Brief Report
Associations Between Coronary Artery Calcium Score and Exacerbation Risk in BLOCK-COPD

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Running Head: Coronary Artery Calcium and Exacerbation Risk in COPD

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Key Words: COPD; coronary artery calcium; beta-blockers; acute exacerbations

Abbreviations:

- BLOCK-COPD (Beta-Blockers for the Prevention of Acute Exacerbations of COPD)
- Coronary Artery Disease (CAD)
- Coronary Artery Calcium (CAC)
- Computed tomography (CT)
- Right Coronary Artery (RCA)
- Left Main (LM)
- Left Anterior Descending (LAD)
- Left Circumflex (LCx)
- Cox proportional hazards (CPH)
- Forced expiratory volume in 1-second (FEV₁)
- Interquartile Range (IQR)
- Adjusted Hazard Ratio (aHR)


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Abstract

Introduction: In 2019, BLOCK-COPD (Beta-Blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease) evaluated the effect of metoprolol on exacerbation risk and mortality in a COPD population without indications for beta-blocker use. We hypothesized that an imaging metric of coronary artery disease (CAD), the coronary artery calcium (CAC) score, would predict exacerbation risk and identify a differential response to metoprolol treatment.

Methods: The study population includes participants in BLOCK-COPD from multiple study sites. Participants underwent clinically indicated thoracic CT scan ± 12 months from enrollment. The Weston scoring system quantified CAC. Adjusted Cox proportional hazards models evaluated for associations between CAC and time to exacerbation.

Results: Data included 109 participants. The mean CAC score was 5.1±3.7, and 92 participants (84%) had CAC scores greater than 0. Over a median (IQR) follow-up time of 350 (280 to 352) days, there were 61 mild exacerbations and 19 severe/very severe exacerbations. No associations were found between exacerbations of any severity and CAC>0 or total CAC. Associations were observed between total CAC and CAC>0 in the LCx and time to exacerbation of any severity (aHR=1.39, CI: 1.08-1.79, p=0.01) and (aHR=1.96, 95% CI: 1.04-3.70, p= 0.04), respectively.

Conclusion: CAD is a prevalent comorbidity in COPD accounting for significant mortality. Our study confirms high prevalence of CAD using the CAC score; however, we did not discover an association between CAC and exacerbation risk. We did find novel associations between CAC in the LCX and exacerbation risk which warrant further investigation in larger cohorts.
Introduction:

The BLOCK-COPD (Beta-Blockers for the Prevention of Acute Exacerbations of COPD) study investigated whether metoprolol would reduce exacerbation risk in patients with COPD who did not have an evidence-based indication for beta-blocker use, namely coronary artery disease (CAD) with recent reperfusion intervention or congestive heart failure (1). This trial was incepted due to prior reports suggesting beta-blockers may be associated with a reduced risk of acute exacerbations (1). BLOCK-COPD failed to demonstrate exacerbation risk reduction with metoprolol but observed an increase in severe-to-very severe exacerbations leading to early study termination. Since BLOCK-COPD largely sought to enroll subjects without CAD, it is not clear whether participants with subclinical or unrecognized CAD might have a differential response to metoprolol. The coronary artery calcium (CAC) score can be used to assess for CAD using chest computed tomography (CT) scans (2). This imaging biomarker evaluates deposition of calcified plaque in the coronary vasculature, and a visual score of greater or equal to 7 is associated with incident coronary vascular events in COPD (3). We hypothesized that CAC would be associated with an increased exacerbation risk and differential response to metoprolol treatment within BLOCK-COPD. Some of the results from this study were previously reported in the form of an abstract (4).

Methods:

The study population includes participants in BLOCK-COPD from five study sites (University of Maryland, University of Michigan, Northwestern University, Temple University, and University of Alabama at Birmingham) who underwent clinically-indicated thoracic CT imaging within a timeframe of 12 months before/after enrollment. Comprehensive clinical, spirometry, exacerbation, and mortality data were collected at regular intervals as part of the BLOCK-COPD
protocol (5). An exacerbation of COPD was defined as an increase in or a new onset of two or more respiratory symptoms that required treatment with antibiotics or systemic steroids for at least 3 days (5). All participants completed informed consent for enrollment in BLOCK-COPD, and the post-hoc analysis was IRB approved.

We used the Weston scoring system to quantify CAC using an ordinal scale wherein 0 indicates no vessel calcium and a score of 1-3 indicates increasing calcification severity (6). The Weston score ranges from 0-12 and is derived by summing the individual scores from each of the four major coronary arteries: right coronary artery (RCA), left main (LM), left anterior descending (LAD), and left circumflex (LCx). An investigator at each clinical site, blinded to clinical parameters, determined the CAC score for each participant.

Cox proportional hazards (CPH) models were used to measure associations between CAC in each vessel (and the interaction between CAC and treatment assignment) and time to exacerbation. Adjusted models included age, sex, race, smoking status, baseline FEV1 % predicted, number of hospitalizations for COPD during the previous year, number of exacerbations treated with glucocorticoids or antibiotics during the previous year, and treatment assignment and were stratified by center. CAC was evaluated both as a continuous variable and as a binary variable indicated by CAC greater than zero. Analyses were performed using R statistical software (version 3.6.0). P-values were not adjusted for multiple comparisons.

Results:

Imaging and clinical data were included for 109 participants. The mean age was 65±8 years; with 54% female, 33% Black race, and 24% active smokers (Table 1). Sixty-one (56%) participants
were assigned to the metoprolol treatment arm. Over a median (IQR) follow-up time of 350 (280 to 352) days, 61 individuals experienced at least one exacerbation.

The mean CAC score was 5.1±3.7, with 92 participants (84%) having CAC >0. Associations were observed between CAC in the LCx and shorter time to exacerbation (aHR= 1.39 for 1 unit increase in score, 95% CI: 1.08-1.79, p=0.01). When treating CAC as a dichotomous variable, associations were again observed between LCx CAC and shorter time to exacerbation (aHR= 1.96, 95% CI: 1.04-3.70, p= 0.04). No associations were observed between LM, LAD, or total CAC and time to exacerbation. No interaction was observed between total or any vessel CAC and treatment assignment to either metoprolol or placebo. A summary of the findings is depicted in Figure 1.

Discussion:

We identified that CAC, as a reflection of underlying CAD, was associated with COPD exacerbation risk in a well-characterized COPD population. However, we did not observe a beneficial effect of metoprolol on exacerbation risk reduction in BLOCK-COPD participants with any visible CAC. Interestingly, we found that CAD (by CAC >0) was highly prevalent in this subgroup of patients despite the BLOCK-COPD design excluding patients with CAD requiring recent revascularization. Our study is novel in that it links an imaging biomarker of CAD with COPD control and further investigated associations between CAC and beta-blocker treatment. CAC is an important imaging biomarker that is implicated in COPD morbidity (3). The observation between LCx CAC and exacerbation risk is thought provoking with several potential mechanisms at play. Elevated CAC scores in the LCx have been implicated in large myocardial ischemia deficits on nuclear perfusion scans (7). Additionally, the LCx can perfuse a
large portion of the left ventricle including the mitral valve. Several publications report
associations between total CAC and left ventricular diastolic dysfunction (8, 9). Given that
diastolic dysfunction is associated with increased risk of severe exacerbations, it is possible that
impaired left ventricular perfusion increases diastolic dysfunction and increases exacerbation risk (10). Interestingly, the LCx perfuses the sinoatrial (SA) node in up to 25% of individuals (11). Existing reports indicate that associations between atrial arrhythmias and increased COPD exacerbation risk, it is reasonable to posit that poor perfusion of the SA node may increase the incidence of arrhythmias and subsequently contribute to exacerbation risk (12). Thus, poor myocardial perfusion and resultant impairment in cardiac function may lead to increased respiratory symptoms. Our study is limited by its post-hoc design, small sample size, which precludes matching between groups or inferences regarding causality. In addition, given that the study was terminated early, some participants had limited follow-up time. Further, we are limited to participants who underwent thoracic CT for clinical reasons outside of the BLOCK-COPD protocol, which may introduce confounding by indication.

Conclusions:

We found associations between CAC in the LCx and exacerbation risk, expanding the relevance of CAC measurement in COPD. Future investigations should incorporate the use of CAC measurement to better understand exacerbation risk prediction as well as to disentangle complex heart-lung interactions.

Acknowledgements:

All authors provided substantial contributions to the conception and design of the study as well as the acquisition, analysis, and interpretation of data for the work. RCW and JMW drafted the
work and all authors revised the manuscript critically for important intellectual content and gave final approval of the version to be published. RCW and JMW agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Data Sharing Statement:**

Requests for de-identified participant data and study related documents can be requested through the corresponding author and data-coordinating center.

**Declaration of Interest:**

RCW, SXL, HV, DM, OC, JYS, RR, JMW report no conflicts of interest; WWL reports personal fees from Konica Minolta and Continuing Education Alliance. ESH has received grant support from the National Institutes of Health and the Department of Defense and clinical trial support from Fisher & Paykel Healthcare; GC reports grants from Boehringer-Ingelheim, Novartis, AstraZeneca, Respironics, MedImmune, Actelion, Forest, Pearl, Ikaria, Aeris, PneumRx, Pulmonx, personal fees from HE Health Care Solutions, Inc, Amirall, Boehringer-Ingelheim, Holaira; RK receives grants and personal fees from AstraZeneca and GlaxoSmithKline, and personal fees from CVS Caremark, Aptus Health, Boston Scientific and Boston Consulting Group; MKH reported receiving grants from the NIH and COPD Foundation and personal fees from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Cipla, Chiesi, Novartis, Pulmonx, Teva Pharmaceutical Industries, Verona Pharma, Merck, Mylan, Sanofi, DevPro Biopharma, Aerogen, Polarian, Regeneron, Amgen, UpToDate, Altesa Biopharma, Medscape, National Association of Colleges and Employers, MDBriefCase, and Integrity; research support paid to the institution from the NIH, Novartis, Sunovion, Nuvaira, Sanofi, AstraZeneca, Boehringer Ingelheim, Gala
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References

Figure 1: Associations between CAC in each vessel and time to exacerbation
Table 1. Baseline Characteristics of BLOCK-COPD Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of participants (N=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65 ± 7.8</td>
</tr>
<tr>
<td>Female</td>
<td>59 (54.1%)</td>
</tr>
<tr>
<td>Black</td>
<td>36 (33.0%)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>26 (23.9%)</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>39.9 ± 16.3</td>
</tr>
<tr>
<td>LTOT</td>
<td>43 (39.4%)</td>
</tr>
<tr>
<td>Assigned to Metoprolol</td>
<td>61 (56.0%)</td>
</tr>
<tr>
<td>No. of courses of systemic glucocorticoids or antibiotic use in previous 12 mo</td>
<td>1.8 ± 1.3</td>
</tr>
<tr>
<td>No. of hospitalizations in previous 12 mo</td>
<td>0.6 ± 1.21</td>
</tr>
<tr>
<td>LAD CAC</td>
<td>1.81 ± 1.27</td>
</tr>
<tr>
<td>LAD CAC&gt;0</td>
<td>81 (74.3%)</td>
</tr>
<tr>
<td>LCX CAC</td>
<td>1.03 ± 1.12</td>
</tr>
<tr>
<td>LCX CAC&gt;0</td>
<td>59 (54.1%)</td>
</tr>
<tr>
<td>LM CAC</td>
<td>1.14 ± 1.26</td>
</tr>
<tr>
<td>LM CAC&gt;0</td>
<td>57 (52.3%)</td>
</tr>
<tr>
<td>RCA CAC</td>
<td>1.08 ± 1.20</td>
</tr>
<tr>
<td>RCA CAC&gt;0</td>
<td>58 (53.2%)</td>
</tr>
<tr>
<td>Total CAC</td>
<td>5.1±3.7</td>
</tr>
<tr>
<td>Total CAC&gt;0</td>
<td>92 (84.4%)</td>
</tr>
</tbody>
</table>

Data expressed as mean ± S.D. or n (%), as appropriate. Abbreviations: yr = year, No = number, FEV₁ = Forced expiratory volume in 1 second, LTOT = long term oxygen therapy, LAD = Left anterior descending, CAC = coronary artery calcium, LCX = left circumflex, LM = left main, RCA = right coronary artery.