Background—Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease. It has a worldwide prevalence of ≈1%, which increases with age, such that 5% of women aged >60 years have RA.1,2 In addition to the classical articular manifestations of the condition, it is also associated with increased mortality,3,4 mostly because of an excess of cardiovascular disease (CVD).5,6 This increased cardiovascular (CV) risk is independent of traditional CV risk factors and is related to systemic inflammation.7,8 Moreover, treatment with anti-tumor necrosis factor-α (anti-TNF-α) agents reduces the risk of developing CVD in RA patients.9

Conclusions—This study demonstrates that RA patients have increased aortic 18F-fluorodeoxyglucose uptake in comparison with patients who have stable cardiovascular disease. Anti-tumor necrosis factor-α therapy reduces aortic inflammation in patients with RA, and this effect correlates with the decrease in aortic stiffness. These results suggest that RA patients exhibit a subclinical vasculitis, which provides a mechanism for the increased cardiovascular disease risk seen in RA. (Circulation. 2012;126:2473-2480.)

Key Words: aortic stiffness • inflammation • positron emission tomography • rheumatoid arthritis • vasculitis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease. It has a worldwide prevalence of ≈1%, which increases with age, such that 5% of women aged >60 years have RA.1,2 In addition to the classical articular manifestations of the condition, it is also associated with increased mortality,3,4 mostly because of an excess of cardiovascular disease (CVD).5,6 This increased cardiovascular (CV) risk is independent of traditional CV risk factors and is related to systemic inflammation.7,8 Moreover, treatment with anti-tumor necrosis factor-α (anti-TNF-α) agents reduces the risk of developing CVD in RA patients.9

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electron emission tomography (18F-FDG-PET), of equivalent severity to that observed in patients with stable CVD. Furthermore, we hypothesized that aortic inflammation and stiffness would both be reduced by anti-inflammatory therapy and that the greatest improvement in aortic stiffness would be observed in those patients with the largest decrease in aortic 18F-FDG uptake.

Methods

Study Population

RA Subjects
Patients with an established diagnosis of RA (1987 American Rheumatism Association criteria) requiring, and eligible, for anti-TNF-α therapy according to the National Institute for Health and Clinical Excellence guidelines, were recruited from Rheumatology Clinics at Addenbrooke’s Hospital, Cambridge. Individuals with known CVD, diabetes mellitus, and renal disease were excluded. Approval was obtained from the National Research Ethics Service, and written informed consent was obtained from each participant.

Control Subjects
Because of ethical constraints relating to radiation exposure in healthy individuals, we used data from patients enrolled in a contemporaneous FDG PET/computed tomography (CT) study as our positive controls. All control subjects had clinically stable CVD disease, defined as a history of myocardial infarction, stroke, or peripheral vascular disease, and were on stable statin therapy. The imaging protocol for RA and control subjects was identical, performed on the same scanner, and analyzed by the same blinded reader.

Experimental Protocols

This was an open-label study, with blinded end points, because it was deemed unethical to withhold treatment in these patients. 18F-FDG PET/CT imaging, blood pressure (peripheral and central), aortic augmentation index, and aortic and brachial pulse wave velocity (PWV), flow-mediated dilatation, fasting lipids, blood glucose, C-reactive protein, erythrocyte sedimentation rate (ESR), and disease activity score were measured at baseline, and again at 8 weeks after the initiation of anti-TNF-α therapy (etanercept or adalimumab).

PET Scan Acquisition

Aortic 18F-FDG PET/CT imaging was performed by using a combined PET/CT scanner (GE Discovery 690) before and 8 weeks after the initiation of anti-TNF-α therapy according to validated, reproducible protocols. FDG (250 MBq) was injected intravenously and allowed to circulate for 90 minutes. This allows uptake of the tracer to ensure excellent coregistration across both imaging time-points. PET and CT data were fused and analyzed by using the open-source Brachial Tools software (Medical Imaging Applications).

Image Analysis

PET and CT data were fused and analyzed by using the open-source DICOM viewer OsiriX (Version 4.0, OsiriX Imaging Software, Geneva, Switzerland). Arterial FDG uptake was quantified by using previously published methods20,21 by a single reader blinded to visit order. In brief, on each 3.27-mm image slice, the maximum standardized uptake values of 18F-FDG within each region of interest, containing the arterial wall and the lumen, were recorded and divided by background blood FDG concentration in the superior vena cava to yield an arterial maximum target-to-background ratio (TBRmax).22 Arterial slices were matched anatomically by using CT to ensure excellent coregistration across both imaging time-points.

After scan analysis, the hottest slice with the greatest FDG uptake was identified on the baseline scans. The TBRmax for the most diseased segment (MDS) was determined by averaging the TBRmax for 3 consecutive slices centered on the hottest slice and the adjacent slices superior and inferior to it, providing ∼1 cm of the most inflamed section of the aortic wall. On the follow-up scan, the same 3 slice locations were used to calculate the MDS TBRmax. In addition, the proportion of hot slices (with a TBR >2.0) in the entire aorta was calculated for both time points. This cutoff was chosen because it was the median TBRmax value across all aortic slices. Finally, frequency histograms of the distribution of TBRmax across all arterial slices were constructed.

Arterial Stiffness and Wave Reflection Measurements

All studies were conducted in a quiet, temperature-controlled room. After 15 minutes of supine rest, peripheral blood pressure was recorded in the brachial artery (OMRON-705CP; Omron Corp, Japan). Radial artery waveforms were obtained with a high-fidelity micromanometer (SPC-301; Millar Instruments, TX) from the wrist, and a corresponding central waveform was generated by using a data acquisition system.23,24 All measurements were made in duplicate and mean values used in the subsequent analysis.

Endothelial Function Measurements

Endothelial function was assessed in the brachial artery of the nondominant arm by using the noninvasive technique of flow-mediated dilatation. This was defined as the maximum percentage increase in vessel diameter in the 5 minutes following the release of the cuff (reactive hyperemia). Vessel diameter was measured by using high-resolution vascular ultrasound (Acuson Aspen, Siemens AG, Germany) with a 4 to 7 MHz linear-array transducer, continuously for 1 minute at baseline, and for an additional 5 minutes after the release of the cuff. The cuff was placed distal to the ultrasound probe and was inflated for 5 minutes to 200 mm Hg. After a 5-minute break, endothelial-independent dilatation was assessed. Vessel diameter was measured continuously for 1 minute at baseline and for 5 minutes after administration of 25 μg of sublingual glyceryl trinitrate. Glyceryl trinitrate–mediated dilatation was defined as the maximum percentage increase in vessel diameter after sublingual glyceryl trinitrate. Anonymized images were analyzed by using Brachial Tools software (Medical Imaging Applications).

Laboratory Measurements and Disease Activity Score

Fasting lipid profile, blood glucose, ESR, and C-reactive protein were determined by using standard methodology. A validated composite disease activity score was calculated by using ESR, a visual analog score of well being, and the number of tender and swollen joints, from a total of 28 joints.25,26

Data Analysis

Data were analyzed by using SPSS software (version 17). Significance was determined by using unpaired 2-tailed Student t tests to compare group differences, with the exception of frequency histograms, where Mann–Whitney test was used. The paired Student t test was used for before and after treatment comparisons in RA group, with the exception of skewed variables (C-reactive protein, ESR, frequency histograms), where Wilcoxon signed rank test was used. Relationship between parameters was determined by using Spearman correlation. Smoothed histograms were generated by using R software version 2.15 (www.r-project.org) that computes kernel density estimates, and the bin width used was 0.2 U. A probability of <0.05 was considered statistically significant. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.
The mean age of the subjects was 58 ± 5 years, and 11 were female (see Table 1 for baseline characteristics). The type of anti-TNF-α therapy for each RA patient is listed in Table 2. Concomitantly, 34 age-matched (58 ± 5 years) control subjects with established CVD were randomly selected from a different contemporaneous PET imaging study in subjects without RA.

### Baseline Comparison between RA and CVD patients

The mean of TBR<sub>max</sub> (Figure 1A) in the whole aorta was significantly higher in RA patients in comparison with CVD patients (2.02 ± 0.22 versus 1.74 ± 0.22, respectively; P = 0.0001). Whereas, the mean TBR<sub>max</sub> in the MDS was not significantly different between the groups (2.51 ± 0.33 versus 2.31 ± 0.43, respectively; P = 0.1; Figure 1B). In addition, the frequency histogram demonstrated a significant rightward shift in the distribution of TBR<sub>max</sub> at baseline in RA patients in comparison with CVD patients (Z = −19.22; P < 0.0001; Figure 2) and RA patients also had a higher proportion of hot slices (defined as TBR<sub>max</sub> > 2.0) within the aorta than CVD patients (49.5 ± 28.9 versus 22.9 ± 24.0%, respectively; P = 0.001).

### The Effect of Anti-TNF-α Therapy

The effects of TNF-α antagonist on aortic inflammation in each RA patient are detailed in Table 2. Figure 3 illustrates typical pre- and posttreatment PET/CT images from our study. Following anti-TNF-α therapy, there was a significant reduction in mean aortic TBR<sub>max</sub> (from 2.02 ± 0.22 to 1.90 ± 0.29, P = 0.03; Figure 1A). The proportion of hot slices was also reduced (from 49.5 ± 28.9 to 33.3 ± 27.1%, P = 0.03)

### Results

Seventeen patients with active RA (disease activity score, 6.52 ± 0.78) were studied before and 8 weeks after the initiation of anti-TNF-α therapy. The mean age of the subjects was 58 ± 5 years, and 11 were female (see Table 1 for baseline characteristics). The type of anti-TNF-α and ancillary therapies for each RA patient are listed in Table 2. Concomitantly, 34 age-matched (58 ± 5 years) control subjects with established CVD were randomly selected from a different contemporaneous PET imaging study in subjects without RA.

#### Table 1. Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>17</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>6/11</td>
</tr>
<tr>
<td>Age, y</td>
<td>58 ± 5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.1 ± 5.8</td>
</tr>
<tr>
<td>Peripheral SBP, mm Hg</td>
<td>139 ± 19</td>
</tr>
<tr>
<td>Peripheral DBP, mm Hg</td>
<td>83 ± 7</td>
</tr>
<tr>
<td>Central SBP, mm Hg</td>
<td>129 ± 18</td>
</tr>
<tr>
<td>Central DBP, mm Hg</td>
<td>84 ± 7</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>72 ± 13</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.4 ± 0.9</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.3 ± 0.6</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.5 ± 1.3</td>
</tr>
<tr>
<td>C-reactive protein, mg/L*</td>
<td>11.0 (4.0–29.0)</td>
</tr>
<tr>
<td>ESR, mm/h*</td>
<td>22.0 (8.5–41.0)</td>
</tr>
<tr>
<td>Disease activity score (DAS28)</td>
<td>6.52 ± 0.78</td>
</tr>
</tbody>
</table>

Values are represented as means ± standard deviation, with the exception of variables that were skewed (*), where the values are represented as medians (interquartile range). SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and ESR, erythrocyte sedimentation rate.

#### Table 2. Type of Anti-TNF-α Therapy, Ancillary Therapies, and the Effect of Anti-TNF-α Therapy on Key Parameters on Each RA Subject

<table>
<thead>
<tr>
<th>Subject</th>
<th>Anti-TNF-α</th>
<th>DMARD and Steroid</th>
<th>Other Drugs</th>
<th>Aortic TBR Pre</th>
<th>Aortic TBR Post</th>
<th>Aortic PWV, m/s Pre</th>
<th>Aortic PWV, m/s Post</th>
<th>CRP, mg/L Pre</th>
<th>CRP, mg/L Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adalimumab</td>
<td>L, P</td>
<td>C, AH, PP</td>
<td>2.31</td>
<td>2.13</td>
<td>2.97</td>
<td>2.48</td>
<td>8.10</td>
<td>8.10</td>
</tr>
<tr>
<td>2</td>
<td>Adalimumab</td>
<td>M, H</td>
<td>C, AH</td>
<td>1.76</td>
<td>1.59</td>
<td>1.96</td>
<td>1.58</td>
<td>8.25</td>
<td>7.55</td>
</tr>
<tr>
<td>3</td>
<td>Etanercept</td>
<td>M, H</td>
<td>AH</td>
<td>2.05</td>
<td>2.03</td>
<td>2.36</td>
<td>2.10</td>
<td>8.2</td>
<td>8.2</td>
</tr>
<tr>
<td>4</td>
<td>Etanercept</td>
<td>M, L</td>
<td>AH</td>
<td>2.30</td>
<td>1.63</td>
<td>3.07</td>
<td>1.54</td>
<td>8.20</td>
<td>8.00</td>
</tr>
<tr>
<td>5</td>
<td>Adalimumab</td>
<td>M, H, P</td>
<td>AH, PP</td>
<td>2.15</td>
<td>2.14</td>
<td>2.83</td>
<td>2.48</td>
<td>9.50</td>
<td>8.60</td>
</tr>
<tr>
<td>6</td>
<td>Adalimumab</td>
<td>M, L, H, P</td>
<td>S</td>
<td>2.32</td>
<td>2.30</td>
<td>2.51</td>
<td>2.05</td>
<td>11.15</td>
<td>10.70</td>
</tr>
<tr>
<td>7</td>
<td>Adalimumab</td>
<td>L</td>
<td>AH, S</td>
<td>2.17</td>
<td>2.08</td>
<td>2.81</td>
<td>2.23</td>
<td>9.75</td>
<td>7.85</td>
</tr>
<tr>
<td>8</td>
<td>Adalimumab</td>
<td>L, P</td>
<td>C</td>
<td>2.10</td>
<td>2.13</td>
<td>2.85</td>
<td>2.44</td>
<td>6.25</td>
<td>6.45</td>
</tr>
<tr>
<td>9</td>
<td>Adalimumab</td>
<td>M, SS, H</td>
<td>A, C, PP</td>
<td>1.75</td>
<td>1.60</td>
<td>2.14</td>
<td>1.89</td>
<td>8.15</td>
<td>8.10</td>
</tr>
<tr>
<td>10</td>
<td>Etanercept</td>
<td>M, H, P</td>
<td></td>
<td>2.09</td>
<td>2.03</td>
<td>2.46</td>
<td>2.17</td>
<td>8.30</td>
<td>7.85</td>
</tr>
<tr>
<td>11</td>
<td>Adalimumab</td>
<td>L, H</td>
<td>PP</td>
<td>2.14</td>
<td>1.62</td>
<td>2.39</td>
<td>1.71</td>
<td>9.60</td>
<td>8.50</td>
</tr>
<tr>
<td>12</td>
<td>Adalimumab</td>
<td>L, P</td>
<td>C, A, AH, PP</td>
<td>1.74</td>
<td>1.61</td>
<td>2.11</td>
<td>1.89</td>
<td>13.45</td>
<td>10.55</td>
</tr>
<tr>
<td>13</td>
<td>Adalimumab</td>
<td>M</td>
<td></td>
<td>1.93</td>
<td>2.04</td>
<td>2.10</td>
<td>2.00</td>
<td>7.6</td>
<td>8.15</td>
</tr>
<tr>
<td>14</td>
<td>Adalimumab</td>
<td>H</td>
<td></td>
<td>2.20</td>
<td>1.85</td>
<td>2.72</td>
<td>2.19</td>
<td>6.9</td>
<td>6.7</td>
</tr>
<tr>
<td>15</td>
<td>Etanercept</td>
<td>L, C, A</td>
<td>AH</td>
<td>1.75</td>
<td>1.78</td>
<td>2.29</td>
<td>1.84</td>
<td>9.4</td>
<td>9.4</td>
</tr>
<tr>
<td>16</td>
<td>Etanercept</td>
<td>H</td>
<td>A, S</td>
<td>1.98</td>
<td>1.98</td>
<td>2.47</td>
<td>2.22</td>
<td>10.8</td>
<td>10.8</td>
</tr>
<tr>
<td>17</td>
<td>Adalimumab</td>
<td>M, SS</td>
<td>C, AH, PP</td>
<td>1.68</td>
<td>1.78</td>
<td>2.58</td>
<td>2.04</td>
<td>10.9</td>
<td>11.2</td>
</tr>
</tbody>
</table>

A indicates analgesic drug; AH, antihypertensive drug; C, COX-inhibitor; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drugs; H, hydroxychloroquine; L, leflunomide; M, methotrexate; MDS, most diseased segment; P, prednisolone; PWV, pulse wave velocity; S, statin; SS, sulfasalazine; TBR, target-to-background ratio; TNF-α, tumor necrosis factor-α; and PP, protein pump inhibitor.
and there was a significant (Z = -14.65; P < 0.0001) leftward shift in the distribution of TBR$_{\text{max}}$ in frequency histograms (Figure 2). TBR$_{\text{max}}$ in the MDS also fell from 2.51±0.33 to 2.05±0.29, P<0.0001 (Figure 1B).

Table 3 summarizes the effect of anti-TNF-α therapy on disease activity, inflammatory markers, and hemodynamics. Disease activity was significantly reduced by treatment (disease activity score, from 6.52±0.78 to 4.38±1.61; P<0.0001), as were markers of inflammation C-reactive protein and ESR (P=0.007 and P=0.04, respectively). Neither mean arterial pressure nor aortic augmentation index were significantly affected by therapy (P=0.9 and P=0.4, respectively). However, aortic PWV fell significantly from 9.09±1.77 to 8.63±1.42 m/s (P=0.04). Concomitantly, flow-mediated dilation responses improved significantly from 3.54±2.34 to 6.66±3.17% (P=0.003) without any significant change to glyceryl trinitrate response (P=0.9) or baseline vessel diameter (P=0.8). Furthermore, there was a significant correlation between the reduction in aortic PWV and the reduction of aortic TBR$_{\text{max}}$ (R=0.60, P=0.01).

Posttreatment Comparisons
In comparison with CVD patients, the mean aortic TBR$_{\text{max}}$ in RA subjects remained significantly higher following therapy (P=0.02; Figure 1A), but the proportion of hot slices fell to a level comparable to CVD patients (P=0.2). Conversely, TBR$_{\text{max}}$ in the MDS was significantly lower in RA patients in comparison with CVD patients after 8 weeks of treatment (P=0.03; Figure 1B).

Discussion
The key findings of this study are that patients with severe RA, but without clinically manifest CVD, have an increased aortic inflammation in comparison with subjects with established, stable CVD. Additionally, we have shown that anti-TNF-α therapy leads to a reduction in inflammation along the whole aorta, and in its MDS, as well. We demonstrated concomitant improvements in endothelial function, circulating markers of inflammation, and aortic stiffness, which correlated with the reduction in aortic inflammation.

At baseline, RA patients had increased aortic inflammation in comparison with patients with established CVD with
and 71%, respectively. The distribution of baseline inflammation by using frequency histograms revealed a similar observation. However, TBR in the MDS of the aorta was similar for both groups. These data clearly demonstrate that inflammation in RA is generalized, rather than being limited to discrete areas of atherosclerotic plaque, because the overall inflammation and the proportion of hot slices were higher in RA than in CVD patients, whereas uptake in its most disease

Table 3. The Effect of Anti-TNF-α Therapy on Disease Activity, Inflammatory Markers, and Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>8 wk</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28 score</td>
<td>6.52±0.78</td>
<td>4.38±1.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP, mg/L*</td>
<td>11.0 (4.0–29.0)</td>
<td>3.0 (2.0–10.0)</td>
<td>0.007</td>
</tr>
<tr>
<td>ESR, mm/h*</td>
<td>22 (8.5–41.0)</td>
<td>13.0 (7.0–17.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>104±11</td>
<td>104±12</td>
<td>0.9</td>
</tr>
<tr>
<td>Augmentation index, %</td>
<td>31±11</td>
<td>33±11</td>
<td>0.4</td>
</tr>
<tr>
<td>Brachial PWV, m/s</td>
<td>9.0±1.23</td>
<td>8.56±1.11</td>
<td>0.06</td>
</tr>
<tr>
<td>Aortic PWV, m/s</td>
<td>9.09±1.77</td>
<td>8.63±1.42</td>
<td>0.04</td>
</tr>
<tr>
<td>Baseline diameter, mm</td>
<td>3.94±0.59</td>
<td>3.91±0.68</td>
<td>0.8</td>
</tr>
<tr>
<td>FMD, %</td>
<td>3.54±2.34</td>
<td>6.66±3.17</td>
<td>0.003</td>
</tr>
<tr>
<td>GTN response, %</td>
<td>9.53±4.26</td>
<td>8.29±5.63</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Values represent means ± standard deviation. Significance was determined by using the paired Student t test, with the exception of skewed variables (*) where Wilcoxon signed rank test was used. n=17. DAS28 indicates disease activity score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MAP, mean arterial pressure; PWV, pulse wave velocity; FMD, flow-mediated dilatation; and GTN, glyceryl trinitrate.
segment, most likely reflecting uptake within a plaque, was comparable with CVD patients. Our imaging findings corroborate the results of a histological study in patients undergoing coronary artery bypass graft surgery, which found that those patients with inflammatory rheumatic disease had a significantly higher number of inflammatory cell infiltrates in the medial and adventitial layers of the aorta than CVD patients without inflammatory rheumatic disease. Moreover, these cells, mainly lymphocytes, were found predominantly outside areas of visible atherosclerotic plaques.

Although, the prevalence of clinical vasculitis in RA is low, the results of the previous histological studies, and the current study, suggest that subclinical vasculitis in RA is relatively common. This provides a potential explanation for the increased CVD seen in this cohort. FDG PET imaging is used as a diagnostic tool in vasculitis, and, although there are not clearly defined cutoff values for the diagnosis, the authors of a study in patients with temporal arteritis proposed a cutoff of standardized uptake values > 1.3 as diagnostic of active vasculitis and standardized uptake values ≥ 2.7 as “intense activity.” Based on these published cutoff values, our RA cohort with a mean aortic standardized uptake value of 2.1, indicating moderate aortic uptake of FDG and, thereby, suggestive of an underlying vasculitis.

Eight weeks of treatment with TNF-α antagonist led to a 7% reduction in FDG uptake across the aorta and an 18% reduction within the MDS. There was also a 32% reduction in the proportion of hot slices and a corresponding leftward shift in the distribution of all slices by the use of frequency analysis. This reduction is within the range of previously reported changes in aortic FDG uptake following statin therapy, and more recently with a novel p38 mitogen-activated protein kinase inhibitor losmapimod. Interestingly, when the posttreatment aortic TBR was compared with the baseline TBR of CVD patients, it still remained significantly higher. This could be due to a relatively short follow-up period of 8 weeks, and perhaps, a longer follow-up would have shown further reductions in TBR. Alternatively, anti-TNF-α therapy may not be sufficient to normalize vascular inflammation, and other agents such as statins may be needed to reduce the aortic inflammation. In contrast, the uptake within the MDS was reduced with treatment, so that after 8 weeks, TBR in the MDS was significantly lower in RA patients than in CVD patients. Furthermore, the change seen in the MDS was more statistically different than that seen in aortic TBR following the therapy. We believe this represents the fact that therapy is significantly more effective in inflamed areas, and, by definition, the MDS is more inflamed than the average of the aorta. Indeed, an inspection of the individual data (Table 2) indicates that all MDS show a reduction following anti-TNF-α-therapy, whereas there is some heterogeneity in the response to all sections of the aorta.

Aortic PWV, but not blood pressure, was reduced after 8 weeks of anti-TNF-α treatment, indicating that the decrease in aortic stiffness was not driven by a change in mean arterial pressure. This replicates our previous findings in patients with RA, in whom a reduction in aortic PWV was seen after 12 weeks treatment with etanercept. Interestingly, we found a strong positive correlation between reduction of aortic inflammation and stiffness. This suggests that vascular inflammation could be the mechanism by which inflammation leads to aortic stiffening. Our results also corroborate data from previous studies demonstrating that anti-TNF-α therapy improves endothelial function. Despite the important role of inflammation in the pathophysiology of endothelial dysfunction, we surprisingly found no correlation between the improvement in flow-mediated dilatation response and the observed reduction in aortic inflammation. However, this may be because endothelial function was assessed in the brachial artery, and inflammation was assessed in the aorta.

Patients with RA have a 48% increased risk of CVD; the risks of myocardial infarction and cerebrovascular accident are increased by 68% and 41%, respectively. Treatment with disease-modifying drugs, such as methotrexate and, in particular, anti-TNF-α agents, considerably reduces the incidence of CVD disease in RA patients. However, the mechanism by which inflammation leads to increased CVD is not fully understood, and perhaps vascular inflammation, as demonstrated by our data, could be the mechanism to explain this phenomenon. Although the clinical significance of the observed vasculitis in unknown, it is well documented that inflammation leads to various deleterious changes in the arterial wall, such as endothelial dysfunction, increased expression of adhesion molecules, smooth muscle proliferation, and aortic stiffening, and directly accelerating the atherosclerotic process and plaque destabilization, as well. Our findings highlight the importance of CV risk management in RA, which is currently inadequately dealt with.

Potential Limitations
We conducted a relatively small, open-label study. This reflects the fact that it was considered unethical to undertake a double-blind, randomized trial in RA patients with severe disease, who were eligible for anti-TNF-α therapy according to national guidelines. Nevertheless, a similar open-label study design has been adopted previously by others. We minimized observer bias by using anonymized and blinded scan analysis. Nevertheless, because of the nonrandomized design of our study, we cannot exclude the possibility of a non–drug-related reduction in TBR and PWV. Moreover, because of the heterogeneity of the ancillary treatment protocols in the RA patients, we cannot rule out the possibility that these different concomitant therapies may account for some of the differences seen after the addition of an anti-TNF-α agent; however, the patients were stable on these ancillary therapies for at least 2 months before baseline measurements and were unchanged throughout the study. Furthermore, we acknowledge the fact that FDG PET is a nonspecific method of assessing inflammation, because numerous inflammatory cells, and smooth muscle cells, as well, can use FDG. Moreover, endothelial cell activation and hypoxia can also enhance FDG uptake by cells. It is clear that more cell-specific imaging ligands need to be developed to fully understand which cells are present in the aortic wall during inflammation. However, retrospective data in patients undergoing PET imaging for oncology have clearly demonstrated that the presence of high vascular FDG uptake can predict future CV events.
Summary
We have demonstrated that patients with RA have increased inflammation along the entire length of the aorta in comparison with age-matched CVD patients and that anti-TNF-α therapy leads to a reduction of inflammation in the whole aorta and in the MDS, as well. Our data suggest that vascular inflammation could underpin the mechanism of increased CVD seen in RA and also demonstrate that PET/CT scanning could be a useful tool for CVD risk stratification and for monitoring risk reduction of anti-inflammatory therapies in patients with chronic inflammatory diseases.

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Dr Östör has worked as a consultant for Abbott and Pfizer.

References
19. Mäki-Petäjä et al Aortic Inflammation in Rheumatoid Arthritis
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