Time-Related Aortic Inflammatory Response, As Assessed With 18F-FDG PET/CT, in Patients Hospitalized With Severe or Critical COVID-19 The COVAIR Study

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Short Report

Keywords: 18 FDG PET CT, arterial inflammation, COVID 19 disease, FDG uptake

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Abstract

Aim

Arterial involvement has been implicated in the coronavirus disease of 2019 (COVID-19). 18F-fluoro-2-deoxy-d-glucose positron emission tomography/computed tomography (18F-FDG PET/CT) imaging is a valuable tool for the assessment of disease severity in different types of vasculitis and is a predictor of outcome. We sought to prospectively assess the presence of aortic inflammation and its time-dependent trend by measuring the 18-FDG uptake in PET/CT in patients with severe or critical COVID-19.

Methods

In this pilot case control study, we recruited 20 patients, who were admitted with severe or critical COVID-19 illness. Patients underwent imaging between 20 to 120 days after hospital admission. Ten age- and sex-matched individuals with prior history of malignancy but free of active disease served as the control group. Arterial inflammation was assessed by measuring 18-FDG uptake in PET/CT and calculating aortic target to blood ratio (TBR).

Results

There was a significant correlation between aortic TBR values and time distance from diagnosis to 18F-FDG PET/CT scan (-rho- =0.547, p=0.015) even after adjustment for confounders (p=0.002). Patients who were scanned less than 60 days (median) from diagnosis had significantly higher TBR values compared to patients examined more than 60 days post-diagnosis (1.55 [1.47-1.61] vs 1.40 [1.33-1.45], respectively, p=0.013).

Conclusion

This is the first study suggesting that 18 FDG PET/CT imaging could be used for assessment of arterial inflammation in patients with severe/critical COVID-19. These findings may have important implications for the understanding of the pathophysiology and the course of the disease and for improving our preventive and therapeutic strategies.

Introduction

The coronavirus disease of 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the result of disruption of the immune, renin-angiotensin-aldosterone (RAA), and thrombotic balance.[1] All these mechanisms converge on vascular dysfunction as a common pathway. The main organs involved in COVID-19, i.e., the lungs, the heart, and the kidneys, exhibit similar findings of endothelial dysfunction and vasculitis with monoclonal cells, lymphocyte infiltration and intravascular thrombosis.[2] Transient increase of arterial stiffness that correlates with hospital stay

length[3] attests to the vascular involvement in COVID-19. Nevertheless, the patients that end up with irreversible myocardial damage at long-term follow constitute a small percentage.[1,4,5]

18F-FDG PET/CT (positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro- D-glucose integrated with computed tomography) imaging is a valuable tool for the diagnosis and assessment of disease severity in different types of vasculitis and aortic inflammation[6,7] and is a predictor of outcome.[7,8] We have shown that aortic FDG uptake is associated with disease severity and response to treatment in patients with lymphoma and hypercholesterolemia.[9,10]

There are very few observational studies regarding 18F-FDG PET/CT in COVID-19 affected patients focusing on the lung FDG uptake.[11,12] We investigated the effects of COVID-19 on a vascular level, by assessing 18F-FDG PET/CT uptake in the aorta in patients with severe illness.

Methods

Between November 2020 and May 2021, we recruited 20 patients from two dedicated Covid 19 hospitalization centers who were admitted with severe or critical Covid-19 illness. Patients underwent whole body 18F-FDG PET/CT imaging between 20 to 120 days after hospital admission. Ten age and sex-matched individuals scheduled for 18F-FDG PET/CT imaging served as the control group. They had a prior history of malignancy but were free of active disease at the time of the 18F-FDG-PET/CT investigation. Image acquisition was obtained following recommended protocols and as previously described.[9,10,13] (see Supplemental material). The arterial target-to-background ratio (TBR) was then derived by dividing the mean aortic SUVmax to the average value of venous SUVmean. Aortic TBR was calculated as the sum of TBRs of ascending and descending aorta, aortic arch, and abdominal aorta divided by 4. Index vessel TBR was designated as the vessel with the highest TBR. The study was approved by the Institutional Research Ethics Committee and conducted according to institutional guidelines and the Declaration of Helsinki.

18f-fdg Pet/ct Imaging Protocol

18F-FDG PET/CT imaging protocol
Image acquisition was obtained following recommended protocols and as previously described. None of the patients had blood glucose levels>180 mg dL-1 before injection. FDG was injected intravenously (3-4MBq/Kg) and scanning was performed at 60-120 min post-injection for aortic tracer uptake assessment. A low dose computed tomography (CT) scan in a supine position was obtained for attenuation correction and image fusion. No CT IV contrast was administered. PET data were reconstructed using an ordered subset expectation maximization iterative reconstruction algorithm. Regions of interest (ROI) around the aortic wall were manually drawn along the entire aorta in consecutive axial slices at intervals of 5 mm. Metabolic activity within each arterial ROI was measured by maximum standardized uptake value (SUVmax). Six consecutive circular ROIs of 3mm diameter, were drawn within the superior vena cava and

an average venous SUVmean value was calculated. The arterial target-to-background ratio (TBR) was then derived by dividing the mean aortic SUVmax to the average value of venous SUVmean. Finally, aortic TBR was calculated as the sum of TBRs of ascending and descending aorta, aortic arch, and abdominal aorta divided by 4. Patients provided written informed consent to participate in this pilot study.

Statistical analysis

Parameters which exhibited a non-normally distribution were log-transformed and presented as the median (25th-75th percentile). For between-groups comparisons, the Student's t-test or chi-square test for continuous and categorical variables respectively were employed. For comparison of TBR values, Mann Whitney U test was performed. To assess the relation between aortic TBR and inflammatory markers, time distance since admission d-dimers and SO2, Spearman's rho was employed. Linear regression analysis was performed using aortic TBR as the dependent variable and time distance from admission, age, sex and systematic inflammation as described by hs-CRP as covariates.

Quantitative data are presented as mean values±SD or medians (interquartile range), while qualitative variables as absolute and relative frequencies. A two-tailed p-value <0.05 was considered significant. All statistical analyses were performed with the SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics are shown in **Table 1**. There was no significant difference in aortic 18F-FDG PET/CT uptake between patients and controls (aortic $TBR_{patients}$=1.45 [1.40-1.57], aortic $TBR_{control}$=1.43 [1.32-1.70], respectively p= 0.422). Similarly, there was no difference in index vessel TBR (index vessel $TBR_{patients}$ =1.60 [1.50-1.67] vs index vessel $TBR_{controls}$=1.47 [1.41-1.62]. Out of all patients, 70% had critical Covid 19 illness and required ICU admission. There was no significant difference in aortic TBR between patients admitted to ICU and patients with severe Covid disease not requiring ICU admission ($TBR_{ICUpatients}$=1.45 [1.40-1.53] vs $TBR_{nonICUpatients}$=1.49 [1.33-1.64], p=0.898. There was a significant association between aortic FDG uptake and CRP (Spearman's rho 0.662, p=0.004). There was no correlation between aortic FDG uptake and troponin or d-dimer levels.

The median (interquartile range) time from diagnosis to the 18F-FDG PET/CT was 60 (45-74) days. There was a significant correlation between aortic TBR values and time distance from diagnosis to 18 FDG PET-CT scan (Spearman's rho 0.547, p=0.015) **Fig. 1**. **Fig. 2** demonstrates a patient assessed 20 days post-diagnosis compared to a patient assessed 64 days after diagnosis of Covid 19 disease. Patients who were scanned less than 60 days (median) from diagnosis (n=10) had significantly higher TBR values compared to patients that were examined more than 60 days post-diagnosis (aortic $TBR_{<60\ days}$=1.55 [1.47-1.61], aortic $TBR_{>60\ days}$ = 1.40 [1.33-1.45], p= 0.013).

Multivariate analysis showed that aortic TBR remained significantly correlated with time distance from diagnosis to 18F-FDG PET/CT and with systemic inflammation assessed by hs-CRP, even after

adjustment for sex and age (**Table 2**).

Discussion

To our knowledge, this is the first study that investigates the course of arterial inflammation in COVID19 disease, as assessed by aortic FDG uptake PET/CT, over time. Our findings demonstrate that there is a significant association between aortic FDG uptake and the time distance from the diagnosis and may suggest that arterial inflammatory involvement is largely transient.

There is limited information on aortic FDG uptake in patients post COVID 19 infection.[11,12] Our numerical, yet statistically non-significant, increased aortic FDG uptake is in accordance with Solini et al[12] who showed in 10 patients that although patients and control subjects had similar vascular scores, as assessed by a semi-quantitative method, there were higher aortic TBR scores in specific aortic regions in patients (thoracic aorta, right iliac artery, femoral arteries). Another interesting finding was that aortic TBR values correlated with CRP levels attesting to the explanation that systemic inflammation is likely the cause of a higher aortic FDG uptake. Regarding the time course, our results are in keeping with indirect evidence from Minamimoto et al[14] who showed an inflammatory response depicted by FDG PET/CT imaging, in mediastinal lymph nodes of patients post COVID 19, which decreased during 4 weeks of observation.

Our results may have important clinical implications. An increase of arterial inflammation in the peri-infection period could aggravate patients' prognosis. COVID-19-induced vasculitis can cause thrombosis (arterial or venous), as well coronary or aortic dissection.[1] Histopathological post-mortem findings in COVID 19 patients have shown increased inflammatory burden in patients with a severe clinical presentation.[1] Furthermore, early CT scan imaging in COVID-19 revealed vascular thickening and enlargement, as well as vascular congestion.[15] On the other hand, our results indicate that arterial involvement resolves over time. Admittedly, a small proportion of patients develop persistent chronic post-COVID-19 syndrome.[1,5,6] Therefore, it is important to recognize, first, those patients with early excess vascular inflammation and, second, those with persistent findings to prevent vascular complications.

Our study is limited by its observational nature and the relatively small number of patients. However, it shows that, despite practical shortcomings in the COVID-19 setting, monitoring of patients with this diagnostic modality is both feasible and useful. Ideally, an earlier scan could have identified higher degrees of inflammation.

In conclusion, this is the first study suggesting that 18 FDG PET/CT imaging could be used for assessment of arterial inflammation in patients with severe/critical COVID-19. These findings may have important implications for the understanding of the pathophysiology and the course of the disease and for improving our preventive and therapeutic strategies.

Declarations

Compliance with Ethical Standards:

Professor Charalambos Vlachopoulos declares he has no conflict of interest,

Dr Dimitrios Terentes-Printzios declares he has no conflict of interest,

Professor Paraskevi Katsaounou declares she has no conflict of interest,

Dr Eirini Solomou declares she has no conflict of interest,

Dr Vassiliki Gardikioti declares she has no conflict of interest,

Dr Dimitrios Exarchos declares he has no conflict of interest,

Dr Dimitrios Economou declares he has no conflict of interest,

Mrs Georgia Christopoulou declares she has no conflict of interest,

Dr Antonios-Dimosthenis Kalkinis declares he has no conflict of interest,

Mr Pavlos Kafouris declares he has no conflict of interest,

Dr Alexios Antonopoulos declares he has no conflict of interest,

Dr Georgios Lazaros declares he has no conflict of interest,

Professor Anastasia Kotanidou declares she has no conflict of interest,

Dr Ioannis Datseris declares he has no conflict of interest,

,Professor Konstantinos Tsioufis declares he has no conflict of interest,

Dr Constantinos Anagnostopoulos declares he has no conflict of interest

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Tables

Due to technical limitations, table 1,2 is only available as a download in the Supplemental Files section.

Figures

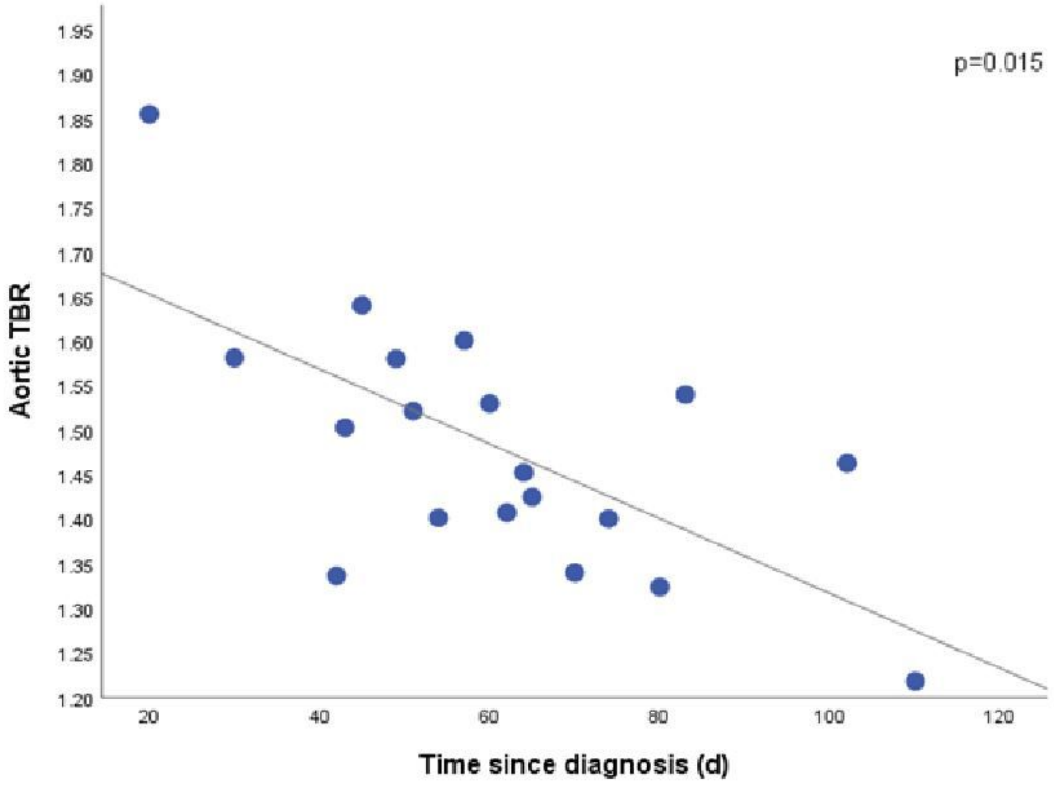

Figure 1

Title : Correlation between aortic TBR values and time distance from diagnosis to 18 FDG PET-CT scan
Legend: There is significant negative correlation between aortic TBR values and time from diagnosis of Covid 19 disease (Spearman's rho 0.547, p=0.015).

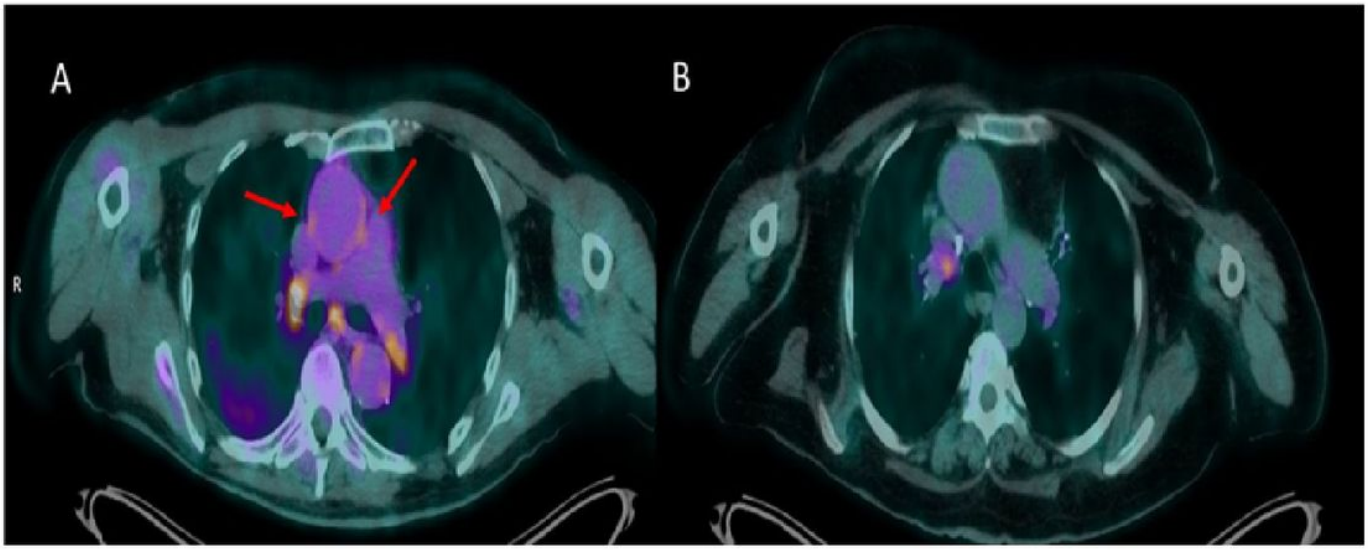

Figure 2

Title: Transaxial views of fused 18 FDG PET/CT images of 2 patients post severe COVID 19 infection.
Legend: A. Twenty days post-diagnosis of severe COVID 19 disease. B. Sixty four days after diagnosis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.pdf
- Table2.pdf