Anti-Tumor Necrosis Factor-α Therapy Reduces Aortic Inflammation and Stiffness in Patients with Rheumatoid Arthritis

Running title: Mäki-Petäjä et al.; Aortic inflammation in rheumatoid arthritis

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Journal Subject Codes: [60] PET and SPECT; [144] Other arteriosclerosis; [97] Other Vascular biology
Abstract:

Background—Rheumatoid arthritis (RA) is a systemic inflammatory condition associated with increased cardiovascular risk. This is not fully explained by traditional risk factors, but direct vascular inflammation and aortic stiffening may play a role. We hypothesised that patients with RA exhibit aortic inflammation, which can be reversed with anti-tumour necrosis factor alpha (TNF-α) therapy, and correlates with aortic stiffness reduction.

Methods and Results—Aortic inflammation was quantified in 17 patients with RA, before and after eight weeks of anti-TNF-α therapy, using 18F-fluoro-deoxyglucose positron emission tomography (18F-FDG-PET) with CT co-registration. Concomitantly, 34 patients with stable cardiovascular disease (CVD) were imaged as positive controls at baseline. Aortic FDG target to background ratios (TBR) and aortic pulse wave velocity (aPWV) were assessed. RA patients had higher baseline aortic TBR compared to CVD patients (2.02±0.22 vs. 1.74±0.22, P=0.0001). Following therapy, aortic TBR fell to 1.90±0.29, P=0.03 and the proportion of inflamed aortic slices (defined as TBR>2.0) decreased from 50±33% to 33±27%, P=0.03. Also, TBR in the most diseased segment of the aorta fell from 2.51±0.33 to 2.05±0.29, P<0.0001. Treatment also reduced aPWV significantly (from 9.09±1.77 to 8.63±1.42 m/s, P=0.04), which correlated with the reduction of aortic TBR (R=0.60, P=0.01).

Conclusions—This study demonstrates, that RA patients have increased aortic 18F-FDG uptake in comparison to stable CVD patients. Anti-TNF-α therapy reduces aortic inflammation in patients with RA, and this effect correlates with the fall in aortic stiffness. These results suggest that RA patients exhibit a sub-clinical vasculitis, which provides a mechanism for the increased CVD risk seen in RA.

Key words: aortic stiffness; inflammation; positron emission tomography; rheumatoid arthritis; vasculitis
Introduction

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

The exact mechanism by which inflammation in RA leads to increased risk of CVD remains unknown. Inflammation is an important component of atherosclerosis, but also has other detrimental effects on the CV system including aortic stiffening and endothelial dysfunction\textsuperscript{10,11,12}. These effects may be due, in part, to direct vascular inflammation in RA. Although large vessel vasculitis in RA is said to be rare, and clinically apparent in only 1-3% of patients\textsuperscript{13,14}, histological studies in patients undergoing coronary bypass graft surgery demonstrate greater mononuclear cell infiltration within the aortic media and adventitia in patients with inflammatory rheumatic disease than controls\textsuperscript{15}, suggesting a sub-clinical vasculitis. This may also explain our previous observations of increased aortic stiffness in RA, which is reversible with anti-inflammatory therapies\textsuperscript{10,16}.

We hypothesised that patients with RA exhibit aortic inflammation, as quantified by \textsuperscript{18}F-fluorodeoxyglucose positron emission tomography (\textsuperscript{18}F-FDG-PET), of equivalent severity to that observed in patients with stable CVD. Furthermore, we hypothesised 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 largest fall in aortic \textsuperscript{18}F-
FDG uptake.

Methods

Study population

Rheumatoid arthritis 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 (NICE) 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 obtained from each participant.

Control subjects

Due to ethical constraints relating to radiation exposure in healthy individuals, we used data from patients enrolled in a contemporaneous FDG PET/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 analysed by the same blinded reader.

Experimental protocols

This was an open-labelled study, with blinded endpoints, as it was deemed unethical to withhold treatment in these patients. 18F-FDG PET/CT imaging, blood pressure (peripheral and central), aortic augmentation index (AIx), aortic and brachial pulse wave velocity (PWV), flow mediated dilatation (FMD), fasting lipids, blood glucose, C-reactive protein (CRP), erythrocyte
sedimentation rate (ESR) and disease activity score (DAS28) were measured at baseline, and
again at 8 weeks after the initiation of anti-TNF-α therapy (etanercept or adalimumab).

**PET scan Acquisition**

Aortic \(^{18}\)F-FDG PET/CT imaging was performed 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\(^{18}\). FDG (250MBq) was injected intravenously and allowed to
circulate for 90 minutes. This allows uptake of the tracer into metabolically active cells,
including macrophages and T cells in the artery wall. After unenhanced CT scans for attenuation
correction and anatomical co-registration, PET data was acquired in 3D mode, covering the
entire aorta, using VUE Point FX\(^{TM}\) time-of-flight reconstruction. The estimate dose of radiation
per patient was 9.8mSv per scan.

**Image analysis**

PET and CT data were fused and analysed using the open-source DICOM viewer OsiriX
(Version 4.0, OsiriX Imaging Software, Geneva, Switzerland). Arterial FDG uptake was
quantified using previously published methods\(^{19,20}\) by a single reader blinded to visit order.
Briefly, on each 3.27 mm image slice, the maximum standardized uptake values (SUVs) of \(^{18}\)F-
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 (TBR\(_{\text{max}}\))\(^{21}\). Arterial slices were matched
anatomically using CT to ensure excellent co-registration across both imaging time-points.

Post scan-analysis, the “hottest” slice (SHS) with the greatest FDG uptake was identified
on the baseline scans. The TBR\(_{\text{max}}\) for the most diseased segment (MDS) was determined by
averaging the TBR\(_{\text{max}}\) for three consecutive slices centred on the SHS and the adjacent slices
superior and inferior to it, providing approximately 1 cm of the most inflamed section of the aortic wall. On the follow-up scan, the same three 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 cut off was chosen as 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, Texas, USA) from the wrist, and a corresponding central waveform was generated using a validated transfer function22,23 (Sphygmocor; AtCor Medical, Sydney, Australia) and aortic (carotid to femoral) and brachial (carotid to radial) PWV were measured as previously described24. 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 non-dominant arm using the non-invasive technique of flow mediated dilatation (FMD)25. This was defined as the maximum percentage increase in vessel diameter in the 5 minutes following the release of the cuff (reactive hyperaemia). Vessel diameter was measured, using high-resolution vascular ultrasound (Acuson Aspen, Siemens AG, Germany) with a 4-7 MHz linear-array transducer, continuously for 1 minute at baseline, and for a further 5 minutes following release of a cuff. The cuff was placed distal to the ultrasound probe and was inflated for 5 minutes to 200 mmHg. After 5 minute break,
endothelial independent-dilatation was assessed. Vessel diameter was measured continuously for
1 minute at baseline and for 5 minutes following administration of 25μg of sublingual glyceryl
trinitrate (GTN). GTN-mediated dilatation was defined as the maximum percentage increase in
vessel diameter after sublingual GTN. Anonymised images were analysed using Brachial Tools
software (MIA, Iowa, USA).

**Laboratory Measurements and disease activity score**

Fasting lipid profile, blood glucose, ESR and CRP were determined using standard methodology.
A validated composite disease activity score (DAS28) was calculated utilising ESR, visual
analogue score of well being and the number of tender and swollen joints, from a total of 28
joints26,27.

**Data Analysis**

Data were analyzed using SPSS software (version 17). Significance was determined using
unpaired 2-tailed Student’s t-tests to compare group differences, except for frequency
histograms, where Mann-Whitney test was used. Paired Student’s t-test was used for before and
after treatment comparisons in RA group, except for skewed variables (CRP, ESR, frequency
histograms), where Wilcoxon Signed ranks test was used. Relationship between parameters was
determined using Spearman’s correlation. Smoothed histograms were generated using R
software version 2.15 (www.r-project.org) which computes kernel density estimates, and the bin
width used was 0.2 units. 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.

**Results**

17 patients with active RA (DAS28, 6.52±0.78) were studied before and eight 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.

Baseline Comparison between RA and CVD patients

The mean of TBR$_{\text{max}}$ (Figure 1A) in the whole aorta was significantly higher in RA patients compared with CVD patients (2.02±0.22 versus 1.74±0.22, respectively; $P=0.0001$). Whereas, the mean TBR$_{\text{max}}$ 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$_{\text{max}}$ at baseline in RA patients in comparison to CVD patients ($Z=-19.22; P<0.0001$; Figure 2) and RA patients also had higher proportion of “hot slices” (defined as TBR$_{\text{max}}>2.0$) 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 post-treatment PET/CT images from our study. Following anti-TNF-α therapy, there was a significant reduction in mean aortic TBR$_{\text{max}}$ (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%, $P=0.03$) and there was a significant ($Z=-14.65; P<0.0001$) leftward shift 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 haemodynamics. Disease activity was significantly reduced by treatment (DAS28 score, from 6.52±0.78 to 4.38±1.61; \( P<0.0001 \)), as were markers of inflammation CRP and ESR (\( P=0.007 \) and \( P=0.04 \), respectively). Neither MAP nor AIX 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, FMD responses improved significantly from 3.54±2.34 to 6.66±3.17\%, (\( P=0.003 \)), without any significant change to GTN 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\(_{\text{max}}\) (\( R=0.60, P=0.01 \)).

**Post treatment comparisons**

In comparison to 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 to CVD patients after eight weeks of treatment (\( P=0.03 \); **Figure 1B**).

**Discussion**

The key findings of this study are that patients with severe rheumatoid arthritis, but without clinically manifest CVD, have an increased aortic inflammation in comparison to subjects with established, stable CVD. Additionally, we have shown that anti-TNF-\( \alpha \) therapy leads to a reduction in inflammation along the whole aorta, as well as in its most diseased segment. 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 when compared to patients with established CVD with approximately 14\% higher aortic TBR. Using a TBR threshold of...
2.0, our results demonstrate that on average 50% of slices were “hot”, whereas with an established cut off of 1.6\(^{21}\), this increased to 90%. In the CVD group, the values were 23% and 71%, respectively. The distribution of baseline inflammation using frequency histograms revealed a similar observation. However, TBR in the most diseased segment (MDS) of the aorta was similar for both groups. These data clearly demonstrate that inflammation in RA is generalised, rather than being limited to discrete areas of atherosclerotic plaque, as the overall inflammation and the proportion of hot slices were higher in RA than in CVD patients, where as uptake in its most disease segment, most likely reflecting uptake within a plaque\(^{28}\), were 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 (IRD) had significantly higher number of inflammatory cell infiltrates in the medial and adventitial layers of the aorta than CVD patients without IRD. Moreover, these cells, mainly lymphocytes, were found predominantly outside areas of visible atherosclerotic plaques\(^{15}\).

Although, the prevalence of clinical vasculitis in RA is low\(^{29}\), the results of the previous histological studies\(^{15}\), and the current study, suggest that sub-clinical 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\(^{30}\) and although there are not clearly defined cut-off values for the diagnosis, the authors of a study in patients with temporal arteritis proposed a cut of SUV>1.3 as diagnostic of active vasculitis and SUV≥2.7 as “intense activity”\(^{31}\). Based on these published cut off values, our RA cohort with mean aortic SUV of 2.1, indicating moderate aortic uptake of FDG, and thereby, suggestive of an underlying vasculitis.

Eight weeks of treatment with TNF-\(\alpha\) 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 using frequency analysis. This reduction is within the range of previously reported changes in aortic FDG uptake following statin therapy\(^3\), and more recently with a novel p38 MAP kinase inhibitor losmapimod\(^2\). Interestingly, when the post-treatment aortic TBR was compared to the baseline TBR of CVD patients, it still remained significantly higher. This could be due to relatively short follow up period of 8 weeks, and perhaps, a longer follow up would have shown further reductions in TBR. Alternatively, anti-TNF-\(\alpha\) therapy may not be sufficient to normalise vascular inflammation and other agents such as statins maybe be needed to reduce the aortic inflammation\(^3\). In contrast, the uptake within the MDS was reduced with treatment, so that after eight 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-\(\alpha\)-therapy whereas there is some heterogeneity in the response to all sections of the aorta.

Aortic PWV, but not blood pressure, was reduced after eight weeks of anti-TNF-\(\alpha\) treatment, indicating that the fall in aortic stiffness was not driven by a change in mean arterial pressure. This replicates our previous findings in patients with RA, where a reduction in aortic PWV was seen after 12 weeks treatment with etanercept\(^1\). 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\textsuperscript{10,34} demonstrating that anti-TNF-\textalpha 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 FMD response and the observed reduction in aortic inflammation. However, this may be due to fact that endothelial function was assessed in the brachial artery and inflammation in the aorta.

Patients with RA have a 48\% increased risk of CVD\textsuperscript{8}; the risks of MI and CVA being increased by 68\% and 41\%, respectively\textsuperscript{35}. Treatment with disease-modifying drugs such as methotrexate and, in particular, anti-TNF-\textalpha agents considerably reduces the incidence of CVD disease in RA patients\textsuperscript{36}. 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, as well as directly accelerating the atherosclerotic process, and plaque destabilisation\textsuperscript{11,12,37,38}. Our findings highlight the importance of CV risk management in RA, which is currently inadequately dealt with\textsuperscript{39}.

**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-\textalpha therapy according to national guidelines. Nevertheless, a similar open-label study design has been adopted previously by others\textsuperscript{10,34,40,41}. We minimised observer-
bias by using anonymised and blinded scan analysis. Nevertheless, due to the non-randomized design of our study, we cannot exclude the possibility of a non-drug related reduction in TBR and PWV. Moreover, due to 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 following the addition of an anti-TNF-\(\alpha\) agent, however the patients were stable on these ancillary therapies for at least 2 months prior baseline measurements and were unchanged throughout the study. Furthermore, we acknowledge the fact that FDG PET is a non-specific method of assessing inflammation, as numerous inflammatory cells, as well as smooth muscle cells can utilise FDG. Moreover, endothelial cell activation and hypoxia can also enhance FDG uptake by cells\(^{42}\). 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\(^{43}\).

**Summary**

We have demonstrated that patients with RA have increased inflammation along the entire length of the aorta in comparison to age-matched CVD patients and that anti-TNF-\(\alpha\) therapy leads to a reduction of inflammation in the whole aorta as well as in the most diseased segment. Our data suggest that vascular inflammation could underpin the mechanism of increased CVD seen in RA, and also demonstrates 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.
Acknowledgements: We sincerely thank Drs. Lea Sarov-Blat and Dennis L. Sprecher for providing access to the cardiovascular control group data.

Funding Sources: KMMP, FRJ, JHFR and IBW were all funded by British Heart Foundation. IBW, JHFR, ME and JC also received funding from the Comprehensive Local Research Network and National Institute for Health Research: Cambridge Biomedical Research Centre. ME also received an award from the Raymond and Beverly Sackler Foundation.

Conflict of Interest Disclosures: AJKÖ has worked as a consultant for Abbott and Pfizer.

References:


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**Table 1.** Demographic and baseline characteristics

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<td>Gender, male/female</td>
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<td>Peripheral DBP, mmHg</td>
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<td>ESR, mm/hr*</td>
<td>22.0 (8.5-41.0)</td>
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<tr>
<td>Disease activity score (DAS28)</td>
<td>6.52±0.78</td>
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</table>

Values are represented as means ± standard deviation, except for the variables that were skewed (*), where the values are represented as medians (inter quartile range). SBP indicates systolic blood pressure; DBP, diastolic blood pressure; 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</th>
<th>DMARD &amp; steroid</th>
<th>Other drugs</th>
<th>Aortic TBR</th>
<th>TBR in MDS</th>
<th>Aortic PWV (m/s)</th>
<th>CRP (mg/L)</th>
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<td>Post</td>
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<td>L</td>
<td>C, A, AH</td>
<td>1.75</td>
<td>1.78</td>
<td>2.29</td>
<td>1.84</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>
</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>
</tr>
</tbody>
</table>

A indicates analgesic drug; AH, anti-hypertensive drug; C, COX-inhibitor; CRP, C-reactive protein; DMARD, disease-modifying anti-rheumatic drugs; H, hydroxychloroquine; L, leflunomide; M, methotrexate; MDS, most diseased segment; P, prednisolone; PWV, pulse wave velocity; S, statin; SS, sulphasalazine; TBR, target to background ratio; TNF-α, tumour necrosis factor-α, PP, protein pump inhibitor
Table 3. The effect of anti-TNF-α therapy on disease activity, inflammatory markers and haemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>8 weeks</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS 28 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, mmHg</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>9.00±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 using paired Student’s t-test, except for skewed variables (*) where Wilcoxon Signed ranks 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; GTN, glyceryl trinitrate.

Figure Legends:

Figure 1. The effect of anti-TNF-α therapy on 18F-FDG uptake. 17 RA subjects had 18F-FDG PET/CT scans at baseline and 8 weeks after the initiation of the anti-TNF-α therapy. An age-matched control group (n=34) were scanned at baseline. Panel A represents tissue to background ratio (TBR) in the whole aorta; panel B, TBR in the most diseased segment (MDS) of the aorta. Bars represent means and 95% confidence intervals of means.

Figure 2. Frequency histograms of target to background ratio in all segments of aorta.

Histograms show TBR data from all RA patients at baseline (red line) and 8 weeks after the initiation of anti-TNF-α therapy (blue line); P<0.0001 and from CVD patients (black line); P<0.001 (for RA at baseline v. CVD comparison).
**Figure 3.** Typical PET/CT images before and after anti-TNF-α therapy. Panel A: axial images of ascending and descending aorta from a typical RA patient. Left to right: CT, FDG-PET and fused PET/CT images. Panel B: 3D multi-planar reformatted images of the proximal aorta and arch from the same patient. Baseline images are shown on the top row and after intervention on the bottom row.
Baseline 8 weeks CVD controls

Aortic TBR

P=0.03

P=0.0001

P=0.02

Baseline

8 weeks

CVD controls
Baseline 8 weeks CVD controls

P<0.0001

P=0.03

P=0.1

TBR in MDS

Baseline

8 weeks

CVD controls
Anti-Tumor Necrosis Factor-α Therapy Reduces Aortic Inflammation and Stiffness in Patients with Rheumatoid Arthritis
Kaisa M. Mäki-Petäjä, Maysoon Elkhawad, Joseph Cheriyan, Francis R. Joshi, Andrew J.K. Östör, Frances C. Hall, James H.F. Rudd and Ian B. Wilkinson

Circulation, published online October 24, 2012;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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