Functional changes in the ageing kidney: is there a role for asymmetric dimethylarginine?

Jan T. Kielstein, Stefanie M. Bode-Böger, Hermann Haller and Danilo Fliser

1Department of Internal Medicine, Medical School Hannover and 2Institute of Clinical Pharmacology, Otto-von-Guericke University Magdeburg, Germany

Keywords: elderly; glomerulosclerosis; hypertension; renal perfusion; renovascular resistance

Age-related changes of renal haemodynamics

Normal human ageing occurs with morphological and functional changes in nearly all organ systems, and the kidney is no exception to this rule. Even in individuals without primary renal disease, kidney structure and function deteriorate with senescence to some extent. Recent studies have revealed, however, that age-related renal changes are accelerated by co-morbid conditions such as hypertension, atherosclerosis and heart failure [1–5].

Results from the seminal ‘Baltimore Longitudinal Study on Aging’ and from several cross-sectional studies have shown that the decrease of glomerular filtration rate (GFR) in healthy elderly subjects is less than was thought previously [1,3,6,7]. In some elderly individuals, even no change of GFR was documented over a time span of at least 25 years [6]. Thus, in a reasonable number of healthy elderly subjects, the GFR remains within the (lower) normal range. In contrast,
effective renal plasma flow (ERPF) decreases proportionally more than GFR, and this finding may explain in part the observed increase of filtration fraction (FF) in elderly individuals, i.e. the ratio between GFR and ERPF [3,7]. Furthermore, the decrease of ERPF out of proportion to the blood pressure in the healthy elderly implies that the renovascular resistance (RVR) must be elevated. Indeed, we and others have shown that RVR is significantly increased in normotensive elderly individuals without cardiovascular disease [3,8]. Renal vasoconstriction is even more pronounced in the elderly with co-morbidity such as hypertension or heart failure [3,7,9]. Thus, the hallmark of renal ageing is increased basal renovascular tone accompanied by reduced perfusion, and these age-related changes are accentuated in patients with cardiovascular co-morbidity. In addition, the ability of (post-glomerular) vessels to dilate in response to stimuli such as acetylcholine, amino acids or nitric oxide (NO) is also reduced in the elderly [10–12]. It is still unresolved whether these age-related changes in renal haemodynamics are caused by structural abnormalities, or whether there also exists a functional abnormality, i.e. reduced capacity of renal vessels to dilate as a consequence of reduced availability of (or responsiveness to) vasodilator substances. Experimental studies and studies in humans support the latter concept [10–13]. In this context, it has to be pointed out that the renal microvasculature is particularly sensitive to NO synthase (NOS) inhibition; this has been demonstrated in animal experiments as well as in human studies [14–16]. The observation points to an important role for NO in the regulation of (basal) medullary blood flow, and in the control of the pressure-natriuresis [16].

**Ageing and asymmetric dimethylarginine**

In a cross-sectional study of a random population sample, a significant positive correlation was found between age, blood pressure and plasma levels of asymmetric dimethylarginine (ADMA), which is an endogenous inhibitor of NOS [17]. ADMA is released from proteins that have been post-translationally methylated and subsequently hydrolysed. These proteins are found largely in the nucleus and appear to be involved in RNA processing and transcriptional control. Two types of enzymes methylate arginine residues: type I protein arginine methyltransferase forms ADMA, whereas type II forms symmetric dimethylarginine, i.e. the biologically inactive stereoisomer of ADMA. ADMA is excreted by the kidneys to some extent, but the predominant degradation pathway is by the enzyme dimethylarginine dimethylaminohydrolase (DDAH), which hydrolyses ADMA to dimethylamine and l-citrulline (Figure 1) [18,19]. Co-localization of DDAH and NOS in various cell types including renal tubular cells supports the hypothesis that the intracellular concentration of ADMA is regulated actively and cell specifically in NO-generating cells [20]. Further evidence for this hypothesis comes from results of a recently published experimental study showing an inhibitory effect of NO on DDAH activity, thus regulating its own (local) concentration via the metabolism of ADMA [21] (Figure 1). Several experimental and clinical studies have documented that DDAH activity is reduced in the presence of hypercholesterolaemia and insulin resistance [19,22], i.e. conditions that have a high prevalence among elderly subjects. Direct measurements

Fig. 1. Biochemical pathways for generation and degradation of the endogenous nitric oxide synthase inhibitor ADMA (for explanation, also see text).
of DDAH activity are not yet available, however, and age-related alterations in DDAH activity have not been reported so far.

### Asymmetric dimethylarginine and renal ageing

Whatever the cause(s) of increased ADMA blood levels in the elderly, they may reduce NO availability by NOS inhibition and thus contribute to endothelial dysfunction and arteriosclerosis, and finally lead to increased renovascular resistance and hypertension [19,23]. This hypothesis is supported by the finding of significantly increased plasma ADMA concentrations even in non-smoking healthy normotensive elderly subjects, in parallel with significantly reduced renal perfusion (Table 1) [24]. Furthermore, in logistic regression analysis, the plasma ADMA level was the only significant predictor of reduced ERPF and increased RVR, explaining a large part of their variability in elderly individuals. A significant relationship between plasma ADMA and the level of blood pressure was also documented, and this observation is in line with recently published results [17]. Although the increase of plasma ADMA levels in normotensive and hypertensive elderly subjects as compared with normotensive young subjects was moderate, we emphasize that according to several studies in different populations, even small differences in mean plasma ADMA levels (i.e. ~1 μmol/l) are associated with a deterioration of endothelial function and a significant increase in the rate of cardiovascular events in the long term [18,25,26]. Taken together, these findings are compatible with the notion that an increase of blood ADMA levels with senescence is linked to the reduction of renal perfusion and increase in blood pressure. Indirect support for this assumption comes from studies in laboratory animals, in which administration of ADMA significantly reduced renal perfusion and increased renovascular tone, and, in parallel, blood pressure [27]. We have confirmed these findings in healthy subjects, in whom systemic ADMA infusion significantly decreased ERPF and increased RVR and mean arterial blood pressure [28].

In summary, recent studies provide evidence for a significant relationship between increased blood levels of the endogenous NOS inhibitor ADMA, and reduced renal perfusion and high blood pressure in senescence. The role of ADMA in the pathophysiology of age-related endothelial dysfunction, resulting in increased renovascular tone and blood pressure, has to be elucidated further.

### References


---

**Table 1.** ADMA blood concentrations, renal haemodynamics and blood pressure in young and elderly normotensive subjects and elderly hypertensive patients

<table>
<thead>
<tr>
<th></th>
<th>Young normotensive (n=24)</th>
<th>Elderly normotensive (n=24)</th>
<th>Elderly hypertensive (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25 ± 1</td>
<td>69 ± 1*</td>
<td>70 ± 1**</td>
</tr>
<tr>
<td>Plasma ADMA (μmol/l)</td>
<td>1.30 ± 0.07</td>
<td>2.77 ± 0.12*</td>
<td>3.53 ± 0.14***</td>
</tr>
<tr>
<td>Plasma L-arginine (μmol/l)</td>
<td>56.0 ± 2.6</td>
<td>56.2 ± 1.3</td>
<td>60.0 ± 1.4</td>
</tr>
<tr>
<td>GFR (ml/min.1.73 m²)</td>
<td>121 ± 2</td>
<td>104 ± 2*</td>
<td>103 ± 3**</td>
</tr>
<tr>
<td>ERPF (ml/min.1.73 m²)</td>
<td>654 ± 11</td>
<td>487 ± 16*</td>
<td>427 ± 12**+</td>
</tr>
<tr>
<td>RVR (mmHg/ml/min)</td>
<td>77 ± 2</td>
<td>125 ± 6*</td>
<td>163 ± 7**+</td>
</tr>
<tr>
<td>24 h MAP (mmHg)</td>
<td>88 ± 1</td>
<td>90 ± 1</td>
<td>107 ± 1**+</td>
</tr>
</tbody>
</table>

Modified after Kielstein et al. [24].

24 h MAP, 24 h mean arterial blood pressure; *P < 0.05, young normotensive vs elderly normotensive; **P < 0.05, young normotensive vs elderly hypertensive; †P < 0.05, elderly normotensive vs elderly hypertensive.


