICU with ARF during a period of 7 years (1988-1994). The overall survival in all of the patients was 58%. MOF was a major problem in which respiratory failure needing artificial ventilation was encountered in about 90% of patients. The major cause of death was MOF/circulatory failure. Bellomo et al. [53] prospectively studied 72 consecutive critically ill ICU patients ≥65 years old with severe ARF and 70 similar control patients less than 65 years old. A greater than 40% survival rate was achieved in the elderly with an in-hospital survival comparable to that of younger patients. Gordon et al. [54] provided hemofiltration and/or HD for 18 patients with a mean age of 73 years (range 60-85 years) and who developed renal failure after operation for ruptured abdominal aortic aneurysm over a 3-year period. Five patients received hemofiltration only, two had HD only, and the remaining 11 had both treatments. The median duration of renal support in the 11 survivors was 24 days, while the 7 patients who died received support for a median of 11 days. By 3 months after the operation, 8 of the 11 survivors were independent of dialysis.

Sixty five consecutive patients with a mean age of 70 years and suffering from severe postcardiac surgery ARF were treated with early and intensive CVVH after coronary artery bypass grafting (56.9%), single valve procedure (16.9%), or combined operations (26.2%) [55]. In 32.3% of patients, intra-aortic balloon counterpulsation was

required and 20% of patients were emergencies. Sustained hypotension despite inotropic and vasopressor support occurred in 40% of patients and prolonged mechanical ventilation in 58.5%. Using an outcome prediction score specific for ARF, the predicted risk of death was 66%, while the actual mortality was only 40%.

All these findings support an aggressive approach to RRT in critically ill elderly ARF patients and suggest that continuous hemodiafiltration may be well suited to their management; however, none of these studies help to discern between the different treatment modalities.

It can thus be concluded that CRRT procedures have certainly made the management of critically ill patients easier. In particular, oligo-anuric patients with diuretic resistance volume overload and hemodynamically unstable patients with ARF and concomitant sepsis or MOF appear to benefit most from continuous treatment. Noncritically ill patients with uncomplicated renal failure can be treated with intermittent HD or PD. Furthermore, intermittent HD is preferable in patients with a hemorrhagic diathesis because it can be easily performed without anticoagulants.

On the other hand, major disadvantages of continuous therapies are the ongoing necessity for continuous anticoagulation, immobilization of the patient, and possible side effects from lactate-containing replacement fluid or dialysate. The immobilization of patients may disturb the planning for diagnostic or therapeutic interventions so often needed in these critically ill patients.

It is thus not surprising that “hybrid techniques” have emerged to provide alternative answers in the polarized discussion between intermittent HD and CRRT. These slow extended daily dialysis (SLEDD) techniques all combine the advantages of CRRT and intermittent HD by using a dialysis monitor and water treatment module for on-line production of dialysate to do slow, but extended and daily HD. Until now, no large-scale studies are available on SLEDD; however, the technique is increasingly being used and the first report was positive [56]. These SLEDD modalities may be particularly indicated in elderly, critically ill ARF patients, although comparative studies between the different dialysis modalities in this particular segment of the patient population are not available.

An interesting new development in this field is the so-called batch HD system developed by Tersteegen for chronic intermittent HD and recently described in detail [57]. This Genius system was recently tested for the treatment of ARF in 20 patients with MODS in the ICU with promising results [58]. High efficiency, simplicity, and flexibility of the system offers the unique opportunity to use the same dialysis machine for extended time periods (18 hours) as well as for shorter intermittent RRT in critically ill patients. We are currently evaluating this system in a number of elderly ARF patients in our ICU.

The biocompatibility of the dialysis membranes

Membrane bioincompatibility issues cover more than complement and leukocyte activation. Other humoral pathways and cellular mechanisms can be activated during dialysis, leading to coagulation disturbances, allergy, leaching, and spallation, making the biocompatibility issue more complex than originally supposed.

Among the dialysis membranes, unsubstituted cellulosic cuprophane obviously imposes the most important complement and leukocyte activation; the remaining cellulosic membranes, even cellulose acetate, induce a less pronounced response [59]. Although the synthetic membranes, in general, are considered to be more biocompatible, variable degrees of complement activation have been observed. In animal experiments, complement activation during the blood-dialyzer interaction with certain, especially unmodified cellulosic membranes (but not with more compatible membranes) can lead to infiltration of activated neutrophils into tissues such as the lungs and the kidneys, which may prolong renal damage [60,61].

In older studies [60,62-64) the use of cuprophane membrane dialyzers had a negative impact on the survival rate of ARF patients, the occurrence of sepsis, the length of oliguria and the rate of renal recovery compared with the use of biocompatible polymethylmethacrylate (PMMA) or AN-69 membrane dialyzers. These benefits were limited to patients who were nonoliguric prior to the onset of HD. In an analysis by Mehta et al. [34], patient outcome was markedly better in patients on membranes with high biocompatibility. This relationship disappeared, however, after correction for severity of disease. Neveu et al. [65], analyzing retrospectively the prognostic factors in ICU patients with ARF with and without sepsis, indicated the nature of the membrane as one of the contributing factors and found that the outcome was more beneficial for noncuprophane dialyzers.

In a multicenter prospective study [66], a positive effect of the biocompatibility of the membrane on survival and recovery of renal function was observed. Divergent outcomes were virtually confined to patients who were nonoliguric at the start of dialysis. Overall trends were the same in all centers involved, and remained present after adjustment for severity of disease. However, in some studies, summarized by us [59,67], a beneficial effect of biocompatible membranes was not observed.

The most recent prospective multicenter European study [68] did not show differences in various outcome parameters between the patients dialyzed with a bioincompatible cuprophane or a biocompatible PMMA membrane. Similar negative results were obtained in a single center experience [69]. It is of note that in studies showing no difference, either cellulose diacetate membranes were considered as “bioincompatible” membranes or PMMA membranes as “biocompatible” membranes.

Both membrane types, however, take an intermediary position on the scale differentiating the degree of biocompatibility.

Further reasons why such divergent results in ARF patients are obtained is that, compared to chronic HD, the course of ARF is probably too short to allow morbidity to be affected by the membrane type. More importantly, other comorbid factors and the experience and skills of the medical and nursing staff in both ICUs and renal divisions have a more dramatic impact on the outcome than the dialysis membrane type. In spite of the divergent results, we feel that there is more evidence that suggests a negative role for complement-activating, bioincompatible membranes on the outcome of ARF than vice versa. Although many studies comparing different dialysis membranes were performed in a general ARF population and did not specifically focus on elderly patients alone, it may be assumed that the results can be extrapolated to this category of patients.

Conclusion

The dialytic management of critically ill ARF patients remains a matter of controversy [17]. In many hospitals, this controversy is enhanced by the conflict of interest between the ICU and the nephrology department. Furthermore, it is our impression that for intermittent as well as for continuous dialysis modalities, modifications of these techniques remain unused. This lack of flexibility in adapting dialysis techniques to the individual needs of patients limits their effect and efficiency.

It is our opinion that all dialysis strategies should be mastered and utilized for the appropriate indications in elderly ARF patients. So far, no hard evidence indicates that any one technique is superior to another, at least when all techniques are used for the correct indications and applied by a skilled ICU and dialysis team. However, in the old patient with ARF, daily "slow" dialysis modalities such as PD, CRRT, and SLEDD may be more appropriate than the "classic" 4 hour dialysis, even if the latter is performed on a daily basis.

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Chapter 11

Intensive care for very elderly patients: outcome and risk factors for in-hospital mortality

Aims

Objectives: to evaluate outcome and risk-factors, particularly the Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system, for in-hospital mortality in the very elderly after admission to an intensive care unit (ICU).

Methods: retrospective chart review of patients ≥ 85 years admitted to the ICU. We recorded age, sex, previous medical history, primary diagnosis, date of admission and of discharge or death, APACHE II score on admission, use of mechanical ventilation and inotropics, and complications during ICU admission.

Results: 104 patients ≥ 85 years (1.3% of total ICU admissions) were studied. The ICU and in-hospital mortality rates for these patients were 22 and 36% respectively. Factors correlated with a greater in-hospital mortality were: an admission diagnosis of acute respiratory failure (χ^2; P=0.007), the use of mechanical ventilation (χ^2; P=0.00005) and inotropes (χ^2; P=0.00001), complications during ICU admission (χ^2; P=0.004) in particular acute renal failure (χ^2; P=0.005) and an APACHE II score ≥ 25 (χ^2; P=0.001). The APACHE II scoring system and the use of inotropes were independently correlated with mortality.

Conclusion: ICU and in-hospital mortality are higher in very elderly patients, particularly in those with an APACHE II score ≥ 25. The most important predictors of mortality are the use of inotropes and the severity of the acute illness.

Introduction

A recent overview of outcomes of intensive care for elderly people in terms of mortality, hospital costs and quality of life, concluded that age alone is not an important predictor and that most patients have an acceptable quality of life after admission to an intensive care unit (ICU) [1].

Although intensive care in elderly patients has been examined [1-6], few studies have concentrated on very elderly people [7,8]. We have studied risk factors for in-hospital mortality in the very old. In particular, we have evaluated the Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system [9].

Materials and methods

We studied patients admitted to the ICU of a 1040-bed university hospital: a 38-bed unit which takes medical and surgical cases.

All patients ≥85 years admitted to the ICU between January 1994 and September 1996 were retrospectively evaluated. Data obtained from the medical records included: sex, age, previous medical history, date of hospital admission and discharge or death, diagnosis on admission to the ICU, date of ICU admission and discharge, APACHE II score on admission to the ICU, need for mechanical ventilation and the use of inotropes and finally, complications during ICU stay.

For patients < 85 years we obtained data on the APACHE II score on admission to the ICU and survival.

In Belgium, admission to an ICU occurs after emergency surgery but there are also elective admissions. We included elderly subjects admitted after elective surgical intervention. We also included patients for whom 'do not resucitate' decisions had been made on admission and who had become medically stable (some of these patients were discharged from hospital).

Statistical Methods: All data are presented as mean values ± SD. Two-tailed Student's t-test and Mann-Whitney U-test were used for continuous variables. The Bonferroni correction was applied for multiple testing effects. The Chi-square test, Pearson or Fisher exact test (as appropriate), were used to compare categorical variables between survivors and non-survivors.

Logistic Regression analysis was used to determine the independent risk-factors for in-hospital mortality. We included in this model the significant factors identified by univariate analysis.

Results

A total of 104 patients (1.3% of ICU admissions) were studied. The mean age of the patients was 88.0 ± 2.03 years (median 87.5 years; 68 female, 36 male). Age and sex were not significantly correlated with a greater in hospital-mortality. Median ICU length of stay was 1.0 day (range 16.6) and median hospital length of stay was 16.0 days (range 179.5). Patients who died in the ICU stayed significantly longer in the ICU (median 3.0 days, range 16.6 days) than did survivors (1.0 days, range 6.6 days; P=0.001). Survivors after ICU admission stayed significantly longer in hospital than other patients (in-hospital length of stay for the very elderly not admitted to the ICU was 16 days).

The ICU mortality for patients ≥ 85 yrs was 22.1% (11% ICU mortality during this study period for the overall ICU population). The overall in-hospital mortality was 36.5% (11% for very elderly subjects not admitted to the ICU).

The reason for admission to the ICU were elective surgery (12 patients), emergency surgery (21), acute respiratory failure (19), cardiac disease (14), infectious disease (13), neurological diseases (11) and other diseases (14).

Mortality was significantly higher only for patients admitted with acute respiratory failure (χ^2; P=0.007). All patients undergoing elective surgery were discharged from hospital. Of the two patients admitted after cardio-pulmonary resuscitation (for ventricular fibrillation), one survived.

The previous medical history — cardiac disease (22 patients), neurological diseases (8), pulmonary diseases (2), gastro-intestinal diseases (7), endocrinologic diseases (9) or a combination of these diseases (38) did not influence mortality.

Patients without ICU complications had a significantly better survival (χ^2; P=0.004). ICU- complications as pneumonia (15 patients) and shock (8 patients) were not associated with a higher mortality rate (χ^2; P=0.76 and P=0.11 respectively). Need for inotropes (15 patients) and mechanical ventilation (30 patients) and acute renal failure (7 patients) were associated with a significantly higher mortality rate (χ^2; P=0.00001; P=0.00005 and P=0.005 respectively).

"Do not resuscitate" decisions were made on admission in 19 patients (7 survivors and 12 non-survivors; P=0.007). All patients (n=11) for whom such a decision was made after therapy was considered futile (>48 h after admission) died.

The mean APACHE II score for survivors and non-survivors was 19.9 ±8.5. The score was significantly higher in non-survivors compared with survivors (24.8 vs. 16.0; P=0.004). As mortality increased with increasing APACHE II scores (Figure 1), we tried to determine a treshold APACHE II score for a higher mortality rate in elderly patients. Mortality rates were significantly higher than in the younger population for APACHE II scores ≥ 25 (χ^2; P=0.001).

Independent risk factors by multiple logistic regression analysis for in-hospital mortality were: the APACHE II score and the use of inotropes (Table 1).

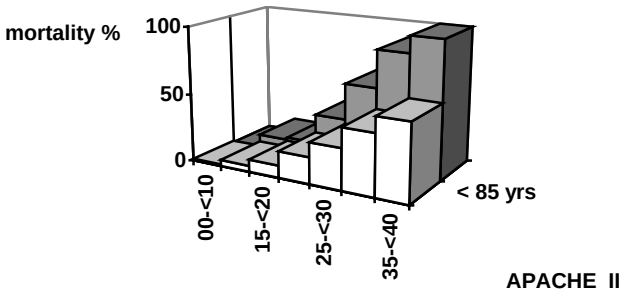

Figure 1: Mortality rate for APACHE II score in patients < 85 yrs and ≥85 yrs

Table 1: Multiple Logistic Regression analysis of risk factors predictive of in hospital mortality

Predictor	**β-coefficient**	***P*-value**
APACHE II score	-0.1408	0.0049
Inotropes	0.9698	0.0321
Acute Renal Failure	4.6139	0.8086

APACHE, Acute Physiology and chronic health evaluation

Discussion

In our study, very old patients represented 1.3% of the total ICU admission, a figure similar to that found in other studies [2]. Previous reports of overall ICU mortality range from 9 to 38% [10-12]. Our mortality rate was 11%. A higher ICU mortality (22%) and overall in-hospital mortality (36.5%) occurred in the very elderly. Overall in-hospital mortality for the very old ranged from 11.9% [13,14] to 39% [7,8,15-18]. The mortality rate for our patients who needed mechanical ventilation was 66.7%, similar to previous studies [19-24]. However, one study reported 100% mortality for patients ≥85 years [25].

We did not compare risk factors for mortality with those in younger age groups as others have already tried to clarify the relation between age, severity of acute illness, functional status and mortality rate. These studies have shown that severity of acute illness is an important predictor of mortality after ICU admission. Age by itself is not a significant predictor.

We wondered if a subgroup of the very elderly could be identified in whom appropriate decisions on life sustaining therapy could be made at an early phase.

We expected to find a higher mortality rate in the very elderly, particularly in those with severe acute illness as measured by an APACHE II score. We also expected a correlation between co-morbidity, reason of admission and complications during ICU admission. We found the risk factors for higher in hospital-mortality to be an admission diagnosis of acute respiratory failure, an APACHE II score ≥25, the need for mechanical ventilation and inotropes, and complications during ICU stay (particularly acute renal failure). After multiple logistic regression analysis, independent risk factors for in-hospital mortality were the APACHE II score and the use of inotropes.

We did not find co-morbidity to be an important risk factor. This is probably the result of methodological constraints. As this is a retrospective chart review, we do not know about the mortality of patients in whom admission to the ICU was not considered or a decision against ICU admission was made. Selection on the basis of functional status was another possible bias, as no patients with APACHE II score ≥40 were admitted. Perhaps we failed to demonstrate a relationship of some risk-factors with mortality because of the small sample size.

Another factor that can complicate the interpretation of these results is difference in healthcare policies between countries. We are aware of the fact that some elderly subjects included in our study would not have been admitted to the ICU in other European countries. We hope that these data will stimulate debate about the appropriateness of admission of very elderly patients to ICUs.

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Chapter 12

Outcome in a post-cardiac surgery population with acute renal failure requiring dialysis: does age make a difference?

Abstract

Background: Acute Renal Failure (ARF), requiring dialysis (ARF-d), develops in 1 to 5% of patients undergoing cardiac surgery and is associated with higher in-hospital mortality. Age is one of the known risk factors for the development of ARF. As the ageing population is increasing, the nephrologist will be faced with a large population of elderly patients requiring dialysis following cardiac surgery. The aim of our study was to evaluate the influence of age on and the risk factors for in-hospital mortality.

Methods: 82 patients with ARF following cardiac surgery and requiring dialysis between January 1997 and October 2001 were included. Two groups of patients were studied: the younger population (< 70 years, 42 patients, mean age 59 ± 10) and an elderly population (≥70 years, 40 patients, mean age 76 ± 4). Severity of disease was evaluated using the SAPS (Simplified Acute Physiology Score), the Liano score and the SHARF (Stuivenberg Hospital Acute Renal Failure) score.

Results: Overall mortality in the population with ARF-d was 56.1%. No difference in mortality rate was found between the younger (61.9%) and elderly patient group (50.0%). The two groups were very similar in baseline and procedural characteristics with exception of body weight (P=0.02) and preoperative glomerular filtration rate (GFR) (P=0.0001). No significant difference was found in the scoring systems between the old and the young (SAPS P=0.52; Liano P=0.96; SHARF T0 P=0.06; SHARF T48 P=0.15). Mortality in the elderly was significantly correlated with hypotension before starting renal replacement therapy (RRT) (P=0.002), mechanical ventilation (P=0.002), presence of multiorgan failure (MOF) (P=0.0001) and higher scores in the severity models (SAPS: P=0.01; Liano: P<0.0001and SHARF: P<0.0001).

Conclusion: The outcome in the elderly requiring dialysis due to ARF post-cardiac surgery, is comparable with the outcome in a younger population. No significant difference was found in severity of disease between the elderly and the younger. Variables predicting mortality in the elderly are the presence of MOF, mechanical ventilation and hypotension 24h before starting RRT. These findings indicate that at the

time the nephrologist is called for an elderly patient requiring dialysis due to ARF following cardiac surgery, age *per se* is not a reason to withhold RRT.

Introduction

The elderly are the fastest growing age group of the general population. In Western Europe and the US, the number of subjects > 60 years is projected to rise from 231 million in 2000 to 395 million in 2050. Because cardiovascular disease is the leading cause of morbidity and mortality in the elderly, the ageing of the population has led to an increasing number of patients with symptomatic coronary heart and valve disease in whom cardiac surgery is needed. A serious complication of cardiac surgery is acute renal failure (ARF). ARF requiring dialysis (ARF-d) occurs in 1-5% of patients following cardiac surgery and is associated with high morbidity and mortality [1-7]. The influence of preoperative and intraoperative factors on the development of ARF-d is well known from previous studies [2-11]. One of the risk factors for developing ARF following cardiac surgery is age [3,6,9-11]. Because of this evolution, the nephrologist will, in the near future, be faced more frequently with the problem of dialysis requiring ARF following cardiac surgery in the elderly. The policy in our hospital until now is to start renal replacement therapy (RRT) in every patient following cardiac surgery developing ARF with a need for RRT.

The aim of this study was to evaluate the question of whether the age of the patient should influence this policy. Therefore, we compared the outcome in the elderly with those in younger patients requiring dialysis following cardiac surgery. Concomitantly, we tried to evaluate whether the risk factors for in-hospital mortality and the underlying severity of disease were comparable in both age groups.

Subjects and Methods

This study is a retrospective chart review of patients developing post-cardiac surgery ARF, requiring dialysis, at the University Hospital Gent. Between January 1997 and October 2001, 3,736 adult patients (20 years or older) of which 1,497 patients 70 years or older (40%), underwent cardiac surgery. Of these population 85 patients or 2.3% developed ARF, requiring dialysis. Three patients with ARF but in whom renal replacement therapy (RRT) had already been started before surgery were excluded. The mean age of the 82 patients was 67.5 ± 11.5 years. For this analysis the population was divided into two groups according to age: the younger (< 70 years, 42 patients, mean age 59 ±10 years) and the elderly (≥70 years, 40 patients, mean age 76 ±4 years). In-hospital mortality was recorded and based on known risk factors [1-11] the following baseline characteristics were evaluated: age, gender, body weight, height, medical

history, medication at time of surgery, preoperative serum creatinine and glomerular filtration rate estimated by Cockcroft-Gault [12], type of cardiac surgery, preoperative use of intraaortic balloon pump (IABP), mechanical ventilation, need of inotropics and nitro-glycerine. In the medical history of the patients, previously known renal impairment, the presence of diabetes (defined as treatment with oral antidiabetics or insulin), peripheral vascular disease (defined as previous vascular procedure, a history of claudication or presence of femoral bruits), previous cerebrovascular insult, arterial hypertension (defined as taking antihypertensive drugs or systolic or diastolic blood pressure higher than 140/90 mmHg at the moment of hospitalisation), chronic obstructive pulmonary disease, recent (<2 weeks) or previous myocardial infarction and dyslipidaemia, were noted. The following perioperative and postoperative variables were studied: the use of and duration of extra-corporeal circulation and cross clamping, the number of distal anastomoses, the insertion of IABP, the presence of intraoperative hypotension (defined as a systolic blood pressure < 90mmHg) and the use of inotropic drugs. Characteristics of RRT such as the type of RRT and the onset and duration of RRT were recorded. Also, the presence of hypotension, mechanical ventilation, cardiac arrest, oliguria, defined as a diuresis < 400 cc over 24 h, and serum creatinine at onset of RRT were noted.

To evaluate the severity of illness associated with ARF, scores to predict mortality in Intensive Care Unit (ICU) patients were retrospectively calculated using the worst values obtained 24h before starting RRT. The first method, of use in ICU patients, is the Simplified Acute Physiology Score II (SAPS II) [13]. Le Gall et al preferred this method to the APACHE II (Acute Physiology and Health Evaluation) method to avoid a systematic bias. Indeed missing values may induce a bias if they are reported as normal values in the APACHE II method. Second, more specific models to predict mortality in patients with ARF such as the Liano score [14] and the SHARF (Stuivenberg hospital acute renal failure) score [15] were applied as well. In a retrospective study comparing various scoring methods Douma et al found that the Liano model was the most accurate predictor of a fatal outcome [16]. The SHARF score was recently developed as a bedside tool and compares favourably with other published scores [15]. The SHARF score was evaluated 24h before and 48h after starting RRT. Because age is included as predictive factor in all these scores, the scores were also calculated without age.

First, a search was performed for differences in baseline characteristics, peri- and postoperative variables, scores of predictive models and dialysis characteristics between the younger and the elderly. They are presented as means with standard deviations for continuos variables and as percentage for dichotomous variables. All statistical comparisons are made across age category (younger and elderly) using the Student's *t*-

test, the Fisher's exact test or χ^2 test where appropriate. Significance was defined as $P < 0.05$.

Secondly, the presence of a difference between the models including age or not was evaluated. Receiver operating curve analysis and area under the curve (AUC) were used to compare the accuracy in predicting mortality, comparing the same score calculated with and without age. If the AUC is significantly different, a difference in the models must be present.

Thirdly, the mortality and the variables correlated with mortality were evaluated in the whole patient group and separately in the elderly group. Univariate analysis was performed using the Student's *t*-test, the Fisher's exact test or χ^2 test where appropriate.

Statistical analysis was performed using the Medcalc package (Medcalc, Mariakerke, Belgium) and SPSS version 10.

Results

Baseline and procedural characteristics

The patient characteristics and clinical data (pre-, peri- en postoperative and 24 hour before starting RRT) are shown in Table 1. The number of isolated Coronary Artery Bypass Grafting (CABG) procedures was comparable in the younger (69%) and the elderly (45%) although there was a significantly higher number of distal anastomoses in the elderly (3.4 ± 0.9) than in the younger patients (2.8 ± 0.9) (P=0.02). Other surgical procedures such as valve replacement and combined surgical interventions were also comparable between the younger and the elderly. Elective surgery was performed in 45% in the young and in 40% in the elderly (P=0.81). No significant difference was found between the young and the elderly in medical history and in the preoperative use of cardiac medication. The cause of ARF was similar in both age groups. The most frequent reason of ARF was acute tubular necrosis (ATN) due to low cardiac output (53.7% in the younger and 58.3% in the elderly; P=0.85) or septic shock (24% in the younger and 8% in the elderly; P=0.12). Other reasons of ARF were underlying chronic renal insufficiency due to nephroangiosclerosis and diabetic nephropathy, contrast-induced nephropathy and cholesterol embolization. No differences in applied type of RRT between the different age groups was found. In the younger age group 54.8% underwent CVVH (continous venovenous haemofiltration), 23.8% underwent CVVHD (continous venovenous haemodialysis and 21.4% haemodialysis. A similar distribution was found in the older age group (65%, 10% and 25% respectively). The most frequent indications for RRT were oliguria (65%), acidosis (8%), hyperkalaemia (12%) and rhabdomyolysis (5%) in both age groups The moment of initiating RRT was the same in the elderly (day 2.42 ± 1.10) as in the young patients (day 2.73 ± 2.57) (P =0.24). RRT was performed during 5.07 ± 4.36 days in the elderly

and 5.69 ± 1.16 days in the young (P =0.61). Five patients younger than 70 years and none of those older than 70 years, remained dialysis dependent after cardiac surgery.

Table 1: Patients demographic and clinical data

	Patients <70 yrs (n=42)	**Patients ≥70 yrs** (n=40)
Gender (M/F)	30/12	21/19
Bodyweight (kg)*	77.5 ± 15.1	69.9 ± 10.5
Serumcreatinine (mg/dl)	1.76 ± 1.11	1.83 ± 1.14
Creatinine clearance (ml/min)†	59.7 ± 30.8	36.1 ± 12.0
Diabetes mellitus (%)	31	35
Preoperative variables		
Inotropics (%)	14.3	12.5
IABP (%)	26.2	37.5
Mechanical ventilation (%)	12	2.5
Peri-&postoperative variables		
ECC (%)	88	80
Duration of ECC (min)	129 ± 45	138 ± 57
Duration of cross clamp (min)	58 ± 29	70 ± 27
IABP insertion (%)	54.8	57.5
Intraoperative hypotension(%)	61	71
Postoperative inotropics (%)	88.1	90.0
Duration ventilation (days)	5.9 ± 6.9	5.4 ± 7.4
Variables 24h before RRT		
Cardiac arrest (%)‡	30	8
Hypotension (%)	48.6	38.9
Oliguria (%)	43.7	51.4
Ventilation (%)	70.3	54.1
Serumcreatinine (mg/dl)	3.8 ± 1.6	3.7 ± 1.1

IABP: Intraaortic balloon pump
ECC: extracorporeal circulation;
*P= 0.01
† estimated by Cockcroft-Gault formula; P= 0.0001
‡P= 0.08

There was no statistically significant difference between the age groups in the values of the different predictive models. However, comparing the scores between the non-survivors in both age groups, a significantly lower score in the elderly was found for the SAPS II. In contrast a significantly higher score in the elderly was found for the SHARF (Table 2).

Table 2: Values of the different scoring systems used to evaluate severity of disease

	Total patient population (n=72)			**Non-survivors (n=41)**		
	<70 yr	≥70 yr	*P*	<70 yr	≥70 yr	*P*
SAPS II	48±21	46±12	0.52	61±18	50±12	0.001
Liano	0.568±0.284	0.571±0.242	0.96	0.744±0.169	0.730±0.174	0.80
SHARF T0	168±26	180±26	0.06	184±15	196±16	0.02
SHARF T48	170±31	181±31	0.15	192±17	205±15	0.01

SAPS II (Simplified Acute Physiology Score II); SHARF (Stuivenberg Hospital Acute Renal Failure Score) T0 (24h before starting renal replacement therapy) T48 (48h after starting renal replacement therapy)

To evaluate whether some scoring systems without age are more useful to predict mortality in our study population, the AUC for the different methods with and without age were compared (Table 3). Only for the SHARF T0 score a significant difference in favour of the models without age was obtained (*P*=0.04).Therefore, we decided to use the scoring systems as validated with age.

Table 3: Evaluating the difference in the methods used to predict mortality calculated with or without age using the area under the curve (with 95% confidence interval)

	With age	**Without age**	*P*
SAPS II	0.830 (0.723,0.908)	0.833 (0.727,0.911)	0.90
Liano	0.904 (0.723,0.908)	0.913 (0.822,0.966)	0.78
SHARF T0	0.875 (0.774,0.942)	0.927 (0.774,0.942)	0.04
SHARF T48	0.929 (0.837-0.977)	0.945 (0.859,0.986)	0.47

SAPS II (Simplified Acute Physiology Score II); SHARF (Stuivenberg Hospital Acute Renal Failure Score) T0 (24h before starting renal replacement therapy) T48 (48h after starting renal replacement therapy)

The overall in-hospital mortality (n=3,736) was 3.7%. Mortality rate was significantly higher in the elderly patients (5.1%) than in the young (2.7%) (*P*=0.004).

A mortality rate of 56% was found in the population with ARF-d. The outcome was comparable in both age group with a mortality rate of 61.9% in the younger and 50% in the elderly. The surgical procedure was not correlated with significant differences in mortality rate between both age groups (mortality rate for CABG and valve replacement of 41.4% and 75% in the younger versus 55.6% and 50% in the elderly). Compared with urgent and emergency surgery, elective surgery was correlated with lower mortality (P=0.02). No significant difference in mortality was found between the younger (45%) or older (40%) elective surgical patients. Patients undergoing CVVH had a significantly higher mortality (65.3%) than patients treated with intermittent haemodialysis (31.6%) (P =0.04). This difference was not present in the elderly population (mortality 57.7% and 40% for CVVH and HD, respectively). No difference between survivors and non-survivors in both age groups was found in the day of appearance of ARF and the peak serum creatinine (2.73±2.57 day and 3.76±1.58 mg/dl in the young versus 2.42±1.10 day and 3.74±1.05 mg/dl in the elderly) at onset of RRT or duration of RRT (5.69±1.16 day in the young versus 5.07±4.36 day in the elderly).

In univariate analysis the variables significantly correlating with in-hospital mortality are shown in table 4. In contrast with the overall population, only hypotension before RRT, the need for mechanical ventilation, the presence of MOF and the score of the predictive models were significantly correlated with mortality in the elderly. The studied baseline, preoperative and postoperative variables not correlating with in-hospital mortality are not mentioned in the table

Table 4: Predictors of in hospital mortality

	Total population			**Patients < 70 year**			**Patients ≥ 70 year**		
	Survivor	*Non-surv.*	*P*	*Survivor*	*Non-surv.*	*P*	*Survivor*	*Non-surv.*	*P*
Elective surgery (%)	58.3	30.4	0.02	75	26.9	0.006	45	35	0.75
Extracorporeal circulation (min)	114±38	148±55	0.005	97±28	150±42	0.0001	126±40	152±74	0.20
Hypotension (%) intraoperative	50.0	74.0	0.045	43.7	69.2	0.19	55.0	80	0.18
IABP insertion (%)	41.6	67.4	0.04	37.5	65.4	0.14	45.0	70.0	0.20
Hypotension before RRT (%)	8.8	74.4	<0.0001	6.3	81.0	<0.0001	11.1	66.6	0.002
MOF (%)	0	71.7	<0.0001	0	76.2	<0.0001	0	66.7	0.0001
Ventilated pt (%)	28.5	92.3	<0.0001	31.3	100	<0.0001	26.3	83.3	0.002
Oliguria (%)	35.5	58.3	0.1	21.4	61.1	0.06	47.0	55.5	0.87
Cardiac arrest (%)	5.7	38.5	0.002	6.2	47.6	0.02	5.2	26	0.15
Methods predicting mortality									
SAPS II	37±12	56±16	0.09	31±11	61±18	<0.0001	41±10	50±12	0.01
Liano	0.371± 0.204	0.737± 0.169	<0.0001	0.333± 0.215	0.744± 0.169	<0.0001	0.411± 0.191	0.730± 0.174	<0.0001
SHARF T0	154±24	190±16	<0.0001	145±21	184±15	<0.0001	162±23	196±16	<0.0001
SHARF T48	150±23	198±17	<0.0001	144±23	192±17	<0.0001	156±23	205±15	<0.0001

SAPS II (Simplified Acute Physiology Score II); SHARF (Stuivenberg Hospital Acute Renal Failure Score) T0 (24h before starting renal replacement therapy) T48 (48h after starting renal replacement therapy)

Discussion

Our study found that age does not influence the outcome of the dialysed ARF patient post-cardiac surgery, suggesting that age may not be a reason for the nephrologist to withhold the elderly patient from necessary RRT in post-cardiac surgery ARF.

First, to avoid bias by changes in surgical techniques or postoperative care, this study was limited to a maximal observation period of 5 years. This contributed to maintain the homogenous care pattern; as a drawback, this limited the number of patients enrolled in this study.

Secondly, a major objection to this conclusion can be the retrospective character of this study, inducing a possible bias. As the policy in our department is to dialyse every patient requiring RRT after cardiac surgery, the selection bias can not occur at the moment of taking the patient in RRT. However, a selection bias made by the surgeon or cardiologist before the surgical intervention cannot be excluded. As figures regarding overall mortality (3.7%) and the development of ARF in the cardiac surgery department (2.2%) are comparable with those observed in the literature [1-7,17,18] our population can be considered as a representative sample for the actual policies in most Western cardiac surgery departments. Therefore, we think that our results can be useful for every nephrologist consulting an elderly patient with ARF in cardiac surgery departments.

It might be surprising that there are no differences in outcome between the elderly and the younger patients. The relatively beneficial outcome in the elderly might, however, be the consequence of a difference in severity of underlying disease. The ageing kidney by itself, due to structural and functional alterations is less able to cope with rapid haemodynamic changes and electrolyte balance [19]. Hence, it can be accepted that ARF develops more easily in the older patients whereas comorbid factors that are at the origin of the ARF, might be less preponderant and/or severe than in the younger population. After all, comorbid conditions probably more frequently lead to a fatal outcome than renal failure *per se*, for which RRT can be offered.

To evaluate our hypothesis, we scored severity of illness at the development of ARF by three different models namely the SAPS II, the Liano and the SHARF score. We expected the score to be higher in the younger population. This was however only the case for the SAPS II score (with or without age as correcting factor) and not for the Liano score or the SHARF score. One way to explain this difference is the fact that in these scoring systems, the same factors are not always weighted. For example, in the SAPS II, a high value is attributed to a low Glasgow coma score. The factor of consciousness is less important in the Liano score and completely absent in the SHARF score. In the younger population a higher percentage of the population developed ARF

after cardiac arrest than in the elderly population. Because of the cardiac arrest, lower Glasgow coma scores could be expected and hence younger people had significantly higher SAPS II scores. So far it was not possible in our study to prove conclusively that the younger and older group are equivalent. Further prospective studies on larger numbers of patients will be necessary to evaluate whether there is a difference in severity of illness between younger and older patients developing post-cardiac surgery ARF-d.

In whatever the underlying condition, the comparable mortality rate between the younger and the elderly population suggests that age is not a reason to withhold the elderly cardiac surgical patient with ARF from RRT. The absence of a relationship between age and poor outcome in the elderly developing ARF in the ICU was already confirmed by us [19] and by other authors [20].

The most predictive factors for in-hospital mortality in our study population were non-elective surgery, duration of extra-corporeal circulation during surgery, and the presence of mechanical ventilation, hypotension before RRT, IABP, MOF and cardiac arrest. Of these variables only the presence of MOF, mechanical ventilation and hypotension pre RRT were predictive in the elderly patients. Only a few other studies considered independent predictors of mortality in ARF-d. Chertow et al. mentioned low cardiac output requiring inotropic support, prolonged mechanical ventilation, cardiac arrest and stroke or coma [10]. Liopart found only postoperative events (sepsis) to be related with higher mortality in ARF-d [8]. Osterman et al. reported a poor outcome in patients with ARF and cardiovascular failure and in patients with three or more failing organ systems before haemofiltration [4].

In conclusion, the outcome in the elderly requiring dialysis due to post-cardiac surgery ARF is comparable with that in a younger population. No significant difference was found in severity of disease between the elderly and the younger. Variables predicting mortality in the elderly are the presence of MOF, mechanical ventilation and hypotension 24h before starting RRT. These findings indicate that at the time the nephrologist is called for an elderly patient requiring dialysis due to ARF following cardiac surgery, age *per se* is not a reason to withhold RRT. We therefore believe that once the cardiologist and cardiac surgeon have decided to perform surgery in a given patient, the nephrologist should not interfere with this decision, once post-surgery ARF develops.

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Addendum to chapter 12

Usefulness of scoring systems to predict mortality in the elderly population developing ARF after cardiac surgery

Although the purpose of the retrospective calculation of the scoring methods was to make an evaluation of the severity of the underlying disease, we made in addendum an evaluation of their ability to discriminate mortality and survival.

When the different scoring systems are valuable, one should expect no significant differences in the values, as the mortality rate in both age groups is comparable. Therefore, the values of the different scoring systems are compared in Table 1. Scoring systems are comparable for the SAPS II and the Liano score. There is a significant difference for the SHARF T0 and a difference, not statistically significant for the SHARF T48.

Table 1: Values for the different scoring systems in both age groups

	With age			**Without age**		
	Pt < 70 y N=38	Pt ≥ 70 y N=38	*P*-value	Pt < 70 y N=38	Pt ≥ 70 y N=38	*P*-value
SAPS II	48±21	46±12	0.52	39±21	29±12	0.02
Liano	0.568±0.281	0.571±0.242	0.96	0.393±0.288	0.343±0.239	0.42
SHARF T0	168±26	180±26	0.06	129±26	129±26	0.98
SHARF T48	170±31	181±31	0.15	132±33	130±32	0.80

SAPS II (Simplified Acute Physiology Score II); Liano-score ; SHARF (Stuivenberg Hospital Acute Renal Failure Score) T0 (24h before starting renal replacement therapy); T48 (48h after starting renal replacement therapy)

The values of the scoring systems without age are especially useful to answer the question if differences in severity of underlying disease are seen between both age groups. As stated in the article, due to the discrepancy in the results, it was not possible to prove conclusively that the younger and older groups are equivalent.

The ability of a model to discriminate, to distinguish between survivors and non-survivors, can be assessed using receiver operating characteristic (ROC) curve analysis. If the area under the curve is 0.5, the model has no discriminatory power, and if the area

is 1.0, the model discriminates perfectly. Analysis of the different ROC curves is given in Figure 1.

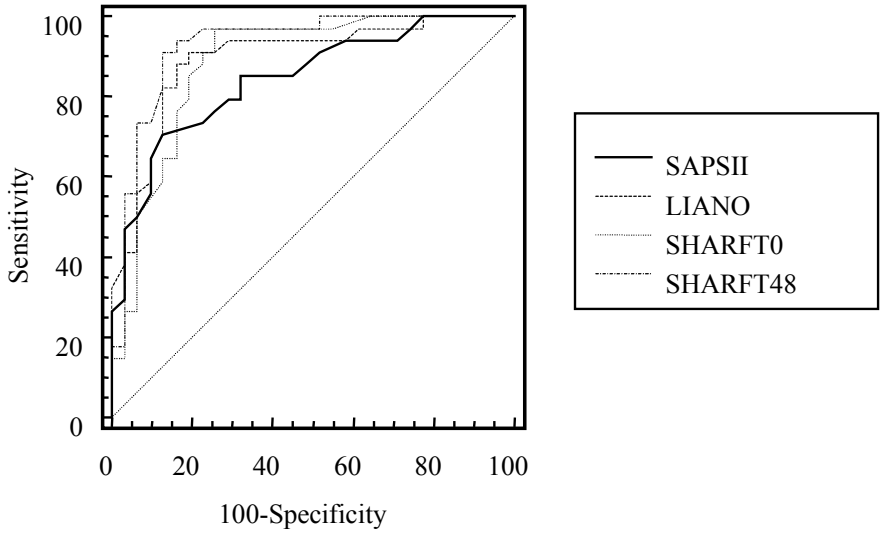

Figure 1: ROC curve analysis for different methods; AUC values for respectively SAPSII, Liano, SHARF T0 and SHARF T48 are 0.830, 0.910, 0.875 and 0.929

ROC curve analysis makes it also possible to calculate a positive and negative predictive value corresponding with the highest accuracy (Table 2)

Table 2: Positive and negative predictive value corresponding with the highest accuracy (minimal false negative and false positive results)

	Cut-off Score	**Ppv** (%)	**Npv** (%)
SAPS II	48	88	69
Liano	0.552	88	84
SCHARFT0	165	82	92
SCHARFT48	176	90	88.5

SAPS II (Simplified Acute Physiology Score II); SHARF (Stuivenberg Hospital Acute Renal Failure Score) T0 (24h before starting renal replacement therapy) T48 (48h after starting renal replacement therapy)

It is also possible to identify a cut-off score at which the mortality rate is 100% (Table 3). At this moment the higher the sensitivity, the better the predictive value of the method.

Table 3: AUC and the cut-off score, at which a 100% specificity is obtained and corresponding sensitivity, in both age groups

	Patients < 70 year			**Patients ≥ 70 years**		
	Score	Sensitivity	AUC	Score	Sensitivity	AUC
SAPS II	52	61.9	0.906	65	5.6	0.716
Liano	0.809	33.3	0.922	0.798	33.3	0.875
SCHARFT0	187	47.6	0.925	204	27.8	0.866
SCHARFT48	198	38.9	0.937	215	31.3	0.934

SAPS II (Simplified Acute Physiology Score II); SHARF (Stuivenberg Hospital Acute Renal Failure Score) T0 (24h before starting renal replacement therapy) T48 (48h after starting renal replacement therapy)

Until now, none of the existing models showed excellent discrimination between survivors and non-survivors. When an excellent model could be developed, this could be helpful to judge whether treatment would be futile and further efforts would only prolong miserable agony. Even these models could only give a direction and should never allow end-of-life decisions to be taken without informed consent of patient and/or family.

Conclusions / Samenvatting

Conclusions and perspectives

As kidney function plays an important role in drug clearance, the clinician wants a reliable estimation of glomerular filtration rate (GFR) as soon as the elderly is admitted to the acute ward. However, the estimation of GFR in the elderly is beset by difficulties.

As outlined in **part 1**, the introduction, studies in the ambulatory elderly already show a wide variation in renal function. Taking into account that most elderly admitted to an acute geriatric ward have underlying diseases, an even greater variation in renal function can be expected.

Therefore, in **chapter 5** we evaluated the renal function and his determinating factors in the old old on an acute geriatric ward. The mean estimated creatinine clearance on admission was 38.1 ± 12.0 ml/min. As expected, a wide variation in clearance was seen, ranging from less than 10 ml/min to more than 80 ml/min. Renal failure was defined as a creatinine clearance less than 30 ml/min. This clearance was found in 26.4% of the patients. In the group of renal failure, no correlation with arterial hypertension, peripheral arterial diseases, heart failure and diabetes could be found. The only significant finding was the association between renal failure and failure to thrive. For most pharmaca, dose reduction is suggested from a clearance around 30 ml/min.This means that in one out of four patients on a geriatric ward it is important to adapt the dose of medication. On the other hand, regular dose reduction should also be avoided as low dosing could also cause harm in some clinical situations.

Due to the variation in renal function and the prevalence of renal failure on an acute geriatric ward, it is important to make an accurate estimation of GFR in the elderly population. Therefore, we evaluated the usefulness of different new methods in the assessment of GFR. In **chapter 6** serum cystatin C, serum creatinine, inversed cystatin C, inversed serum creatinine, the Cockcroft-Gault formula, the MDRD formula and the measured urinary creatinine clearance were prospectively analysed and compared with a gold standard, the ^{51}Cr-EDTA clearance. All studied methods were found to have comparable value as markers of renal function in the overall older population. Our data could not confirm the superiority of serum cystatin C over more traditional methods for the detection of early renal impairment. Interestingly, the MDRD formula showed a systematic bias (slight overestimation) in the older population. The Cockcroft-Gault formula underestimates renal function in elderly people with a GFR greater than 60 ml/min. This formula is less accurate in a healthy elderly population. For routine clinical practice and when there is a clinical indication, the clinician should estimate GFR using at least two different methods. In the case of

discrepancy, a more sophisticated method such as the plasma clearance of ^{51}Cr-EDTA should be applied.

In **chapter 7** is demonstrated how the method used to measure serum or urinary creatinine may influence the estimation of GFR. Due to the existence of a protein error, a systematic overestimation of serum creatinine occurs in the so-called uncompensated Jaffé method. As a consequence, measured creatinine clearance obtained by the uncompensated Jaffé method strongly underestimates GFR. In contrast, measured creatinine clearance by enzymatic and compensated Jaffé methods slightly overestimate the GFR, which is due to a degree of tubular secretion of creatinine. Estimated creatinine clearance as obtained by the Cockcroft-Gault formula and the MDRD-formula is valid for the HPLC, enzymatic and compensated Jaffé method. However, the same Cockcroft-Gault formula strongly underestimates GFR when the calculations are based on uncompensated Jaffé test results and can explain why previous studies, mentioned in the introduction, show a weaker accuracy for the Cockcroft-Gault compared with the ^{51}Cr-EDTA clearance than our study.

Ageing is associated with a progressive loss of renal mass and kidney length as well as a progressive decline in GFR. In clinical practice, ultrasonography (US) is a non-invasive method to evaluate kidney volume or length. Therefore, we examined in **chapter 8** the correlation between GFR, measured by ^{51}Cr-EDTA clearance, and kidney length or kidney volume, as measured by US. We also evaluated the usefulness of kidney length in the assessment of GFR. Our findings show a significant correlation between kidney length, kidney volume and GFR in the old old. Although, due to its low specificity in detecting renal impairment, kidney length is not very useful in estimating GFR. However, it was possible to detect a cut-off value for kidney length above which all the old old had a GFR greater than 60 ml/min. This suggests that normal kidney length can be used to exclude renal impairment in the old old at risk for underestimation of GFR by a calculated creatinine clearance.

In the third part of this work, we examined the outcome of the elderly developing acute renal failure (ARF) on an intensive care unit and after cardiac surgery.

Chapter 9 gives, by way of introduction, an overview of acute renal failure in the elderly. The structural and functional alterations with ageing makes the kidney more vulnerable for ischaemic and haemodynamic injury. The vulnerability of the ageing kidney is reflected in the incidence figures of acute renal failure where 70% of all cases of ARF are 70 years and older. The aetiology is often multifactorial, so that classification of ARF poses problems of definition. Prerenal causes due to hypovolaemia or haemodynamic alterations by pharmaca such as NSAID or ACE-inhibitors are major causes of renal failure. As in the younger population, post-ischaemic acute tubular necrosis (ATN) is by far the most frequent cause of ARF.

Especially in community- and hospital-ward associated ARF, urinary obstruction is one of the important causes of postrenal ARF in the elderly.

Management and dialytic strategies of ARF are broader reviewed and discussed in **chapter 10**. Although peritoneal dialysis offers some theoretical advantages, there are several medical and technical reasons why it is currently less frequently used. The choice between intermittent haemodialysis (HD) and continuous renal replacement therapy (CRRT) is determined by a number of considerations, the most important ones being haemodynamic stability, the need for hyperalimentation and/or ultrafiltration, and the local experience with one or both techniques. Some recent studies with CRRT in elderly ARF patients describe favourable results. However, none of these studies help to discern between the different treatment modalities. An alternative under evaluation is the slow extended daily dialysis (SLEDD) techniques. This technique combine the advantages of CRRT and intermittent HD. Until now, no large studies on SLEDD particularly in elderly are available.

In **chapter 11** the outcome of the very elderly admitted to the intensive care unit was studied. A significantly higher mortality rate was found for patients admitted to the ICU and who need inotropics, mechanical ventilation and who developed ARF. Compared with the younger population, the mortality rate was higher in the elderly with an APACHE II score higher than 25.

The influence of age on the outcome of acute renal failure, requiring dialysis, in a post-cardiac surgery population was studied in **chapter 12**. No difference in mortality rate was found between the younger (mean age 59 ± 10 years) and the elderly (mean age 76 ± 4 years) patient group. To rule out the possibility that the relatively beneficial outcome in the elderly was the consequence of a difference in severity of underlying disease, we scored severity of illness at the development of acute renal failure by three different methods, namely the SAPS II, the Liano and the SHARF score. Only different scores for both age groups in the SAPS II score and not in the Liano and the SHARF score, both developed for acute renal failure patients, were observed. Therefore, it was not possible to conclusively prove that the severity of disease was equivalent in both age groups. Variables predicting mortality in the elderly are the presence of multi-organ failure, mechanical ventilation and hypotension 24h before starting renal replacement therapy. These findings indicate that at the time the nephrologist is called for an elderly, post-cardiac surgery patient, age per se is not a reason to withhold renal replacement therapy.

In conclusion, the second part of this work showed that a wide variation in renal function is observed in an acute geriatric ward. Therefore, a good estimation of renal function is important on admission of the patient. In clinical practice, the Cockcroft-Gault can be used to estimate creatinine clearance when creatinine is measured using a rate-blanked, compensated Jaffé method. When other methods as inversed serum creatinine, MDRD formula, serum cystatin C or kidney length measured by US are not confirming the result obtained by the Cockcroft-Gault formula, a gold standard evaluation of renal function as ^{51}Cr-EDTA clearance should be obtained.

The third part of this work showed that age per se is not a reason to withhold renal replacement therapy post cardiac surgery or after admission to an intensive care unit in an elderly population. Scores predicting mortality are difficult to interpret and are often confusing in the elderly. Strategies of renal replacement therapy are based on evidence in a younger population, because no data are available in the management of ARF in the elderly population.

Future studies should concentrate on the influence of renal failure on functional status and vice versa in the hope to optimize treatment for the frail elderly. A further follow up of new methods to assess GFR and an evaluation of their usefulness in an elderly population are necessary.

In the elderly ARF patient one should concentrate on the development of specific prognostic scoring systems. The hypothesis, that incorporating functional status at the moment of admission to the hospital could ameliorate the prognostic value of different scoring systems, should further be examined. Also an evaluation of the optimal dialysis strategy seems to be necessary as the incidence of ARF is increasing, especially in the elderly population.

Samenvatting en toekomstperspectieven

Een betrouwbare inschatting van de nierfunctie door middel van de glomerulaire filtratie snelheid (GFR) is vaak wenselijk bij opname van de oudere op een acute afdeling gezien de invloed van de nierfunctie onder andere op de klaring van bepaalde geneesmiddelen. Een goede inschatting maken van de nierfunctie bij de oudere is echter niet zo eenvoudig.

Zoals reeds in de inleiding, **deel 1**, werd beschreven, vinden we een grote variatie in de nierfunctie van een gezond ouder wordende populatie. Daarenboven hebben de meeste ouderen op een acute geriatrie afdeling vaak onderliggende aandoeningen waardoor een nog grotere variatie in de nierfunctie kan verwacht worden.

Daarom hebben wij getracht, in **hoofdstuk 5**, de variatie in nierfunctie op onze afdeling en mogelijks beïnvloedende factoren van de nierfunctie in kaart te brengen. De gemiddelde creatinine klaring op onze afdeling bedroeg 38.1 ± 12.0 ml/min. Zoals verwacht vonden wij een enorme variatie in de klaring, gaande van minder dan 10 ml/min tot meer dan 80 ml/min. Wij definieerden nierfalen als een klaring minder dan 30 ml/min. Bij 26.4% van de ouderen werd een klaring in deze grootte orde gevonden. In deze groep kon geen significante correlatie worden weerhouden met bloeddruk, perifeer vaatlijden, diabetes mellitus of hartfalen. De enige significante correlatie was de aanwezigheid van "achteruitgang van de algemene toestand" en nierfalen. Voor de meeste geneesmiddelen is dosis reductie aangewezen bij een klaring van minder dan 30 ml/min. Wat betekent dat op een acute G-dienst bij één op vier patiënten dosisreductie noodzakelijk is. Systematische dosisreductie op een G-dienst kan leiden tot inadequate dosering van bepaalde geneesmiddelen in sommige klinische situaties.

Gezien de variatie in nierfunctie en de prevalentie van nierfalen op een acute G-dienst, is het dus belangrijk een goede inschatting te maken van de nierfunctie bij de oudere. De bruikbaarheid van nieuwere methodes om de creatinine klaring en GFR in te schatten werden onderzocht in de oudere populatie. Daartoe werden in **hoofdstuk 6** serum cystatin C, serum creatinine, inversed serum cystatin C, inversed serum creatinine, de Cockcroft-Gault formule, de MDRD formule en de urinaire creatinine klaring prospectief geëvalueerd als parameter voor nierfalen ten opzichte van een gouden standaard namelijk ^{51}Cr-EDTA klaring. Alle bestudeerde parameters waren vergelijkbaar in de detectie van nierfalen. De superioriteit van cystatin C in de vroegtijdige diagnose van nierfalen kon niet worden bevestigd in onze studiepopulatie. Interessant is de bevinding dat de MDRD formule een systematische overschatting maakt van de nierfunctie. De Cockcroft-Gault formule daarentegen maakt een onderschatting van de nierfunctie van zodra de klaring groter is dan 60 ml/min. Dit verklaart waarom deze formule minder bruikbaar is in een populatie van gezonde

ouderen. Wanneer het van klinisch belang is om een goede inschatting te maken van de nierfunctie, lijkt het in de dagelijkse praktijk wenselijk om de klaring met twee verschillende methodes te berekenen. Zo er belangrijke verschillen gevonden worden, zijn meer verfijnde bepalingen van de klaring door middel van isotopen onderzoek, zoals ^{51}Cr-EDTA klaring, aangewezen.

In **hoofdstuk 7** blijkt hoe de wijze waarop het serum of urinair creatinine wordt bepaald, invloed kan hebben op het inschatten van de klaring. De uncompensated Jaffé methode lijkt door de aanwezigheid van een eiwitfout, het serum creatinine systematisch te overschatten. Dit leidt tot een onderschatting van de gemeten creatinine klaring op basis van een 24 uurs urine collectie. Gemeten creatinine klaringen op basis van enzymatische en compensated Jaffé methodes daarentegen overschatten de GFR ten gevolge van de beperkte tubulaire secretie van creatinine. Geschatte creatinine klaringen door middel van de Cockcroft-Gault formule en de MDRD formule zijn betrouwbaar indien de creatinine gemeten is aan de hand van HPLC, enzymatische of compensated Jaffé methodes. Echter, wanneer de Cokcroft-Gault formule wordt berekend aan de hand van een creatinine gemeten door een uncompensated Jaffé methode, blijkt de Cockcroft-Gault formule de werkelijke klaring sterk te onderschatten. Dit kan verklaren waarom de klaring berekend door middel van de Cockcroft-Gault formule vergeleken met de ^{51}Cr-EDTA klaring, minder nauwkeurig blijkt in vorige studies dan in onze studie.

Verouderen is geassocieerd met een progressief verlies van massa en lengte van de nier. Bovendien is er ook een progressief verlies van GFR. In de klinische praktijk is ultrasonografie een niet invasieve methode om volume en lengte van de nier te bepalen. Daarom hebben we in **hoofdstuk 8** de associatie onderzocht tussen de GFR, gemeten door de ^{51}Cr-EDTA klaring, en de lengte en het volume van de nier, gemeten door middel van ultrasonografie. Ook de bruikbaarheid van de nierlengte voor het inschatten van de nierfunctie werd nagegaan. We vonden een significante correlatie tussen lengte, volume van de nier en GFR in de hoogbejaarde. Nochtans is de nierlengte niet bruikbaar voor het inschatten van de GFR, gezien de lage specificiteit van de nierlengte voor de detectie van nierfalen. Wel was het mogelijk om een cut-off waarde te detecteren boven dewelke alle hoogbejaarden een GFR hadden groter dan 60 ml/min. Deze bevinding suggereert de mogelijkheid dat een normale nierlengte kan gebruikt worden om een verminderde nierfunctie uit te sluiten bij hoogbejaarden waar een berekende klaring de nierfunctie onderschat.

In het derde deel van dit werk, onderzochten we de prognose van de oudere met acuut nierfalen op de afdeling Intensieve Zorgen of na cardiale chirurgie.

Hoofdstuk 9 geeft, bij wijze van inleiding, een overzicht van acuut nierfalen bij de oudere. De structurele en functionele veranderingen welke gepaard gaan met het

verouderen, maken de nier kwetsbaarder voor ischemische en hemodynamische schade. Dit wordt bevestigd door de incidentie van acuut nierfalen, immers 70% van de patiënten met acute nierinsufficiëntie is 70 jaar en ouder. Gezien de vaak multifactoriële oorzaak, stelt het opmaken van een classificatie van de oorzaken van acuut nierfalen bij de oudere vaak problemen. Prerenale oorzaken ten gevolge van hypovolemie of hemodynamische veranderingen door farmaca zoals NSAID of ACE-inhibitoren zijn frequente oorzaken van acuut nierfalen. Zoals in een jongere populatie is acute tubulus necrose veruit de frequentste oorzaak van acuut nierfalen op een intensieve zorgen afdeling. In de huisartspraktijk of op een ziekenhuisafdeling is daarentegen, is acuut nierfalen vaak het gevolg van postrenale oorzaken.

Een uitgebreider overzicht van de behandeling en dialyse strategieën in de oudere met acuut nierfalen wordt in **hoofdstuk 10** gegeven. Alhoewel peritoneale dialyse theoretisch enkele voordelen heeft ten opzichte van hemodialyse, zijn er verschillende medische en technische redenen waarom peritoneale dialyse momenteel minder frequent wordt gebruikt. De keuze tussen intermittente hemodialyse en continue dialyse wordt bepaald door verschillende overwegingen, waaronder de hemodynamische stabiliteit van de oudere, de behoefte aan hyperalimentatie en/of ultrafiltratie en de lokale ervaring met de verschillende technieken. Alhoewel enkele recente studies bij de oudere met continue dialyse technieken gunstige resultaten beschrijven, helpen geen van deze studies om een keuze te maken tussen de verschillende dialyse mogelijkheden. Een mogelijk alternatief voor de toekomst zijn de "slow extended daily" dialyse (SLEDD) technieken. Deze technieken combineren de voordelen van continue en intermittente hemodialyse. Tot nu toe zijn geen studies met deze SLEDD technieken in een oudere populatie beschikbaar.

In **hoofdstuk 11** wordt de prognose van de hoogbejaarde op de afdeling Intensieve Zorgen bestudeerd. Een significant hogere mortaliteit werd gevonden voor de oudere behandeld met inotropica en kunstmatige ventilatie en voor de oudere die acuut nierfalen ontwikkelde. De mortaliteit was significant verhoogd voor de hoogbejaarde van zodra de APACHE II score groter was dan 25.

De mogelijke invloed van leeftijd op de prognose van acuut nierfalen, gedefinieerd als nood aan dialyse, na hartchirurgie werd onderzocht in **hoofdstuk 12**. We vonden geen verschil in mortaliteit tussen de jongere (gemiddelde leeftijd 59 ± 10 jaar) en de oudere patiënten populatie (gemiddelde leeftijd 76 ± 4 jaar). Om de mogelijkheid uit te sluiten dat de relatief gunstige prognose van de oudere te maken had met een minder ernstig onderliggende aandoening, werd de ernst van de aandoening op moment van acuut nierfalen bepaald aan de hand van drie methodes namelijk de SAPS II, de Liano en de SHARF score. Enkel voor de SAPS II score werd een hogere score weerhouden voor de jongere dan voor de oudere patiënten populatie. Deze bevinding

kon niet worden bevestigd voor de twee andere scores, speciaal ontwikkeld voor een populatie met acuut nierfalen. Daarom was het onmogelijk aan de hand van deze resultaten een definitieve conclusie te trekken betreffende de ernst van de onderliggende aandoening in beide leeftijdsgroepen. Variabelen geassocieerd met een hogere mortaliteit in de oudere zijn de aanwezigheid van multi-orgaan falen, de nood aan kunstmatige ventilatie en hypotensie 24 uur voor het starten van nierfunctie vervangende therapie. Deze bevindingen geven aan dat op het ogenblik dat een arts wordt geroepen bij een oudere patiënt na hartchirurgie, leeftijd op zich geen reden is om nierfunctie vervangende therapie te weigeren.

Tot besluit, het tweede deel van dit werk toont dat er bij de patiënten op een acute G-dienst een grote variatie in de nierfunctie gevonden wordt. Daarom is een goede inschatting van de nierfunctie bij opname wenselijk. In de klinische praktijk kan de Cockcroft-Gault formule gebruikt worden om de nierfunctie in te schatten op voorwaarde dat het serum creatinine is bepaald door een compensated Jaffé of enzymatische methode. Wanneer andere methodes als inversed serum creatinine, MDRD formula, serum cystatin C of lengte van de nier, gemeten door ultrasonografie, de resultaten van de Cockcroft-Gault niet bevestigen, dan lijkt verdere evaluatie van de nierfunctie door middel van een gouden standaard als ^{51}Cr-EDTA wenselijk.

Het derde deel van dit werk bewijst dat leeftijd op zich geen reden mag zijn om een oudere persoon nierfunctie vervangende therapie na hartchirurgie of een opname op intensieve zorgen te weigeren. Score systemen die de mortaliteit inschatten zijn moeilijk te interpreteren en vaak verwarrend in een oudere populatie. Dialyse strategieën bij de oudere zijn vaak gebaseerd op evidentie uit een jongere populatie gezien geen data ter beschikking zijn voor een oudere populatie.

Studies in de toekomst kunnen gericht zijn op de invloed van nierfalen op de functionele status van de bejaarde met als doel de behandeling van de “kwetsbare oudere” te optimaliseren. Een verdere toetsing van nieuwe methodes om de nierfunctie in een oudere populatie te bepalen, lijkt wenselijk.

Voor de oudere patiënt met acuut nierfalen lijkt een specifiek score systeem om de kans op overlijden in te schatten wenselijk. De hypothese dat het incorporeren van de functionele status bij opname in het ziekenhuis, de prognostische waarde van de verschillende score systemen in de oudere kan verbeteren, verdient verder onderzoek. Ook een evaluatie van de optimale nierfunctie vervangende therapie lijkt zich, met de toenemende incidentie van acuut nierfalen in een oudere populatie, op te dringen.

Dankwoord

Dankwoord

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Nele