Pathophysiology of Vascular Function in CKD

Gérard M. London
INSERM U970
Hôpital Européen Georges Pompidou
Paris
Arterial Pathophysiology and Cardiovascular Diseases in CKD

- **Arteriosclerosis** ↔ **Atherosclerosis**
  - Systolic BP; Diastolic BP
  - (Decreased coronary perfusion)

- **Adaptive LVH**
  - Volume* Overload
  - (Decreased coronary reserve)

- **Maladaptive LVH**
  - Systolic/diastolic dysfunction

- **CEREBROVASCULAR DISEASE**
  - Hgb; AVF; Na+

- **CORONARY ARTERY DISEASE**
  - HEART FAILURE
  - SUDDEN DEATH
  - SUDDEN DEATH
Prevalence of discrete plaques on common carotid artery in control subjects and ESRD patients

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ESRD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.5 ± 16</td>
<td>51 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Plaques (%)</td>
<td>17.8%</td>
<td>56.3%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Type of plaques</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Calcified</td>
<td>23.1%</td>
<td>91.5%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>• Soft/mixed</td>
<td>77%</td>
<td>9%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

London et al Sem Dial 1999
Age related changes in arterial internal diameters

Controls (r = 0.400; P < 0.01)
ESRD (r = 0.438; P < 0.0001)

Controls (r = 0.525; P < 0.01)
ESRD (r = 0.277; P = 0.065)
Evolution of Carotid diameter with progression of CKD stages

P = 0.02, linear trend

Age related changes in Carotid IMTh

Graph showing the relationship between age and common carotid artery intima-media thickness (IMTh) with age (years) on the x-axis and common carotid artery IMTh on the y-axis. The graph compares controls and ESRD patients, with different markers for each group.
Mechanical stresses in the blood vessel

- Circumferential wall stress: \( sq = \frac{P \times R}{h} \)
- Fluid shear stress: \( t = \frac{4 \mu Q}{P \times R^3} \)
## Brachial artery characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ESRD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline BA diameter (mm)</strong></td>
<td>4.12 ± 0.13</td>
<td>4.56 ± 0.11</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>BA compliance (m².kPa⁻¹.10⁻⁷)</strong></td>
<td>0.45 ± 0.02</td>
<td>0.37 ± 0.02</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>BA distensibility (kPa⁻¹.10⁻³)</strong></td>
<td>3.5 ± 0.22</td>
<td>2.6 ± 0.19</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>BA incremental elastic modulus (kPa.10³)</strong></td>
<td>3.0 ± 0.22</td>
<td>5.0 ± 0.42</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Baseline mean flow velocity (cm/s)</strong></td>
<td>4.6 ± 0.40</td>
<td>3.4 ± 0.30</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Baseline mean flow (ml/min)</strong></td>
<td>39 ± 4.6</td>
<td>33 ± 3.6</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Baseline mean SR (s⁻¹)</strong></td>
<td>53 ± 2.9</td>
<td>39 ± 3.5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Baseline peak SR (s⁻¹)</strong></td>
<td>365 ± 23</td>
<td>324 ± 26</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>Whole blood viscosity (cPoise)</strong></td>
<td>3.57 ± 0.07</td>
<td>2.79 ± 0.06</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Baseline mean SS (dynes/cm²)  
19 ± 1.15  
10.7 ± 1.0  
< 0.001  

Baseline peak SS (dynes/cm²)  
129 ± 9  
83 ± 5  
< 0.001  

Verbeke et al JASN 2007
Paracrine effect(s) of endothelial MPs predisposing to endothelial dysfunction in vivo

A. $r = -0.770$
   $P < 0.0001$

B. $r = -0.648$
   $P < 0.0001$

C. $r = -0.291$
   $P = 0.100$

D. $r = -0.082$
   $P = 0.672$

Boulanger Ch et al Hypertension 2007
circumferential wall stress

\[ sq = \frac{P \times R}{h} \]

![Box plot showing comparisons between controls and ESRD patients. Controls have a mean of 100±16 kPa, and ESRD patients have a mean of 111±28 kPa. The p-value is less than 0.001.](London GM (submitted))
Evolution of Carotid Circumferential wall stress with progression of CKD stages

Control population (n=104)
Circumf. stress = 24.4±6.1

ESRD patients (n=163)
Circumf. stress = 28.0±6.1 (p=0.027)

Common Carotid artery relative wall thickness (Th/r)

R= 0.349
P <0.001

R= −0.154
P= 0.050

Common Carotid artery systolic BP (mm Hg)

London GM et al (submitted)
ESRD with absence of carotid artery calcifications

ESRD with carotid artery calcifications

Common Carotid artery relative wall thickness (Th/r)

Common Carotid artery systolic BP (mm Hg)

London GM et al (submitted)
Dialysis Accelerates Medial Vascular Calcification in Part by Triggering Smooth Muscle Cell Apoptosis

![Graph A](image1.png)

![Graph B](image2.png)

Shroff et al Circulation 2008;118:1748-57
Common Carotid artery elastic modulus

Control subjects
ESRD patients

ESRD carotid calcifications –
ESRD carotid calcifications +

Common Carotid artery systolic BP (mm Hg)

All categories P<0.00001

London GM et al (submitted)
Evolution of Carotid elastic modulus with progression of CKD stages

P = 0.001, linear trend

**-** P < 0.0001

AGE vs HRPWV
Aortic and arm pulse wave velocities as a function of age

Avolio et al. Circulation 1983
## Characteristics of arterial system in controls and ESRD patients

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral/femoral PWV (m/s)</td>
<td>11.0 ±1.75</td>
<td>11.20 ±1.80</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.5 ± 16</td>
<td>51 ± 16</td>
</tr>
<tr>
<td>Aortic PWV (m/s)</td>
<td>9.70 ±1.80</td>
<td>10.60 ±2.5**</td>
</tr>
</tbody>
</table>
Aortic PWV

Brachial PWV

Femoral PWV

\( \chi^2 = 72.8 \)
\( P < 0.00001 \)

\( \chi^2 = 1.78 \)
\( P = 0.411 \)

\( \chi^2 = 2.34 \)
\( P = 0.310 \)

Pannier et al. Hypertension 2005
Correlation between age and arterial calcium (Ca) concentration in the aorta and internal iliac artery in nonuremic control subjects

Correlation between aortic calcification score and aortic PWV in ESRD patients

Pannier et al. Artery 2007
Aortic PWV (m/s) vs. Common carotid artery Pulse pres. (mm Hg)

- Scatter plot with regression line
- Correlation coefficient: $R = 0.633$, $P < 0.0001$

CCA Augmented pressure (mm Hg) vs. Common carotid artery Pulse pres. (mm Hg)

- Scatter plot with regression line
- Correlation coefficient: $R = 0.784$, $P < 0.00001$

Systemic reflection coefficient vs. Common carotid artery Pulse pres. (mm Hg)

- Scatter plot with regression line
- Correlation coefficient: $R = -0.595$, $P < 0.00001$
Pressure wave analysis

- measured pressure wave
- forward/incident pressure wave
- reflected pressure wave
- pulse wave
- velocity

Young subjects

Old subjects
Diagrammatic representation of the effects of arterial degeneration (right) on aortic systolic pressure time index (orange area) and aortic diastolic pressure time index (yellow area).

O'Rourke M.F.: The arterial pulse, Lea Fibiger, 1992
Correlation between left ventricular mass and aortic pulse wave velocity

London et al KI 1989
Subendocardial viability ratio (DPTI/SPTI) vs. Aortic PWV (m/s)

$r = -0.406$

$P < 0.0001$
Arterial system as « hydraulic filter »

Cyclic high and pulsatile pressure

Pressure (mm Hg)

Flow (mls)

Aorta

Microcirculation capillaries

Continuous low pressure

Pressure (mm Hg)

Flow (mls)

Cyclic highly pulsatile flow

Continuous flow and perfusion
A. Systole
In normally compliant arterial system important part of the stroke volume is stored in the arteries during ventricular systole stretching the arterial walls.

B. Diastole
During ventricular diastole the previously stretched arterial walls recoils with the stored volume insuring continuous perfusion of tissues and organs.
Rigid arteries

<table>
<thead>
<tr>
<th>Systole</th>
<th>Diastole</th>
</tr>
</thead>
<tbody>
<tr>
<td>A volume of blood equal to the entire stroke volume must flow through the capillaries during systole.</td>
<td>Flow through the capillaries ceases during diastole.</td>
</tr>
</tbody>
</table>

C. When the arteries are rigid, virtually none of the stroke volume can be stored in the arteries. 
D. Rigid arteries cannot recoil appreciably during diastole.
Oxygen Limitation Model

Blood Velocity

Capillary Transit Time

$O_2$ Extraction

Smaller Fraction of $O_2$ Available for Metabolism

Normally 2-3 seconds

(NO capillary recruitment)
Relationship between PWV and cognitive status (normal cognitive function, MCI, AD, and VaD). $P<0.0001$, adjusted for age, gender, SBP, education level, antihypertensive therapy, presence of cardiovascular diseases.
Univariate association and confidence intervals between the pulse wave velocity (PWV) and the annual change in Mini-Mental Examination State (MMSE) score ($r = -0.333$, $P < 0.001$).
Correlation Between CCr (C-G formula) and Aortic PWV

\[ r = -0.30 \]

\[ P < 0.0001 \]

Bortolotto et al KI 2001
Arterial Impedance Gradients
Zc-characteristic impedance; Zr-peripheral resistance

Reflection Coefficient ($\Gamma$) = \( \frac{Z_R - Z_C}{Z_R + Z_C} = \frac{P_b}{P_f} \)

Aorta

Peripheral arteries

Resistance vessels

PWV=6 m/s

PWV=10 m/s

PWV=12 m/s

PWV=11 m/s
Pressure transmission in the presence of arterial stiffness gradients

Pressure mm Hg

Aorta
PWV 6 m/s

Large arteries
PWV=10 m/s

Resistance vessels

Microvascular network

Incident pressure

Reflected pressure

Terminal pressure
Pressure transmission in “low peripheral resistance” organs (kidney; brain) when arterial stiffness gradient is decreased or abolished.
Systemic Reflection Coefficient vs. \((Aortic \ PWV/Brachial \ PWV)^{0.5}\)

- Correlation coefficient: \(r = -0.46\)
- Statistical significance: \(P < 0.0001\)

London GM (submitted)
Systemic reflection coefficient

London GM (submitted)

$r = -0.455$

$P < 0.001$
Distance from the aorta to reflecting sites (% of body height)

\[ r = 0.165 \]
\[ P = 0.014 \]

London GM (submitted)
### Characteristics of arterial system in controls and ESRD patients

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Forward pressure (mm Hg)</strong></td>
<td>38 ± 11</td>
<td>44 ± 16**</td>
</tr>
<tr>
<td><strong>Wave reflection (% of PP)</strong></td>
<td>17 ±17</td>
<td>25 ±15***</td>
</tr>
<tr>
<td><strong>Reflected pressure (mm Hg)</strong></td>
<td>11 ± 6</td>
<td>14 ± 8*</td>
</tr>
<tr>
<td><strong>Reflected wave arrival time (ms)</strong></td>
<td>128 ±15</td>
<td>108 ± 16**</td>
</tr>
<tr>
<td><strong>Zr (dynes.s.cm-5)</strong></td>
<td>2309 ±530</td>
<td>2260 ±1175</td>
</tr>
<tr>
<td><strong>Zc (dynes.s.cm-5)</strong></td>
<td>179 ± 52</td>
<td>214 ±103**</td>
</tr>
<tr>
<td><strong>Γ (reflection coefficient)</strong></td>
<td>0.85 ± 0.04</td>
<td>0.81 ±0.06**</td>
</tr>
<tr>
<td><strong>Aortic PWV (m/s)</strong></td>
<td>9.70 ±1.80</td>
<td>10.60 ±2.5**</td>
</tr>
<tr>
<td><strong>Peripheral/femoral PWV (m/s)</strong></td>
<td>11.0 ±1.75</td>
<td>11.20 ±1.80</td>
</tr>
</tbody>
</table>

*P<0.05; **P<0.01; ***P<0.001

ESRD: fmin=4.62Hz; Control: fmin=3.90Hz
Aortic PWV/femoral PWV (ratio)

Controls: 0.84 ± 0.15
ESRD: 0.97 ± 0.25

P < 0.01
Schematic representation of reactive hyperemic response in the human forearm after five minutes of ischemia.
Postischemic Flow repayment (%) vs. Systemic Reflection Coefficient

$r = 0.391$

$P < 0.0001$

London GM (submitted)
Arterial changes in CKD

- **Premature Aortic Aging**: increased diameter and stiffness.
- **Accelerated in the presence of calcifications**
- **Lost or Impairement of Hydraulic Filter**: high Systolic and Pulse pressure in Aorta and Central arteries (LVH poor Coronary perfusions), and abnormal pressure transmission to microcirculation (impaired vasodilation)
Common Carotid Pulse Pressure and Cardiovascular mortality in ESRD patients
(log rank p<0.0001)

Cox model: $P=0.0049$
adjusted for age and mean BP

Safar et al Hypertension 2002
Superimposed simultaneous phasic recording of aortic (Ao), left ventricular (LV) pressures and coronary blood flow (CBF) (Buckeberg et al. Circ Res. 1972)
GAS EXCHANGE ACROSS THE PULMONARY CAPILLARY
Is Complete Within ¼ Second

- at rest pulmonary transit time [¾ second] is more than that required to complete gas exchange [¼ second].
- during exercise, despite increased cardiac output, pulmonary transit time remains > ¼ second & gas exchange is complete.
- in pulmonary fibrosis, reduced gas exchange is often seen in patients during exercise. At rest, the additional time spent in the capillary is sufficient to compensate for the thickened barrier.
- elite athletes with very high cardiac outputs have pulmonary transit times below ¼ second during intense exercise → inadequate oxygen exchange at the lungs → low oxygen levels in the blood [arterial hypoxemia]
Effects of age on arterial stiffness and wave reflections
For males (circle and solid lines) and females (squares and dashed line)

Figure 2. Regression curves representing the effect of age on parameters of arterial stiffness and wave reflection for males (circles, solid lines) and females (squares, dashed lines). Panel A represents augmentation pressure

Carmel M. McEniery et al. JACC 2005;46:1753
Aortic tapering (Aortic root/aortic bifurcation)

Controls: $1.76 \pm 0.24$

ESRD: $1.64 \pm 0.3$

$P = 0.03$
Postischemic Flow repayment (%) vs Systemic Reflection Coefficient

$r = 0.391$

$P < 0.0001$

London GM (submitted)
# Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=59)</th>
<th>ESRD (n=121)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>48±13</td>
<td>51±15</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>76±15</td>
<td>64±13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Height (m)</strong></td>
<td>1.70±0.11</td>
<td>1.64±0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Systolic BP (mm Hg)</strong></td>
<td>144±21</td>
<td>152±30</td>
<td><strong>0.020</strong></td>
</tr>
<tr>
<td><strong>Diastolic BP (mm Hg)</strong></td>
<td>86±14</td>
<td>83±15</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Mean BP (mm Hg)</strong></td>
<td>105±15</td>
<td>106±18</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Pulse Pressure (mm Hg)</strong></td>
<td>58±15</td>
<td>68±24</td>
<td><strong>&lt;0.0001</strong></td>
</tr>
</tbody>
</table>
Coronary Artery Calcification in Young Dialysis Patients

N=39

*Determined by EBT.

Calcification scores nearly doubled in a majority of patients with positive initial scan when rescanned at 20 months.
Effect of arterial stiffness on timing of forward and reflected Waves

PWV 8 m/sec  PWV 12 m/sec

Systolic Augmentation Pressure (Aix)

- Forward-traveling wave
- Backward-traveling reflected wave
- Actual (composite) wave

T - traveling time of pressure wave to reflecting sites and back
Pressure wave analysis

- measured pressure wave

- forward/incident pressure wave

- reflected pressure wave

- pulse wave

- velocity
GAS EXCHANGE ACROSS THE PULMONARY CAPILLARY
Is Complete Within \( \frac{1}{4} \) Second

- at rest pulmonary transit time \( \frac{3}{4} \) second is more than that required to complete gas exchange \( \frac{1}{4} \) second.
- during exercise, despite increased cardiac output, pulmonary transit time remains > \( \frac{1}{4} \) second & gas exchange is complete.
- in pulmonary fibrosis, reduced gas exchange is often seen in patients during exercise. At rest, the additional time spent in the capillary is sufficient to compensate for the thickened barrier.
- elite athletes with very high cardiac outputs have pulmonary transit times below \( \frac{1}{4} \) second during intense exercise → inadequate oxygen exchange at the lungs → low oxygen levels in the blood [arterial hypoxemia].
Oxygen Limitation Model

Blood Velocity

Capillary Transit Time

$O_2$ Extraction

Smaller Fraction of $O_2$ Available for Metabolism

Normally 2-3 seconds

(Not capillary recruitment)
Rigid arteries

<table>
<thead>
<tr>
<th>Systole</th>
<th>Diastole</th>
</tr>
</thead>
<tbody>
<tr>
<td>A volume of blood equal to the entire stroke volume must flow through the capillaries during systole.</td>
<td>Flow through the capillaries ceases during diastole.</td>
</tr>
</tbody>
</table>

C. When the arteries are rigid, virtually none of the stroke volume can be stored in the arteries.  
D. Rigid arteries cannot recoil appreciably during diastole.
Aortic PWV/femoral PWV (ratio)

P < 0.01

Controls
0.84±0.15

ESRD
0.97±0.25
Aortic tapering (Aortic root/aortic bifurcation)

Controls: 1.76±0.24
ESRD: 1.64±0.3

P = 0.03
Compliant arteries

Systole: Arterial blood flows through the capillaries throughout systole.

Diastole: Arterial blood continues to flow through the capillaries throughout diastole.

A. When the arteries are normally compliant, a substantial fraction of the stroke volume is stored in the arteries during ventricular systole. The arterial walls are stretched.

B. During ventricular diastole, the previously stretched arteries recoil. The volume of blood that is displaced by the recoil furnishes continuous capillary flow throughout diastole.

Rigid arteries

Systole: A volume of blood equal to the entire stroke volume must flow through the capillaries during systole.

Diastole: Flow through the capillaries ceases during diastole.

C. When the arteries are rigid, virtually none of the stroke volume can be stored in the arteries.

D. Rigid arteries cannot recoil appreciably during diastole.
Mechanical stresses in the blood vessel

- Circumferential wall stress
  \[ \sigma_\theta = \frac{P x R}{h} \]

- Fluid shear stress
  \[ t = \frac{4 \mu Q}{p R^3} \]
Postischemic Flow debt repayement (%) vs Systemic Reflection Coefficient

$r = 0.391$
$P < 0.0001$

London GM (submitted)