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Renal hemodynamic response to maximal vasodilating stimulus in healthy older subjects

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Background. It is still unclear whether age per se is associated with preservation of renal functional reserve, that is, of the increase in glomerular filtration rate (GFR) induced by appropriate vasodilating stimulus.

Methods. To gain insights into this issue, we evaluated the renal response to a maximal vasodilating stimulus, represented by the combined infusion of mixed amino acid solution (AA) and dopamine at renal dose (D), in 10 young subjects (median age of 30 years, range of 19 to 32) and in 11 subjects of older age (median age of 67 years, range of 65 to 76). Two further age-matched groups of young ($N = 15$) and older ($N = 11$) living kidney donors underwent renal needle biopsy immediately before nephrectomy to perform semiquantitative scoring (0 to 3) of arteriosclerosis in intrarenal arteries. All of the study subjects were nonsmokers with healthy status proven by extensive diagnostic evaluation excluding any risk factor of renal dysfunction.

Results. Basal renal plasma flow (RPF) and GFR were proportionally lower in older subjects (RPF, 361 ± 29 vs. 618 ± 34 mL/min/1.73 m^2, $P < 0.001$; GFR, 79 ± 4 vs. 127 ± 5.8 mL/min/1.73 m^2, $P < 0.001$). After AA + D, a significant increase of RPF and GFR was observed in both groups, but the older subjects exhibited a smaller percentage increment (RPF, 25.5 ± 4.8 vs. 42.4 ± 5.8, $P < 0.05$; GFR, 19.6 ± 5.7 vs. + 33.8 ± 6.4, $P < 0.05$). Furthermore, the maximal vasodilating stimulus was not able to restore renal hemodynamics in older subjects to the level measured in young controls at baseline. Renal vascular resistances were higher ($P < 0.05$) in the older subjects both at baseline (0.19 ± 0.02 vs. 0.09 ± 0.004 mm Hg/mL/min) and after AA + D (0.14 ± 0.01 vs. 0.06 ± 0.004). Light microscopy examination detected the presence of a greater degree of arteriosclerosis at the level of interlobular and arcuate arteries (0.89 ± 0.15 vs. 0.45 ± 0.08) and interstitial fibrosis/tubular atrophy (1.18 ± 0.13 vs. 0.53 ± 0.13) in older than in young subjects.

Conclusions. Therefore, aging has adverse effects on renal function despite the absence of any risk factor for renal disease, including chronic smoking: (*1*) GFR and RPF are lower, and (*2*) the renal response to maximal vasodilating stimulus is impaired. These aging-related alterations of renal hemodynamics are possibly due to organic lesions in renal vasculature.

Key words: aging, glomerular filtration rate, renal functional reserve, dopamine, arteriosclerosis, blood pressure.

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The age-related changes in basal glomerular filtration rate (GFR) and renal plasma flow (RPF) measured by inulin and *p*-aminohippurate (PAH) clearance, respectively, have been extensively investigated [1–7]. All of these studies document a significant reduction of both GFR and RPF in patients who are healthy in advanced age, even though the absolute values are particularly variable.

A relevant question is whether the decrease in renal hemodynamics in the physiologic older population is irreversible as a result of morphological changes or rather functional because of an imbalance between vasodilating and vasoconstricting factors and, consequently, potentially reversible. This difference is critical since it is likely associated with a different renal adaptation to the acute ischemic injury, which is major cause of acute renal failure (ARF) in older subjects [8].

The assessment of the renal hemodynamic response to an appropriate vasodilating stimulus may be considered as an index of the functional integrity of the aging kidney. Indeed, if the stimulus allows GFR and RPF to increase adequately, it is reasonable to assume that the lower level of renal function is not related to structural, and therefore irreversible, alterations of renal vessels. Recently, some investigators have evaluated the acute renal vasodilatory response to an amino acid (AA) infusion [6]. They reported a similar and moderate increase of GFR in younger and older subjects, the so-called renal functional reserve (RFR). However, while the young subjects showed a slight but significant increment of RPF (4%), the older individuals were not able to significantly

increase RPF in response to the AA load (2%), so that they did not exhibit any renal hemodynamic reserve (RHR). These findings do not allow discernment of whether the inability of RPF to increase is a typical feature of aging or whether it is merely dependent on the moderate vasodilating stimulus used in the early studies. The sole AA infusion, in fact, does not elicit a maximal vasodilation that, in contrast, is induced by the combined administration of AA load and dopamine (D) at "renal dose" [9]. This association leads to maximal increments of RPF and GFR by additive renal vasodilating effects [9]. It is therefore extremely intriguing to evaluate the effects of the contemporaneous infusion of AA and D on renal hemodynamics in older subjects.

Of note, to the proper assessment of the effects of aging per se on kidney function, it is mandatory to study the active, normal, older population, as well as to define carefully and exclude any further determinant of renal dysfunction by extensive diagnostic determinations [10]. This methodological approach, commonly used to identify potential kidney donors, has not been considered in the previous studies determining basal renal function and RFR in aging [1–7, 11]. Furthermore, it has been demonstrated that chronic cigarette smoking can induce a significant impairment of renal function in healthy older subjects in comparison with age- and sex-matched controls [12]. Nevertheless, no study has evaluated RFR in nonsmoking older subjects.

The aim of our study was to establish in subjects who were nonsmokers and eligible for kidney donation the effects of aging on (*1*) renal hemodynamics in basal condition, (*2*) the renal vasodilatory response to combined AA + D infusion, and (*3*) the morphology of intrarenal vessels, as assessed by light microscopy, in renal biopsies obtained immediately before removal of the kidney for donation.

METHODS

Selection of subjects

Both younger and older subjects were recruited in the course of the clinical assessment of their suitability as potential kidney donors. Extensive diagnostic evaluation was carried out to exclude unsuspected, and potentially relevant, renal and extrarenal diseases. Inclusion criteria were (*1*) absence of personal and family history of diabetes mellitus, hypertension, hyperlipidemia, obesity, and cardiovascular or renal disease; (*2*) normal physical examination; (*3*) absence of fasting glycemic values greater than 120 mg/dL, absence of arterial blood pressure levels greater than 140/90 on three separate occasions, plasma levels of cholesterol and triglycerides below 200 and 170 mg/dL, respectively, and plasma lipoprotein high-density lipoprotein >40 mg/dL; (*4*) absence of hypertensive or atherosclerotic retinopathy; (*5*) no evidence of cardiac insufficiency or hypertrophy or valvular heart or atherosclerotic vascular disease, as assessed by color Doppler echocardiography; (*6*) normal urine chemistry and sediment and negative urine culture; (*7*) serum creatinine ≤1.2 mg/dL; (*8*) absence, at both ultrasound evaluation and urography, of renal cyst, nephrolithiasis, pyelonephritis, urinary tract ectasis, residual volume of urine in the bladder (>50 mL), or prostatic hypertrophy; (*9*) daily proteinuria <150 mg; (*10*) absence of any medication (*11*) absence of drug or alcohol dependency; and (*12*) no smoker habits, as established according to a recent study [12]. All participants gave their informed consent. The subjects were divided into healthy young (age >18 and ≤39 years old) and older (≥65 years old). Both groups were matched for body weight. They were encouraged to continue their usual isocaloric diet. Daily dietary salt and protein intake were assessed by measurements of 24-hour urinary sodium and urea excretion. Thereafter, the diets were modified by a dietitian in order to obtain a controlled intake of salt (8 g/day) and protein (1.0 g/kg body wt/day). Compliance to diet was verified by repeated determinations of 24-hour sodium and urea excretion. No subject took any medication during the study.

Protocol

Body weight was measured in our clinic. The daily urinary sodium and urea excretion were also checked weekly in order to verify the compliance of patients to the prescribed diet. We also measured the baseline serum levels of creatinine, urea nitrogen, protein, sodium, potassium, glucose, cholesterol, triglycerides, aminotransferases, and glutamyl transferase, as well as of the hematological values and 24-hour urinary protein.

All subjects underwent clearance studies in a random order to assess the renal plasma flow and glomerular filtration rate before and after AA + D infusion. In brief, subjects were examined in the supine position in a quiet environment. Renal plasma flow and glomerular filtration rate were determined after 12-hour fasting by measuring PAH (C_{PAH}) and inulin (C_{In}) clearance, respectively. PAH (0.8%) and inulin (1.2%) were infused intravenously in a 5% glucose solution at the constant rate of 1 mL/min to maintain plasma concentration of inulin at 10 to 20 mg/dL and PAH at 1.0 to 2.0 mg/dL. An additional 5% glucose infusion (5 mL/min) was started to enhance urinary volume in order to allow several clearance periods in a relatively short time.

As previously described in other articles of our group [13, 14], after a 60-minute equilibration period and when a steady state of urine flow was achieved (that is, when the magnitude of changes in urine volume did not exceed 10% in three consecutive urine collections), three 30-minute renal clearances were performed. A preliminary evaluation in six healthy subjects has shown that an infusion of 5% glucose at the rate of 5 mL/min does not change GFR and RPF values.

Thereafter, renal hemodynamic reserve was evaluated during the combined intravenous infusion of two solutions: (*1*) a 7.5% AA solution (Solamin®, Pierrel, Italy) at an infusion rate of 4 mL/min and (*2*) a D solution (in 250 mL of 5% glucose; Revivan, Astra, Italy) at an infusion rate of 1 mL/min that delivered approximately 2 μg/min/kg body weight. During this second phase, the 5% glucose infusion was discontinued. Therefore, renal hemodynamics were studied during AA and D infusion under the same conditions of the basal clearances. After a new 60-minute equilibration period, three further 30-minute clearance periods were performed.

At the beginning and at the end of each clearance period, plasma samples for determination of PAH, inulin, sodium, and potassium concentrations were obtained. Urine was collected by spontaneous voiding to determine concentrations of PAH, inulin, sodium, and potassium. Blood pressure and heart rate were monitored every 10 minutes during the study.

Laboratory procedures

Determinations were obtained in the central laboratory by technicians not aware of the age of the subjects studied. Inulin levels were determined by diphenylamine method and PAH by method of Smith as previously described [13]. In all of the analytical determinations, the standard curves of inulin and PAH were determined by linear regression analysis; the correlation coefficient (r) of these curves was always greater than 0.996. Replicate measurements of both GFR and RPF in the same individual showed a mean coefficient of variation of 3% (three repeated measurements in 10 subjects). The plasma levels of urea and creatinine (Beckman Autoanalyzers, Beckman Instruments, Fullerton, CA, USA), sodium and potassium (by Beckman flame photometry), glucose (by glucose oxidase method) were also measured. Renal blood flow (RBF) was calculated as RPF/1 − Hct, where RPF is the renal plasma flow and Hct is the hematocrit. Renal vascular resistances (RVR; mm Hg/mL/min) were determined by the ratio between mean arterial pressure and RBF. RFR and RHR were calculated as the percentage increase versus baseline of C_{In} and C_{PAH}.

Kidney biopsy study. For the evaluation of aging on renal vascular pathology, baseline kidney biopsies were reviewed from two groups of younger ($N = 15$) and older ($N = 11$) healthy kidney donors. These were selected with criteria similar to those used for the hemodynamic studies from a larger group of living donors whose baseline biopsy findings have been in part previously published [14]. All needle biopsies had been performed during the nephrectomy procedure, immediately before removal of the kidney for donation using an automated punch device (BioptyCut; Radioplast, Bromma, Sweden) with an 18-gauge needle. Specimens were processed for light microscopy as previously described [14, 15]. Light microscopical changes had been semiquantitatively estimated according to a scoring system partly based on the Banff schema [14, 16, 17] grading (0 to 3) the following variables: arteriosclerosis (as), arteriolar hyalinosis (ah), glomerulosclerosis (gsc), interstitial mononuclear cell infiltration (mi), and interstitial fibrosis/tubular atrophy (if/ta). In particular, arteriosclerosis was graded on the basis of the severity of the fibrointimal thickening of arteries. Arteriolar hyalinosis was defined as periodic acid Schiff-positive insudation or hyaline thickening of the arterioles and scored on the basis of the percentage of the circumference affected. In order to increase the sensitivity of the method, the score of arteriosclerosis (as) of each artery within each biopsy was recorded, and the sum of artery scores was added, giving a ratio of as score/number of arteries in each biopsy. An identical approach was made for the scoring of arteriolar hyalinosis. Glomerulosclerosis (gsc) was defined according to the extent of increase in mesangial matrix. The fraction of globally sclerosed glomeruli (gsg) was calculated in the section with the highest number of glomeruli in each biopsy; a combined score of glomerulosclerosis (gsc) was then calculated combining the grades of sclerosis in preserved glomeruli and the fraction of gsg [14, 15]. A combined score of if/ta was given in each case. The chronicity index (CI) of each baseline biopsy in the present article is defined as the sum of the scores of as + gsc + mi + if/ta.

Statistical analysis

All values are reported as mean ± SD or as median and range. All of the clearance data have been corrected for a body surface area of 1.73 m^2. Differences were evaluated by Wilcoxon's test for paired samples to compare baseline versus post-AA and D values, and Mann–Whitney test to compare the two cohorts, that is, younger versus older subjects. Linear regression analysis was also used where appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

We evaluated basal and stimulated renal hemodynamics in 21 Caucasian, healthy, male, nonvegetarian subjects. The analytical data of all subjects undergoing the study are summarized in Table 1. We examined 10 healthy subjects of young age (median age of 30 years, range of 19 to 32) with a median serum creatinine of 0.9 (range 0.8 to 1.1) mg/dL and 11 healthy older subjects (median age of 67 years, range of 65 to 76) with a median serum creatinine of 1.0 (range of 0.9 to 1.2) mg/dL. A direct linear correlation between basal inulin and creatinine clearance was observed in both younger ($r = 0.88$, $P < 0.005$) and older ($r = 0.91$, $P < 0.001$) subjects. The serum levels of glucose, cholesterol, triglycerides,

Table 1. Characteristics of the study population at baseline

	Young	Elderly	*P*
Number	10	11	
Age *years*	30 ± 1.7	67 ± 2.1	
Serum creatinine *mg/dL*	0.9 ± 0.04	1.0 ± 0.05	NS
Systolic blood pressure *mm Hg*	126 ± 2.1	135 ± 2.3	<0.05
Diastolic blood pressure *mm Hg*	77 ± 1.5	86 ± 2.4	<0.005
U-urea *g/24 h*	22 ± 2.4	20 ± 3.1	NS
U-Na *mmol/24 h*	115 ± 5.3	125 ± 7.2	NS
GFR *mL/min/1.73 m²*	127 ± 5.9	79 ± 4.1	<0.001
RPF *mL/min/1.73 m²*	618 ± 34	361 ± 29	<0.001
FF *%*	20.9 ± 1.3	23.2 ± 1.8	NS
RVR *mm Hg/mL/min*	0.09 ± 0.004	0.19 ± 0.02	<0.001

Abbreviations are: U, urinary excretion; GFR, glomerular filtration rate; RPF, renal plasma flow; FF, filtration fraction; RVR, renal vascular resistance.

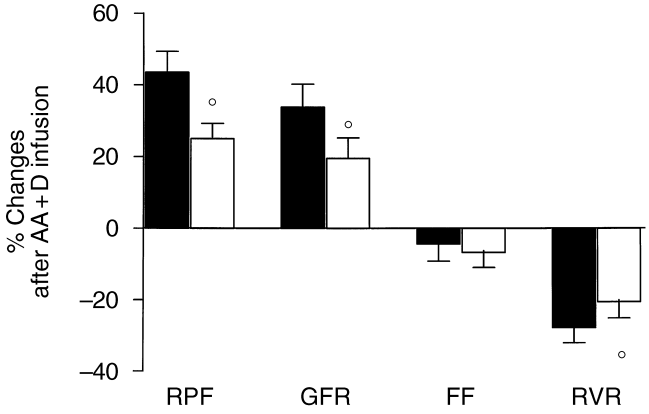

Fig. 1. Percent changes of renal plasma flow (RPF), glomerular filtration rate (GFR), filtration fraction (FF), and renal vascular resistances (RVR) in younger (■) and older (□) subjects ($P < 0.05$ for the difference in the ΔRPF, GFR, and RVR between the 2 groups).

aminotransferases, glutamyl transferase, and the hematological values were within the normal range in all subjects. Although both systolic and diastolic blood pressure were higher in older subjects (Table 1), arterial pressure levels were lower than 140/90 mm Hg in all the older subjects except one, in which systolic pressure was 150 mm Hg. Thus, all individuals had normal blood pressure, except one with borderline isolated systolic hypertension. All subjects exhibited optimal compliance to diet; both urea and sodium excretion values were compatible with the prescribed diet in each subject and were similar in younger and older groups. The median age of the younger and older living donors that underwent renal biopsy was 34 years (range 20 to 39 years) and 68 years (range 65 to 72 years), respectively.

To assess the reliability of urine collections, urinary creatinine excretion was measured in both experimental periods: A coefficient of variation within 5% in the different collections was obtained in each subject. At baseline, GFR and RPF were proportionally lower in older subjects as compared with younger subjects ($P < 0.001$; Table 1). Filtration fraction did not differ, averaging 20.9 ± 1.3% in young subjects and 23.2 ± 1.8% in older subjects. Older patients also exhibited greater RVR values (0.19 ± 0.02 vs. 0.09 ± 0.004 mm Hg/mL/min, $P < 0.001$).

The infusion of AA + D did not influence either arterial blood pressure or heart rate throughout the study. After infusion of AA + D, a significant increase of GFR and RPF was observed in both groups without any modification of filtration fraction (Fig. 1). The glomerular filtration rate increased from 79.4 ± 4.1 to 94 ± 16.7 mL/min ($P < 0.005$) in older subjects and from 126.6 ± 5.9 to 166.6 ± 4.3 mL/min ($P < 0.0005$) in younger subjects. Renal plasma flow increased from 361.1 ± 28.8 mL/min ($P < 0.005$) in older subjects and from 618.3 ± 33.7 to 865.7 ± 56.16 mL/min ($P < 0.0005$) in younger subjects. The percent changes of RPF and GFR were lower in older subjects as compared with younger subjects (RPF, 25 ± 4.2% vs. 43 ± 5.8%, $P < 0.05$; GFR, 20 ± 5.7% vs. 33.8 ± 6.4%, $P < 0.05$; Fig. 1). Inverse linear correlations were found between baseline values of RPF and GFR and their respective increments induced by AA + D infusion ($r = 0.75$, $P < 0.01$, and $r = 0.79$, $P < 0.01$, respectively) in younger but not in older subjects. RVR significantly decreased in both older (from 0.19 ± 0.02 to 0.14 ± 0.01 mm Hg/mL/min) and younger subjects (from 0.09 ± 0.004 to 0.06 ± 0.004). Of note, in the older group, the values of GFR and RPF measured after AA + D infusion remained lower than those observed in the younger subjects at baseline ($P < 0.005$). The single values of the two parameters are reported in Figures 2 and 3. Serum potassium concentrations were not modified throughout the study, and glucose infusion did not alter the blood concentration of glucose.

Table 2 depicts the main aging-induced changes of renal morphology obtained in the groups of younger and older donors shortly before the removal of the kidney for donation. Of note, among the different variables scored, only arteriosclerosis of intrarenal vessels (interlobular and arcuate arteries) and interstitial fibrosis/tubular atrophy were significantly greater in older patients. The grading of the other variables considered in fact led to results that were not statistically different in older and younger kidney donors. Nevertheless, the sum of the scores, that is, the CI, was significantly higher in the older group.

DISCUSSION

In this study, the criteria adopted to enroll the older subjects represent a critical point of difference with the early work. In the previous studies evaluating renal function and/or RFR in advanced age, the investigators either recruited older subjects from wards of general hospitals, and therefore with some potentially relevant disease, or

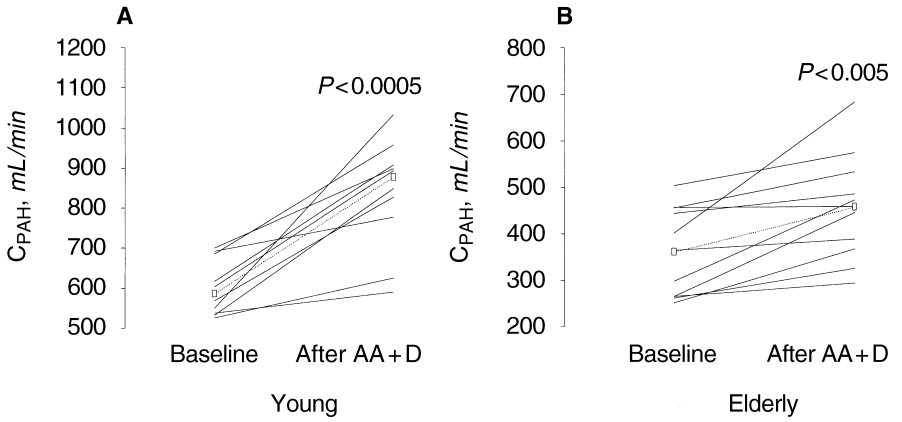

Fig. 2. Single values of inulin clearance in younger and older subjects at baseline and after amino acid + dopamine (A + D) infusion. The dotted line with squares represents the median value. *P* values indicate the statistical difference between baseline and after AA + D.

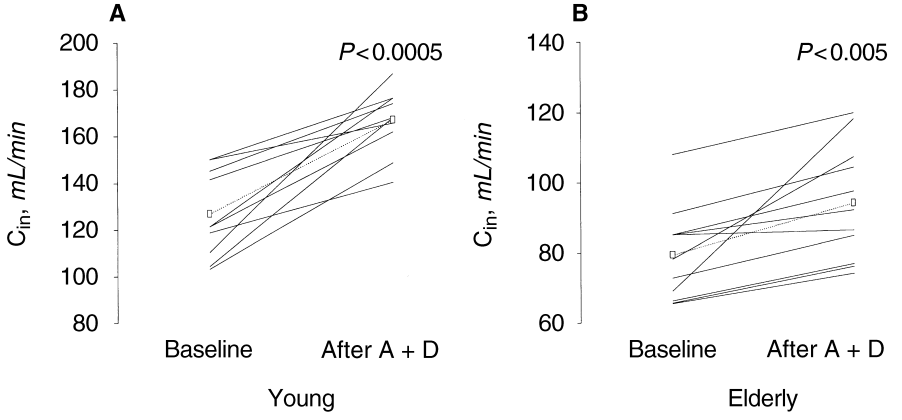

Fig. 3. Single values of PAH clearance in younger and older subjects at baseline and after amino acid + dopamine (A + D) infusion. Dotted line with squares represents the median value. *P* values indicate the statistical difference between baseline and after AA + D.

Table 2. Light microscopical changes in kidney biopsies obtained from 15 young and 11 elderly kidney donors

	Young	Elderly	*P*
Arteriosclerosis			
N of arteries examined	77	48	
Mean ± SE	0.45 ± 0.08	0.89 ± 0.15	<0.05
Arteriolar hyalinosis			
N of arterioles examined	239	163	
Mean ± SE	0.267 ± 0.04	0.33 ± 0.10	NS
Glomerulosclerosis			
N of biopsies examined	15	11	
Mean ± SE	0.56 ± 0.13	1.0 ± 0.19	NS
Combined glomerulosclerosis			
N of biopsies examined	15	11	
Mean ± SE	0.53 ± 0.29	1.1 ± 0.30	NS
Mononuclear infiltration			
N of biopsies examined	15	11	Not
Mean ± SE	0.0	0.18 ± 0.12	comparable
Interstitial fibrosis/tubular atrophy			
N of biopsies examined	15	11	
Mean ± SE	0.53 ± 0.13	1.18 ± 0.13	<0.02
Chronicity index			
N of biopsies examined	15	11	
Mean ± SE	2.13 ± 0.42	4.10 ± 0.56	<0.02

did not exclude the risk factors for vascular damage and the abnormalities of urinary apparatus by means of strict selection criteria [5–7, 11]. In contrast, as underlined by Epstein [10], in the assessment of phenomena related to senescence, it is mandatory to select older subjects from a segment of the population residing actively in the community and to exclude any factor other than age affecting the "well-being" state.

To overcome this methodological problem, we studied a unique subset of individuals, represented by potential kidney donors. All of the study subjects were identified by means of extensive and specific investigations that excluded any known condition interfering with the evaluation of the independent role of advanced age on renal hemodynamics. These criteria allowed us to examine, to our knowledge for the first time, the effects of aging per se on basal and stimulated renal function and on renal morphology as well.

Under these controlled conditions, both basal RPF and GFR resulted in lower values in older subjects in comparison with younger control subjects, demonstrating that age is per se a significant determinant of the decline in basal renal perfusion and function. Similarly, cross-sectional and longitudinal studies have shown that GFR decreases progressively after the age of 30 to 40 years [18–20]. At variance with these data, Fliser et al showed that basal GFR is only slightly lower in older than in younger subjects, with the mean GFR values being 103 and 102 mL/min in the two groups of older individuals studied [6, 7]. These values are definitively higher than those reported in the present study (79 mL/min) and by De Santo et al (84 mL/min) in an early work [5]. Since in all these studies GFR was measured by similar methods of inulin clearance, the variability of GFR values may be determined by a nonhomogenous interaction between environmental and genetic factors [21].

The significant increment in RPF (+25%) and GFR (+20%) of the aging kidney after AA + D, in the absence of blood pressure changes, demonstrates that healthy older subjects are able to reduce significantly the intrarenal resistances in response to a maximal vasodilating stimulus. Other authors have reported that GFR increases in both older (+17%) and younger (+16%) subjects after AA infusion [6], whereas RPF increases slightly in the younger (+4%) but not in the older subjects (+2%). The absence of an increase of RPF in the older group after AA infusion may have been due to the use of a nonmaximal vasodilating stimulus. It is well known, in fact, that the simultaneous infusion of AA and D has additive vasodilating effects on renal hemodynamics [9].

Therefore, the aging kidney is able to significantly augment renal perfusion during the combined infusion of AA + D. Nevertheless, this study also demonstrates that the vasodilatory response is actually diminished when compared with the extent of response measured in the young group. Indeed, the increment of both RPF and GFR resulted smaller in older than in younger subjects. Furthermore, in the older group, the mean values of stimulated RPF and GFR remained lower with respect to the values measured in young control subjects in basal conditions. This was associated with RVR values that after AA + D still resulted higher than the values measured in young subjects at baseline.

In contrast, the previous studies on the effects of AA infusion or a meat meal on RFR in older individuals indicate a preserved response, that is, increments of GFR of extent similar to that of young subjects [5, 6, 11]. Our study is not comparable with the early work since it evaluates for the first time the response of renal hemodynamics to the concomitant administration of AA and D. Hence, our study demonstrates that the aging kidney is characterized by a reduced ability to vasodilate when maximally stimulated.

The impaired renal vascular responsiveness may be secondary to the presence of organic abnormalities of the intrarenal vessels that are strictly dependent on age. In this regard, Hollenberg et al demonstrated in the early 1970s a reduction of the renal vasodilatory response to acetylcholine in older kidney donors [22]. Unfortunately, however, no data were provided on the GFR response. In a subsequent study, the same group suggested that the alterations of renal hemodynamics in physiologic aging are independent from changes in angiotensin II levels [23]. A comparable vasodilating response to acute angiotensin-converting enzyme inhibition was in fact detected in young and old subjects on either low (10 mEq/day) or normal (200 mEq/day) salt diet. On the other hand, angiotensin II does not interfere with the vasodilation induced by means of AA + D infusion. We have in fact previously demonstrated that this maximal vasodilatory stimulus in healthy young individuals leads to an increase of GFR and RPF that is not affected by the profound functional renal vasoconstriction secondary to marked salt depletion [24]. Furthermore, in that study, the AA + D stimulus efficaciously restored renal hemodynamics, altered by the depletion, to the same level observed in basal state. Overall, the previous and the current study indicate that the renal response to the combined AA + D infusion may allow discerning between structural and functional causes of renal hypoperfusion. Interestingly, in our early work [24], an inverse correlation between resting GFR and the extent of RFR after salt depletion was also detected, indicating that subjects with a lower GFR (due to major vasoconstriction) show a greater increment of GFR in response to AA + D. At variance with the results obtained in the young subjects of the previous and the current study, the older individuals enrolled in the present work do not show any correlation between resting and stimulated

RPF/GFR; again, this finding may be compatible with a reduced vasomotor capacity related to a fixed reduction of the vessel lumen.

Despite that the previous hemodynamic studies suggest the presence of a lesion of renal vasculature in healthy older individuals, to date, no morphological study has been designed to compare the structure of renal vessels in healthy old and young subjects. One of the authors has recently shown that in normotensive living donors aged 21 to 72 years, arteriosclerosis of renal vasculature tends to be more pronounced in middle-aged and older individuals [14]. The current study specifically evaluates, to our knowledge for the first time, whether the renal morphology is different in two distinct groups of young and old healthy donors. The results of the kidney biopsy study support the hypothesis that the age-related impairment of renal hemodynamics may be primarily dependent on a greater degree of arteriosclerosis in interlobular and arcuate arteries and the associated interstitial fibrosis/tubular atrophy. Of note, this abnormality, although of low grade, mainly accounts for the higher CI; in fact, the score of the other variables examined, such as glomerulosclerosis and interstitial mononuclear infiltration, did not significantly differ in young and old donors.

In conclusion, in older subjects of proven healthy status (nonsmokers and those eligible for kidney donation), basal GFR and RPF are proportionally lower, and the renal response to the maximal vasodilating stimulus is diminished. The increment of intrarenal vascular resistances is possibly due to the presence of arteriosclerotic lesions at the level of interlobular and arcuate arteries.

Taken together, these data contribute to elucidation of the independent role of age in the pathophysiology of the enhanced risk of ARF. It is well known that hypovolemia and renal hypoperfusion are the most prominent risk factors for ARF in older patients [8]. According to the findings of the current study, the susceptibility to hemodynamically mediated ARF is enhanced because aging per se is coupled with a physiologic decrease of renal perfusion of organic nature. The presence of cardiovascular risk factors, including chronic cigarette smoking [12], may increase this susceptibility further.

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APPENDIX

Abbreviations used in this article are: AA, amino acid; ah, arteriolar hyalinosis; ARF, acute renal failure; as, arteriosclerosis; CI, chronicity index; C_{In}, clearance of inulin; C_{PAH}, clearance of para-aminohippurate; D, dopamine; GFR, glomerular filtration rate; gsc, glomerulosclerosis; gsg, globally sclerosed glomeruli; Hct, hematocrit; HDL, high density lipoprotein; if/ta, interstitial fibrosis/tubular atrophy; mi, interstitial mononuclear cell infiltration; RBF, renal blood flow; RHR, renal hemodynamic reserve; RPF, renal perfusion flow; RVR, renal vascular resistance.

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