Atherosclerotic renal artery stenosis (ARAS) produces lumen occlusion, eventually lowering kidney perfusion and accelerating hypertension. ARAS is strongly associated with cardiovascular disease and progressive renal dysfunction. Although the kidneys can adapt to partially reduced blood flow without major loss of oxygenation and viability (as they receive more blood than needed for their metabolic activity), severe reductions in renal blood flow (RBF) eventually lead to tissue fibrosis and what has been labeled ischemic nephropathy. Recent experimental studies underscore the development of renal microvascular changes distal to a stenosis in the renal artery and over time, rarefaction of the distal arterioles. Severe degrees of vascular occlusion lead to overt cortical hypoxia associated with fibrogenesis and loss of renal function.

The benefits of revascularization procedures to restore blood flow in ARAS remain ambiguous. Only a fraction of patients treated with renal revascularization have improved blood pressure levels or reduced medication requirements, and kidney function after revascularization infrequently improves and sometimes declines. Notably, most clinical studies in humans evaluating the response to revascularization...
WHAT IS KNOWN

- Although renal artery stenosis is known to accelerate hypertension and reduce kidney function, revascularization often produces only minor benefits to blood pressure control and often fails to restore kidney function.

WHAT THE STUDY ADDS

- This article demonstrates that severe renovascular disease is associated with tissue hypoxia and increased renal venous markers of inflammatory cytokines (monocyte chemoattractant protein-1 and tumor necrosis factor-α) and tissue injury (neutrophil gelatinase–associated lipocalin).
- Revascularization can reduce hypoxia and partially restore blood flow, but failed to alter markers of inflammation, suggesting that additional measures may be needed to reverse the process of kidney injury.

are limited to changes in serum creatinine, glomerular filtration rate (GFR), blood pressure, or number of medications. The effects of restoring blood flow after revascularization on kidney tissue hypoxia, regional perfusion within the kidney, and markers of renal injury are not known.

Blood oxygen level–dependent (BOLD) MRI has been used to provide estimates of in vivo tissue oxygenation in humans noninvasively by determining local levels of deoxyhemoglobin within the kidney. Studies of patients with moderate to high-grade renal artery stenosis but with preserved tissue volume demonstrate elevated medullary and cortical deoxyhemoglobin signals that fall after intravenous furosemide. These observations suggest that viable kidneys may show regional hypoxic changes associated with tubular transport activity. When ARAS produces more severe occlusion, overt tissue hypoxia and renal injury can be identified. We have previously shown elevated renal vein levels of neutrophil gelatinase–associated lipocalin (NGAL) in the poststenotic kidney (STKs) of patients with ARAS, as well as release of inflammatory markers from the post-STKs. Whether these inflammatory changes can be reversed in humans remains unknown.

The purpose of this study was to examine the effect of renovascular revascularization on regional tissue perfusion and renal tissue hypoxia in post-STKs (STKs) using BOLD MRI. We sought to evaluate markers of renal injury as reflected by renal vein levels of the acute phase reactant (NGAL), the inflammatory cytokines monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-α (TNF-α) from hypertensive human subjects with ARAS as compared with patients with essential hypertension (EH). Our hypothesis was that restoring blood flow to the stenotic kidney would reverse tissue hypoxia detected by BOLD MRI and reduce renal injury in human subjects with ARAS.

Renal Function and Blood Pressure Measurements

The first study day included measurement of sodium excretion and of GFR by iothalamate clearance (iothalamate meglumine, Conray, Mallinckrodt) after oral hydration (20 mL/kg) during three 30-minute timed collection periods, as described previously. Single kidney (SK) GFR was determined by apportioning the measured iothalamate clearance by percentage of blood flow for each kidney. Blood pressure was measured by automated oscillometric recordings, including 3 values taken 3× daily (an automated oscillometric unit, Omron blood pressure, measured blood pressure at 5, 7, and 9 minutes after a 5-minute rest).

Tissue Oxygenation Determined by BOLD MRI

On the second day, BOLD MRI examinations were performed on a GE Twin Speed Signa EXCITE 3.0T system (GE Medical Systems, Waukesha, WI) using a 12-channel torso phased array coil. Three-plane single shot fast spin echo localizers were performed during suspended respiration followed by additional scout images (single shot fast spin echo) oriented parallel to the long axis of each kidney. These long axis scout images were then used to prescribe transverse BOLD images in a plane orthogonal to the long axis. BOLD imaging consisted of a 2-dimensional fast spoiled gradient echo sequence with multiple echo times. Twelve echoes were obtained for each section location, with echo times ranging from 2.5 to 50.0 ms. Imaging parameters for the BOLD acquisition included the following: repetition time, 140 ms; flip angle, 45°; section thickness, 5 mm; imaging matrix, 224×160 to 192; and field of view, 32 to 40 cm, with 0.7 to 1.0 partial phase field of view. Image matrix and repetition time were adjusted in patients with limited breath-hold capacity and the field of view and partial field of view adjusted according to patient size. BOLD images were prescribed transverse to the long axis of the kidney using the long axis localizers and acquired during suspended respiration through the midpole hilar region of each kidney. Parametric images of R2* were then generated by fitting signal intensity versus echo time data to an exponential function on a voxel-by-voxel basis and solving...
CT Data Analysis

MDCT images were reconstructed and displayed with the Analyze software package (Biomedical Imaging Resource, Mayo Clinic, MN). ROI were selected from cross-sectional images from the aorta, renal cortex, and medulla. Average tissue attenuation in each region was plotted over time and fitted by curve-fitting algorithms to obtain measures of renal function as described previously.\textsuperscript{24,25} Cortical and medullary volumes were calculated by Analyze and RBF as the sum of the products of cortical and medullary perfusions and corresponding volumes.

Renal Vein and Urine Sampling

Renal vein blood samples for NGAL and inflammatory cytokine analysis were obtained from the STK renal vein of all patients, as previously described.\textsuperscript{18,19} Samples were stored at \(-80^\circ\text{C}\) until measurement. Collected samples were centrifuged, and the supernatant was stored. NGAL (ng/mL) was tested by ELISA according to the manufacturer’s protocol (BioPorto Diagnostics, Cat no. KIT 036). Levels of TNF-\(\alpha\) and MCP-1 were measured by luminex (Millipore, cat no.: MXPHCYTO-60K). Signals were read by the Bio-plex 200 systems (BIO-RAD). All measurements were performed by a single investigator blinded to the clinical data.

Statistical Analysis

Data were analyzed using JMP software package version 8.0 (SAS Institute Inc, Cary, NC). Results were expressed as mean and SD or median (interquartile range) for quantitative data, as appropriate, or as number (percentage) for qualitative variables. Comparisons between independent groups with EH or ARAS were performed using paired \(t\) test with unequal variance (or the Wilcoxon rank-sum test for skewed data) and a \(\chi^2\) test or Fisher exact test for categorical variables as appropriate. Comparisons between stenotic or CLKs within the same individuals (pre- and post furosemide and before and after revascularization) were performed using paired \(t\) tests (or Wilcoxon signed-rank test for skewed data). No formal correction was made for multiple comparisons, and thus a significance level of 0.05 was accepted. Spearman rank correlation analysis was used to test for associations between basal fractional hypoxia, inflammatory markers and RBF, tissue perfusion, and GFR.

Results

Demographic Comparison Between Patients With ARAS and EH

Complete data were available for 17 patients in the ARAS group and for 32 patients in the EH group. The demographic and clinical features of the patients studied are summarized in Table 1. Age, weight, body mass index, and most biochemical values were not significantly different between groups. Triglyceride levels, serum creatinine, and systolic blood pressure were higher in patients with ARAS, whereas GFR was lower.

Figure 1. Blood oxygen level–dependent (BOLD) MR. Selection of regions of interest (ROI) on an axial image: A, Fractional tissue hypoxia was determined by outlining the entire axial kidney slice located within parenchyma. An additional ROI was placed to outline a wide segment cortical area excluding the renal collecting system, incidental cysts, and the hilar vessels. B, \(R^2*\) parametric map for the selected axial slice reflecting widely variable \(R^2*\) levels and deoxyhemoglobin at different sites within the kidney, particularly in medullary zones. This method of BOLD analysis bypasses observer selection of specific ROIs in the medulla and allows estimation of the fraction of the entire slice that exceeds the threshold >30/s (see text).
**Table 1. Clinical, Laboratory, and Demographic Data of Patients With EH and ARAS**

<table>
<thead>
<tr>
<th></th>
<th>EH (n=32)</th>
<th>ARAS (n=17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % (men)*</td>
<td>59</td>
<td>76</td>
<td>0.35</td>
</tr>
<tr>
<td>Age, y</td>
<td>63.1±16.3</td>
<td>68±8.8</td>
<td>0.17</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>99±24.9</td>
<td>147±20</td>
<td>0.0004</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>182±30</td>
<td>184±95.6</td>
<td>0.04</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>52±12</td>
<td>45±6.21</td>
<td>0.30</td>
</tr>
<tr>
<td>Microalbumin, mg/24 h†</td>
<td>19 (13–29)</td>
<td>96±32.8</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Values represent mean±SD. ACE indicates angiotensin converting enzyme; Anti-HTN, antihypertensive; ARAS, atherosclerotic renal artery stenosis; ARB, angiotensin receptor blockers; BMI, body mass index; DBP, diastolic blood pressure; EH, essential hypertension; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, number of patients; and SBP, systolic blood pressure.

*Fisher exact test.
†Median (interquartile range) reported because of skewed data, P value obtained from Wilcoxon rank-sum test.

**Reduced RBF in ARAS STKs Improved After Revascularization, Whereas GFR Remained Reduced**

Results from quantitative MDCT measurements of hemodynamics of individual kidneys are summarized in Table 2. The total volume of poststenotic kidneys was reduced, primarily because of reduction in cortical volume as compared with EH kidneys but 3 months after technically successful stent revascularization, total kidney volume increased (P=0.01). Both cortical and medullary perfusions (flow per unit tissue volume) were reduced in the STK compared with kidneys from EH (P<0.001 and P=0.03). Measurements after renal artery stenting demonstrated increased cortical (P=0.01) but not medullary perfusion. Whole kidney blood flow was reduced in the STK as compared with EH kidney (P<0.001), with partial restoration after revascularization (P=0.02). SK iohalamate GFR (ml/min per kidney) in STKs was lower than EH kidneys (P=0.0009) and did not change after stent revascularization (P=0.12).

**Renal Revascularization Reduced Elevated Levels of Fractional Kidney Hypoxia in ARAS**

Tissue oxygenation levels defined by both RBF* values and fractional hypoxia (RBF*>30/s) are summarized in Table 3. Pretenting basal and post-furosemide fractional hypoxia levels were higher in STK than EH kidneys as illustrated in Figure 2. Fractional tissue hypoxia fell after furosemide administration, but remained above those of EH. The fractional hypoxia levels in the stenotic kidneys fell to near normal levels when remeasured 3 to 4 months after renal artery stenting (Figure 3A). The fractional hypoxia basal levels correlated inversely with GFR (Spearman rank correlation coefficient, r=−0.38; P=0.007), RBF (r=−0.4; P=0.005) and also with cortical/medullary perfusion (r=−0.4; P=0.004).

Representative axial BOLD images (RBF* parametric maps) illustrating the change in hypoxia in ARAS kidney before and after revascularization are illustrated in Figure 3B.

**ARAS Was Associated With Elevated Markers of Renal Inflammation, Which Persisted After Revascularization**

Renal vein basal levels of NGAL, MCP-1, and TNF-α were elevated in ARAS compared with EH (P=0.0006, 0.005, and 0.0003, respectively; Table 4). These venous levels remained unchanged 3 months after revascularization (Figure 4). Levels of renal vein NGAL correlated inversely with GFR (r=−0.45; P=0.007). Also, MCP-1 (r=−0.4; P=0.007) and TNF-α correlated inversely with GFR (r=−0.6; P<0.0001).

The statin therapy, a potential anti-inflammatory, showed no consistent effects on the inflammation markers, RBF, RBF*.
and GFR on this studied cohort (both in renal artery stenosis and EH; Table I in the online-only Data Supplement).

**Discussion**

This study demonstrates, for the first time, the effect of renal revascularization to reduce the fractions of kidney parenchyma that were measurably hypoxic as a result of reduced blood flow. Cortical blood flows and perfusion were reduced in the poststenotic kidney and rose after technically successful revascularization, although medullary flows remained below those of EH or the nonstenotic CLKs. Hence, the levels of overall fractional tissue hypoxia were reversed by restoring blood flow in the STK. Despite these changes, no consistent changes in SK filtration (GFR) or renal venous levels of NGAL, MCP-1, and TNF-α. Measured levels of SK GFR did not change in the poststenotic kidney in these patients and combined GFR for both kidneys remained below those of EH. Our results extend the results observed in experimental swine models of ARAS that demonstrate microvascular rarefaction, oxidative stress injury, and interstitial fibrosis within the poststenotic kidney parenchyma. These results are consistent with increased renal inflammation in patients with ARAS, as evidenced by high levels of NGAL (which is an acute phase protein induced in inflammatory conditions and acute ischemic injury, often used as a biomarker for acute kidney injury) and proinflammatory cytokines TNF-α and MCP-1. MCP-1 is an inflammatory cytokine known to recruit macrophages to the kidney. We have recently shown that transforming growth factor-β expression associated with macrophage infiltration within the human kidney with ARAS is higher than normal kidneys and that renal vein levels of inflammatory cytokines such as interleukin-6, IF-γ, E selectins, and others are elevated in human ARAS. Studies using murine models of

![Figure 2. Examples of T2* images and R2* parametric maps for a subject with essential hypertension (A and C) and a subject with atherosclerotic renal artery stenosis (ARAS; B and D) obtained using the same color scale for R2*. Fractional hypoxia >30/s in ARAS was greater than in essential hypertension (28.5% vs 11.3%).](http://circinterventions.ahajournals.org/)

<table>
<thead>
<tr>
<th>Single Kidney</th>
<th>EH (n=32)</th>
<th>STK (n=17)</th>
<th>CLK (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 mo</td>
<td>Baseline</td>
</tr>
<tr>
<td>Fractional hypoxia (% (R^2*&gt;30/s))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre furosemide</td>
<td>8.7 (3.5, 13.3)</td>
<td>19.2 (9.2, 28.3)</td>
<td>14.3 (3.7, 15.4)</td>
</tr>
<tr>
<td>Post furosemide</td>
<td>2.6 (1.35, 6.4)</td>
<td>12.5 (3.2, 21.5)</td>
<td>5.6 (2.6, 10)</td>
</tr>
<tr>
<td>Cortex (R^2*) (s−1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre furosemide</td>
<td>18.5±2.7</td>
<td>21±4.4</td>
<td>18±2.3</td>
</tr>
<tr>
<td>Post furosemide</td>
<td>16.7±2.2</td>
<td>19.5±4.6</td>
<td>17.6±3.9</td>
</tr>
</tbody>
</table>

Data are Mean±SD. BOLD indicates blood oxygen level–dependent; CLK, contralateral kidneys; EH, essential hypertension; and STK, stenotic kidney.

- *P<0.05 vs EH; †P<0.05 vs STK baseline; ‡P<0.05 vs EH; and §P<0.001 pre (furosemide) vs post (furosemide).
- Median (interquartile range) reported because of skewed data (P-value derived from Wilcoxon rank-sum test or from Wilcoxon signed-rank test as appropriate).
renal artery stenosis demonstrate early and sustained activation of transforming growth factor-β in both the stenotic
and the CLK as kidney injury develops.31 Smad3-knockout models that eliminate downstream effects of transforming
growth factor-β seem to protect the poststenotic kidney from injury from reduced blood flow.32 We interpret all of
these data to suggest activation of multiple inflammatory injury pathways in poststenotic kidneys. Although several
of these are recognized to be triggered by tissue hypoxia,33 it is equally clear from the results of our study that removing
the hypoxic stimulus failed to reverse this process once it has been established.

Perhaps relevant is the observation that reperfusion by percutaneous angioplasty in swine model of ARAS increases
cytokine levels (MCP-1) for several hours and is associated 4 weeks later with multiple markers of inflammatory injury,
oxidative stress, apoptosis, and interstitial fibrosis.34 These data suggest that inflammatory signals related to reperfusion
procedures may participate in activating intracellular or mitochondrial stress injury. We cannot exclude a role for atheroem-
bolic injury associated with renal artery stenting, although no clinical signs were evident in these patients. Our data provide
further insights into human treatment trials related to recovery of renal function after revascularization. Although some
patients recover some portion of reduced GFR after renal artery stenting, the majority either has no evident change or
progress to further loss.11 As a result, average values for GFR do not change after successful revascularization,35 despite
technical success of restoring blood flow. Hence, prospective trials, including The Angioplasty and Stenting for Renal
Artery Lesions (ASTRAL) and Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired
Renal Function (STAR), up to now fail to demonstrate major benefits of restoring blood flow alone to alter the course of
renal injury in human ARAS.11,36

The present study provides evidence that although advanced renovascular disease does indeed lead to renal tissue hypoxia,
restoring blood flow and reversing hypoxia alone regularly failed to alter local inflammatory signals reflecting active pro-
cesses of tissue injury and inflammation. These data suggest that additional measures that may abrogate those pathways
may be essential to halt the progression of injury and perhaps allow repair of functional renal structures. Recent experimen-
tal studies using endothelial progenitor cells37–39 or intrarenal infusion of mesenchymal stem cells indicate that recovery
of renal microvessels, blood flow, and glomerular filtration is possible in the poststenotic kidney.40 Additional maneu-
vers targeting mitochondria at the time of restoring blood

### Table 4. Renal Vein Levels of NGAL, MCP-1, and TNF-α

<table>
<thead>
<tr>
<th></th>
<th>EH</th>
<th>STK (Baseline)</th>
<th>STK (3 mo)</th>
<th>P Value vs EH</th>
<th>P Value vs Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP-1, pg/mL</td>
<td>154±71</td>
<td>208.2±83</td>
<td>200±93.6</td>
<td>0.005</td>
<td>0.6</td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>4.7±4.2</td>
<td>8.4±5.8</td>
<td>9±5.8</td>
<td>0.0003</td>
<td>0.3</td>
</tr>
<tr>
<td>NGAL, ng/mL</td>
<td>69.7±36.5</td>
<td>121.2±55</td>
<td>108.8±35</td>
<td>0.0006</td>
<td>0.6</td>
</tr>
</tbody>
</table>

EH indicates essential hypertension; MCP-1, monocyte chemoattractant protein-1; NGAL, neutrophil gelatinase–associated lipocalin; STK, stenotic kidney; and TNF-α, tumor necrosis factor-α.
flow offer the potential to protect the poststenotic kidney from reperfusion damage.34

This study has limitations. It was not a randomized study, but enrolled patients were selected for revascularization based on clinical criteria. Most of the patients were men. Our control group comprised subjects with EH of similar age, rather than normal individuals. The EH group did include some healthy individuals with normal kidney hemodynamics and function. Individuals with ARAS had lower GFR, although most had relatively preserved function and were limited to r serum creatinine levels <2.5 mg/dL. Subjects with diabetes mellitus were specifically excluded.

Conclusions

Our results indicate that renal revascularization partially restored cortical and RBFs and reversed regional tissue hypoxia within the poststenotic kidneys. Despite improving blood flow, SK GFR did not recover nor did markers of tubulointerstitial injury (NGAL) and inflammatory cytokines change. These data underscore the importance of ongoing inflammatory and profibrotic injury that revascularization alone fails to reverse in patients with ARAS. They demonstrate the urgent need to identify and develop supplemental management strategies to restore kidney structure and function for patients with vascular occlusive disease.

Sources of Funding

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Disclosures

None.

References

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Renal Revascularization Role on Kidney Hypoxia


Stent Revascularization Restores Cortical Blood Flow and Reverses Tissue Hypoxia in Atherosclerotic Renal Artery Stenosis but Fails to Reverse Inflammatory Pathways or Glomerular Filtration Rate

Ahmed Saad, Sandra M.S. Herrmann, John Crane, James F. Glockner, Michael A. McKusick, Sanjay Misra, Alfonso Eirin, Behzad Ebrahimi, Lilach O. Lerman and Stephen C. Textor

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Data Supplement (unedited) at:

http://circinterventions.ahajournals.org/content/suppl/2013/07/30/CIRCINTERVENTIONS.113.000219.DC1

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SUPPLEMENTAL MATERIAL:

Table 1: comparison analysis between the two groups of patients (EH and RAS patients) with or without statins therapy.

<table>
<thead>
<tr>
<th></th>
<th>EH=32</th>
<th>Statin (=16)</th>
<th>No Statin (=16)</th>
<th>P value</th>
<th>RAS=17</th>
<th>Statin (=12)</th>
<th>No statin (=5)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBF (ml/min)</td>
<td></td>
<td>379.5 ± 188</td>
<td>421.6 ± 161</td>
<td>0.5</td>
<td></td>
<td>226.8 ±106.8</td>
<td>247.3 ± 160</td>
<td>0.7</td>
</tr>
<tr>
<td>Single kidney</td>
<td></td>
<td>42.5 ± 12.9</td>
<td>46.5 ± 14</td>
<td>0.4</td>
<td></td>
<td>26 ± 10.9</td>
<td>32.4 ± 25</td>
<td>0.6</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical R2*</td>
<td></td>
<td>19.1 ± 3.2</td>
<td>17.8 ± 1.9</td>
<td>0.18</td>
<td></td>
<td>20.2 ± 3.1</td>
<td>24.5 ± 7.9</td>
<td>0.36</td>
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<tr>
<td>(sec⁻¹)</td>
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<tr>
<td>Fractional</td>
<td></td>
<td>10.8 ± 8.2</td>
<td>8.2 ± 5</td>
<td>0.3</td>
<td></td>
<td>19.4 ± 11.7</td>
<td>33.1 ± 27</td>
<td>0.38</td>
</tr>
<tr>
<td>hypoxia (%R2* &gt;30 sec⁻¹)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>NGAL (ng/ml)</td>
<td></td>
<td>69.3 ± 43.9</td>
<td>70.5 ± 18.6</td>
<td>0.9</td>
<td></td>
<td>133.1 ±62</td>
<td>94.6 ± 39</td>
<td>0.3</td>
</tr>
<tr>
<td>MCP-1 (pg/ml)</td>
<td></td>
<td>171.7 ± 83</td>
<td>137.7 ± 55.5</td>
<td>0.2</td>
<td></td>
<td>238 ± 77</td>
<td>166.6 ± 47.6</td>
<td>0.1</td>
</tr>
<tr>
<td>TNF-a (pg/ml)</td>
<td></td>
<td>4.5 ± 2.5</td>
<td>3.7 ± 2.2</td>
<td>0.7</td>
<td></td>
<td>25.2 ± 15</td>
<td>7.1 ± 2.1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Mean ± SD.