Renal Functional Reserve in Healthy Elderly Subjects

Danilo Fliser, Martin Zeier, Rainer Nowack, and Eberhard Ritz

ABSTRACT

The increase in GFR after an amino acid (AA) load, the so-called renal functional reserve, is impaired in the aged rat. Whether the renal functional reserve predicts the progression of renal disease in humans is controversial, but it is possible that age-related alterations of renal hemodynamics are relevant for the evolution of renal disease in the elderly. We compared renal hemodynamics before and after an AA infusion in 15 healthy normotensive subjects of young age (seven women, eight men; median age, 26 yr; range, 23 to 32) and in 10 subjects of old age (six women, four men; median age, 70 yr; range, 61 to 82) on normal dietary protein intake. Baseline GFR and effective RPF were measured after 12 h of fasting by the inulin (Cin) and para-aminohippurate (Cpah) steady-state infusion techniques. The renal functional reserve was examined after an overnight AA infusion (7% solution; 83 mL/h). Median basal Cin and Cpah were significantly lower (P < 0.01) in the elderly (102 and 339 mL/min per 1.73 m²) than in the young subjects (122 and 647 mL/min per 1.73 m²), but virtually all GFR values of the elderly were still within the normal range. Median Cin upon infusion of AA was 118 mL/min per 1.73 m² (range, 98 to 137) in the elderly and 146 (range, 120 to 171) in the young, respectively. Corresponding values of Cpah were 349 mL/min per 1.73 m² in the elderly versus 689 mL/min per 1.73 m² in the young. Cin increased significantly (P < 0.01) after the AA load in both young and elderly subjects. The median percent rise of Cin was not significantly different in young (+16%) and elderly (+17%) subjects and was independent of gender. Median Cpah, however, increased significantly (P < 0.01) in the young subjects, but not in the elderly. Median renal vascular resistance, both at baseline (175 versus 83 mm Hg/L per min) and after the AA load (170 versus 77), was significantly higher (P < 0.01) in the elderly as compared with the young subjects. The same was true for filtration fraction. The results document that, in humans, (1) GFR and effective RPF are slightly lower in the elderly in the absence of underlying renal disease, (2) renal vascular resistance and filtration fraction are elevated in old age, and (3) renal functional reserve is demonstrable at least until the age of 80 yr in women and men.

Key Words: Amino acid infusion, elderly, progression of renal disease, renal functional reserve, renal hemodynamics

Both in animals and in humans, GFR and effective RPF (ERPF) have been reported to decline with age in the absence of renal disease (1–6). Furthermore, glomerular hemodynamics are thought to play an important role in the progression of chronic renal disease (7,8). Past (9,10) and more recent (11,12) studies documented that, in experimental animals and in healthy humans, acute protein ingestion as well as acute amino acid (AA) infusion raise GFR and ERPF; a rise of the filtration fraction (FF) is less consistent (13–18). In patients with renal failure, the acute renal vasodilatory response to AA, the so-called renal functional reserve (RFR), is blunted or absent (19,20), and the idea has been advanced that in diseased kidneys glomeruli work at maximal capacity so that RFR is exhausted. These findings, however, have not been confirmed by all authors (21,22), and whether loss of RFR is related to progression continuous to be a matter of debate (23,24).

Recently, Baylis et al. (25) documented that in the male senescent rat the renal hemodynamic response to AA infusion is strikingly impaired. Despite uncertainties about the interpretation of RFR, this observation may bear on the evolution of renal disease in elderly individuals. To further address this issue, we compared renal hemodynamics before and after an AA infusion in healthy normotensive young and elderly subjects without evidence of renal disease.

SUBJECTS AND METHODS

Subjects

The protocol of this study was approved by the ethical committee of the University of Heidelberg.
TABLE 1. Clinical data of the young subjects (N = 15) at baseline

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex/Age (yr)</th>
<th>BMI (kg/m²)</th>
<th>MAP (mm Hg)</th>
<th>SCR (mg/dL)</th>
<th>GFR (mL/min per 1.73 m²)</th>
<th>ERPF (g/day)</th>
<th>U-Urea (g/day)</th>
<th>U-Na⁺ (mmol/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/23</td>
<td>22.5</td>
<td>75</td>
<td>0.9</td>
<td>109</td>
<td>641</td>
<td>21.8</td>
<td>121</td>
</tr>
<tr>
<td>2</td>
<td>M/26</td>
<td>24.7</td>
<td>88</td>
<td>0.9</td>
<td>110</td>
<td>647</td>
<td>17.8</td>
<td>158</td>
</tr>
<tr>
<td>3</td>
<td>F/25</td>
<td>20.4</td>
<td>87</td>
<td>0.9</td>
<td>110</td>
<td>688</td>
<td>10.1</td>
<td>110</td>
</tr>
<tr>
<td>4</td>
<td>M/28</td>
<td>22.3</td>
<td>92</td>
<td>1.0</td>
<td>116</td>
<td>504</td>
<td>16.3</td>
<td>184</td>
</tr>
<tr>
<td>5</td>
<td>F/29</td>
<td>22.9</td>
<td>97</td>
<td>0.9</td>
<td>117</td>
<td>585</td>
<td>18.2</td>
<td>150</td>
</tr>
<tr>
<td>6</td>
<td>F/24</td>
<td>17.6</td>
<td>90</td>
<td>0.9</td>
<td>120</td>
<td>667</td>
<td>18.0</td>
<td>151</td>
</tr>
<tr>
<td>7</td>
<td>F/27</td>
<td>21.8</td>
<td>97</td>
<td>0.8</td>
<td>120</td>
<td>610</td>
<td>21.2</td>
<td>143</td>
</tr>
<tr>
<td>8</td>
<td>M/23</td>
<td>23.5</td>
<td>94</td>
<td>1.0</td>
<td>122</td>
<td>638</td>
<td>20.8</td>
<td>189</td>
</tr>
<tr>
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<td>85</td>
<td>0.8</td>
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<td>758</td>
<td>19.9</td>
<td>117</td>
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<tr>
<td>10</td>
<td>F/26</td>
<td>22.2</td>
<td>88</td>
<td>0.9</td>
<td>128</td>
<td>606</td>
<td>19.7</td>
<td>139</td>
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<tr>
<td>11</td>
<td>M/26</td>
<td>25.1</td>
<td>92</td>
<td>1.0</td>
<td>129</td>
<td>717</td>
<td>25.5</td>
<td>198</td>
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<tr>
<td>12</td>
<td>F/29</td>
<td>19.3</td>
<td>94</td>
<td>0.8</td>
<td>130</td>
<td>683</td>
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<td>181</td>
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<td>1.1</td>
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<td>550</td>
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<td>135</td>
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<td>138</td>
<td>812</td>
<td>17.5</td>
<td>124</td>
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<tr>
<td>15</td>
<td>M/32</td>
<td>25.4</td>
<td>86</td>
<td>1.0</td>
<td>142</td>
<td>790</td>
<td>25.4</td>
<td>128</td>
</tr>
</tbody>
</table>

Median 26 22.5 89 0.9 122 647 19.9 143

BMI, body mass index; SCR, serum creatinine; U-Urea, urinary urea excretion; U-Na⁺, urinary sodium excretion.

TABLE 2. Clinical data of the elderly subjects (N = 10) at baseline

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex/Age (yr)</th>
<th>BMI (kg/m²)</th>
<th>MAP (mm Hg)</th>
<th>SCR (mg/dL)</th>
<th>GFR (mL/min per 1.73 m²)</th>
<th>ERPF (g/day)</th>
<th>U-Urea (g/day)</th>
<th>U-Na⁺ (mmol/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/66</td>
<td>22.2</td>
<td>91</td>
<td>1.0</td>
<td>88</td>
<td>284</td>
<td>25.1</td>
<td>132</td>
</tr>
<tr>
<td>2</td>
<td>F/74</td>
<td>23.1</td>
<td>97</td>
<td>0.9</td>
<td>94</td>
<td>358</td>
<td>16.7</td>
<td>130</td>
</tr>
<tr>
<td>3</td>
<td>M/72</td>
<td>26.4</td>
<td>91</td>
<td>1.1</td>
<td>95</td>
<td>281</td>
<td>28.1</td>
<td>184</td>
</tr>
<tr>
<td>4</td>
<td>F/68</td>
<td>18.9</td>
<td>77</td>
<td>0.9</td>
<td>97</td>
<td>360</td>
<td>19.6</td>
<td>134</td>
</tr>
<tr>
<td>5</td>
<td>F/61</td>
<td>20.7</td>
<td>99</td>
<td>0.7</td>
<td>99</td>
<td>433</td>
<td>17.7</td>
<td>191</td>
</tr>
<tr>
<td>6</td>
<td>M/70</td>
<td>23.9</td>
<td>101</td>
<td>1.0</td>
<td>104</td>
<td>277</td>
<td>30.0</td>
<td>105</td>
</tr>
<tr>
<td>7</td>
<td>F/76</td>
<td>20.2</td>
<td>90</td>
<td>1.0</td>
<td>106</td>
<td>333</td>
<td>20.2</td>
<td>118</td>
</tr>
<tr>
<td>8</td>
<td>M/82</td>
<td>24.3</td>
<td>92</td>
<td>0.9</td>
<td>107</td>
<td>318</td>
<td>20.7</td>
<td>152</td>
</tr>
<tr>
<td>9</td>
<td>M/69</td>
<td>25.8</td>
<td>97</td>
<td>0.9</td>
<td>110</td>
<td>344</td>
<td>21.8</td>
<td>155</td>
</tr>
<tr>
<td>10</td>
<td>F/68</td>
<td>23.5</td>
<td>96</td>
<td>0.8</td>
<td>111</td>
<td>346</td>
<td>14.5</td>
<td>123</td>
</tr>
</tbody>
</table>

Median 70 23.3 94 0.9 102 339 20.4 133

Abbreviations are as defined in the footnote to Table 1.

and all participants gave informed consent. We examined 15 healthy subjects of young age (seven women, eight men; median age, 26 yr; range, 23 to 32 yr) with a median serum creatinine of 0.9 (range 0.8 to 1.1) mg/dL. In addition, we examined 10 healthy elderly subjects (six women, four men; median age, 70 yr; range, 61 to 82 yr) with a median serum creatinine of 0.9 (range, 0.7 to 1.1) mg/dL (Tables 1 and 2). None of the participants took any medication. Subjects with a history of cardiovascular or renal diseases were excluded. Urinary pathology was excluded by examination of urinary chemistry and sediment (by phase-contrast microscopy) and heart failure in the elderly subjects by echocardiography. All volunteers were studied under outpatient condition. Participants were advised not to change dietary habits at least 1 week before the study. Daily dietary salt and protein intakes were assessed by measurements of 24-h urinary sodium and urea excretion.

Protocol

Basal GFR (inulin clearance [Cin]) and ERPF (para-aminohippurate clearance [Cpah]) were examined on the morning of the first day after 12 h of fasting by steady-state infusion techniques as described before (26). In brief, subjects were examined in the supine position in a quiet environment. A diuresis of approximately 100 mL/h was maintained by the administration of fluid. After an overnight infusion of 0.9% saline at a rate of 83 mL/h, a priming dose of 1.500 mg of inulin/m² (Inutest®: Laevosan Co., Linz, Austria) and of 500 mg of para-aminohippurate (PAH)/m² (Nephrotest®, Biologische Arbeitsgemeinschaft GmbH, Lich, Germany) was given. This was followed by continuous infusions of inulin (10 mg/m² per min)
DAY 1

sham infusion

clearance

2 h a.m. 8 h a.m. 11 h a.m.

DAY 2

amino acid infusion

clearance

2 h a.m. 8 h a.m. 11 h a.m.

Figure 1. Study protocol.

and PAH (8 mg/m² per min), maintained with ultra-
precise pumps (Perfusor FT: Braun AG, Melsungen,
Germany). After a 90-min equilibration period, base-
line clearances were determined (Figure 1). In a pre-
vious control series, a saline infusion at the rate of
83 mL/h had caused no change of GFR in three
healthy volunteers. Renal hemodynamics (GFR and
ERPF) were examined again on the morning of the
day after an overnight infusion of a 7% AA solution
(Aminoplasma*: Fresenius AG, Bad Homburg, Ger-
many) under the same conditions as the baseline
clearances (Figure 1). The rate of the AA infusion
was 83 mL/h, yielding a rate of approximately 1.5
mg of AA/kg per min. Venous blood samples for AA
concentrations were drawn before and after the AA
infusion.

Measurements and Calculations

Mean arterial blood pressure (MAP) and heart rate
were measured by a noninvasive oscillometric tech-
nique (Dinamap®: Criticon Inc., Tampa, FL) throughout
the clearance measurements.

Inulin was measured enzymatically with inulinase
as described by Kühnle et al. (27), and PAH was
measured photometrically by the method of Bratton
and Marshall (28). Recovery of inulin by the enzy-
matic technique was 93 ± 5%. Replicate measure-
ments of CIN in the same individual showed a mean
coefficient of variation of 7% (three repeated meas-
urements in six individuals). Plasma AA concen-
trations were measured by HPLC. Serum and urine
chemistry were analyzed by standard laboratory
methods (autoanalyzer). CIN and Cpah were calcu-
lated from the delivered dose:

\[ C = \frac{(I_r \times I_c)}{S_c}; \]

where C is the clearance, Ir is the infusion rate in
milliliters per minute, Ic is the concentration of the
analyzed compound in the infusion fluid (in milli-
grams per milliliter) and Sc is the concentration of
the analyzed compound in the serum (in milligrams
per milliliter) (29). FF was calculated as the ratio of
CIN/Cpah. Renal vascular resistance (RVR) was cal-
culated by the equation: RVR = MAP/ERPF x (1 –
hct), where hct is hematocrit. The renal extraction
of PAH was not measured.

Statistics

Data are given as median and range. Differences
were evaluated by Wilcoxon’s test for paired samples
to compare baseline versus post-AA values, and Wil-
coxon’s test for random data was used to compare
the two cohorts, i.e. young versus elderly subjects.
Differences were regarded as significant at \( P < 0.05. \)

RESULTS

Median MAP, body mass index, and 24-h urinary
sodium and urea excretion were comparable in young
and elderly subjects (Tables 1 and 2). The median
dietary protein intake, estimated on the basis of 24-
h urinary urea excretion was similar in the young
and elderly subjects, i.e., 1.0 g/kg per day (range, 0.8
to 1.2) versus 1.1 (range, 0.9 to 1.3).

Baseline median CIN was significantly (\( P < 0.01 \))
lower (102 mL/min per 1.73 m²; range, 88 to 111) in
elderly as compared with young (122 mL/min per
1.73 m²; range, 109 to 142) subjects. The same was
true for median Cpah (339 mL/min per 1.73 m²;
range, 277 to 433, versus 647 mL/min per 1.73 m²;
range, 504 to 812) (Tables 1 and 2). In response to
the AA infusion, elderly subjects reached signifi-
cantly (\( P < 0.01 \)) lower median postinfusion values
of CIN and Cpah. The median CIN after the AA infu-
sion was 118 mL/min per 1.73 m² (range, 98 to 137)
in the elderly and 146 mL/min per 1.73 m² (range,
120 to 171) in the young subjects. Corresponding
values of Cpah were 349 mL/min per 1.73 m² (range,
286 to 406) and 689 mL/min per 1.73 m² (range,
522 to 815). Individual values for GFR and ERPF at base-
line and in response to AA infusion are given in
Figures 2 and 3. The increase in median GFR after
the infusion of AA was statistically significant (\( P < 0.01 \))
in both groups. The median ERPF increased
significantly (\( P < 0.01 \)) in the young group but failed
to do so in the elderly group (0.10 > \( P > 0.05 \)). The
median increase in CIN was +16% in the young and
+17% in the elderly; the difference was not statisti-

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**Figure 2.** GFR in young and elderly subjects at baseline and after the AA infusion. Squares, men; asterisks, women; circles, median.

The median increase in 

**Figure 3.** ERPF in young and elderly subjects at baseline and after the AA infusion. Squares, men; asterisks, women; circles, median.

DISCUSSION

This study clearly documents that (1) GFR is only slightly lower in elderly normotensive individuals on normal dietary protein intake than in young control subjects, and (2) renal functional reserve is preserved in the elderly human at least up to the age of 80 yr. This is true for both men and women.

Previous reports documented lower baseline levels of GFR and higher FF in elderly subjects (2,30,31). Although median baseline GFR was slightly but significantly lower in elderly compared with young subjects, GFR remained within the normal range in all but one elderly individual. Mean GFR (Clm) has been reported to fall from approximately 120 mL/min per 1.73 m² at the beginning of the fourth decade of life to about 90 mL/min per 1.73 m² in the sixth decade and to remain virtually stable thereafter (30,32–34). Longitudinal studies on renal function with advancing age, however, have documented unchanged GFR (determined with the creatinine clearance) in up to 30% of elderly people (35,36). It is possible that we have excluded subjects with a progressive decline of GFR from our cross-sectional study by following strict inclusion criteria. For example, in the Baltimore longitudinal study on aging (37), it has been shown that loss of renal function is accelerated in the elderly with even moderate increase in blood pressure. Therefore, an effort was made to restrict this study to normotensive subjects. A recent study showed that the age-related fall in GFR was primarily a function of dietary intake of protein (38). Our observation of an almost normal GFR in elderly nor-
TABLE 3. Median (and range) of RVR and FF in young and elderly subjects at baseline and after the AA load

<table>
<thead>
<tr>
<th></th>
<th>RVR (mm HgfL per min)</th>
<th>FF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>83 (58–104)</td>
<td>0.19 (0.16–0.25)</td>
</tr>
<tr>
<td>After AA</td>
<td>77 (57–101)</td>
<td>0.20 (0.18–0.26)</td>
</tr>
<tr>
<td>Elderly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>175 (124–240)</td>
<td>0.32 (0.23–0.38)</td>
</tr>
<tr>
<td>After AA</td>
<td>170 (130–213)</td>
<td>0.35 (0.27–0.41)</td>
</tr>
</tbody>
</table>

* a p < 0.01.

TABLE 4. Median (and range) of preinfusion and postinfusion AA levels in plasma in the elderly subjects

<table>
<thead>
<tr>
<th></th>
<th>Before AA Infusion</th>
<th>After AA Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartic acid</td>
<td>19 (15–31)</td>
<td>19 (16–29)</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>84 (68–116)</td>
<td>78 (48–102)</td>
</tr>
<tr>
<td>Serine</td>
<td>103 (80–167)</td>
<td>162 (87–255)</td>
</tr>
<tr>
<td>Glutamine</td>
<td>216 (169–284)</td>
<td>330 (221–538)</td>
</tr>
<tr>
<td>Proline</td>
<td>202 (140–413)</td>
<td>328 (196–625)</td>
</tr>
<tr>
<td>Glycerine</td>
<td>259 (184–473)</td>
<td>242 (186–403)</td>
</tr>
<tr>
<td>Alanine</td>
<td>372 (259–560)</td>
<td>413 (293–526)</td>
</tr>
<tr>
<td>Valine</td>
<td>256 (192–306)</td>
<td>415 (238–591)</td>
</tr>
<tr>
<td>Cystine</td>
<td>7 (4–20)</td>
<td>9 (5–20)</td>
</tr>
<tr>
<td>Leucine</td>
<td>136 (114–191)</td>
<td>291 (130–645)</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>69 (54–90)</td>
<td>144 (78–335)</td>
</tr>
<tr>
<td>Methionine</td>
<td>21 (18–39)</td>
<td>80 (31–113)</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>65 (54–95)</td>
<td>60 (43–108)</td>
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<tr>
<td>Phenylyalanine</td>
<td>60 (50–70)</td>
<td>109 (64–183)</td>
</tr>
<tr>
<td>Lysine</td>
<td>231 (179–245)</td>
<td>330 (213–437)</td>
</tr>
<tr>
<td>Histidine</td>
<td>90 (72–117)</td>
<td>130 (81–184)</td>
</tr>
<tr>
<td>Arginine</td>
<td>65 (33–85)</td>
<td>92 (73–147)</td>
</tr>
</tbody>
</table>

* a p < 0.05.

* a p < 0.01.

Figure 4. FF in young and elderly subjects at baseline and after the AA infusion. Squares, men; asterisks, women; circles, median.

motensive individuals on normal dietary intake of protein is consistent with this observation and suggests that age per se is not the major determinant of the decline of GFR with age.

The hemodynamic pattern of the renal vasodilatory response to AA infusion deserves comment. Whereas Cin increased significantly in both groups after AA infusion, CpaH increased significantly only in the young subjects. In both groups, the relative increase in GFR after the AA load was far greater than the elevation of ERPF. Consequently, FF rose after the AA infusion in the young as well as in the elderly subjects. This observation is in agreement with the results of Rulope, Krishna, and Rodriguez-Iturbe and their coworkers (13–15). The hemodynamic response to AA infusion depends on several factors, particularly on prior intakes of salt and protein, which modulate the activities of the renal renin-angiotensin and prostaglandin systems (39). We therefore verified that salt intake was constant in all our subjects. Tuttle et al. (40) documented that baseline GFR returns to normal after prolonged fasting even in hyperfiltering diabetics. Therefore, standardization of the time of nutrient administration is crucial as are duration of fasting, duration of infusion, and the amount and type of AA infused. Maximal stimulation of RFR is seen between 15 and 180 min after the start of AA infusion, with an infusion rate varying between 1 and 8 mg/kg per min (39). The amount of AA infused in our study was about 1.5 mg/kg per min for 8 h, and the protocol was designed to avoid the above artifacts. Significant changes of postinfusion AA plasma concentrations were observed for the following AA: arginine, phenylalanine, histidine, lysine, valine, glutamine, leucine, isoleucine, methionine, proline, serine, and threonine, but not glycine.

We confirmed previous observations of a higher FF in the elderly, and this was also noted after AA
stimulation (2,31). It is well known that aging is associated with a loss of renal mass (4,41). Involution of tissue occurs primarily in the renal cortex, with relative sparing of the renal medulla (30). Selective loss of cortical and preservation of juxtedudillary nephrons with higher FF may explain, at least in part, the rise in FF with age. A lower extraction ratio for PAH would result in erroneously low values of Cph and might also cause higher values of FF. Although four decades ago, an unchanged extraction ratio for PAH was found in the elderly (42), it would be desirable to confirm this observation.

RVR was significantly elevated in elderly individuals without evidence of renal disease or hypertension. RVR decreased after AA infusion in the young, but not consistently so in the elderly subjects. In parallel, ERPF increased after AA in all young but in only some elderly subjects. In contrast to the differences in the AA-induced changes of RVR and ERPF, the increase in GFR after AA infusion was almost identical in young and elderly individuals. The preserved vasodilator response to AA contrasts with attenuated renal vasodilatation after acetylcholine in the elderly (30). Further research to elucidate the causes of such discrepant reaction to different stimuli is warranted.

In the old rat, the renal response to AA was more markedly impaired at the age of 24 months than at the age of 18 months (25). Thus, the renal abnormality increases with progressive age. The oldest patient with intact RFR in our cohort was 82 yr, but this does not exclude that RFR may be abnormal at a still higher age.

In conclusion, our results confirm that, in humans, GFR and ERPF are modestly lower at higher age, whereas FF and RVR are higher. Our study further documents preservation of RFR at least until the age of 80 yr in both men and women. This result may be of interest with respect to the progression of renal disease in the elderly.

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