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## Transcutaneous CO-Oximetry Differentiates Asthma Exacerbation and Convalescence in Children

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Asthma; Carboxyhemoglobin; pulse CO-Oximetry; Asthma Exacerbation; Pediatric Asthma

### To the editor

There is a paucity of inflammatory biomarkers for asthma exacerbation and current options require patient effort or discomfort and have not significantly impacted management<sup>1</sup>.

Biologic production of carbon monoxide (CO) as a result of hemeoxygenase-1 (HO-1) upregulation in response to oxidative stress<sup>2</sup> has consistently been associated with asthma activity<sup>3</sup>. Elevated levels of exhaled breath condensate CO and arterial carboxyhemoglobin are associated with loss of control and decrease with appropriate steroid therapy<sup>4–6</sup>.

In this context, we tested whether pulse CO-Oximetry (SpCO) is associated with asthma exacerbation in a prospective observational cohort<sup>7</sup>. Children aged 6–17 years with a history of physician-diagnosed asthma were enrolled during an emergency ward visit for acute asthma exacerbation and returned for a follow-up research visit six weeks later for a convalescent visit, when they had returned to symptomatic baseline (supplementary Figure E1). A comparison cohort of similar subjects with asthma, but not identified by exacerbation, was derived from the baseline assessment of the School Inner City Asthma intervention study (SICAS-2; ClinicalTrials.gov:NCT02291302). The study was approved by the Boston Children's Hospital Institutional Review Board.

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SpCO was measured by the Rad-57 device (Masimo corporation, Irvine, CA) at exacerbation and convalescent visits. Paired t-tests evaluated the mean difference between exacerbation and convalescence values for SpCO measurements in the primary analysis and by t-test for comparison to ambulatory visit measures (SICAS-2). Complete study methods are provided in this article's Online Repository.

Fifty-nine subjects were included in the paired analysis. Subjects had a mean age of 11 years and were predominately black (37%) and Hispanic (39%). Fifteen percent of subjects were white. Eight subjects (14%) had frequent environmental tobacco smoke exposure (Table E1 in the Online Repository). Compared to the primary cohort, the SICAS-2 comparison group was younger (11.0 vs. 7.7 years old), was less aeroallergen sensitized (91% vs. 60% with any aeroallergen sensitization), and had lower FEV1 (109.6 vs. 98.6% predicted), but not level of obstruction based on FEV1/FVC ratio.

There was a significant difference between exacerbation and convalescent mean SpCO ( $6.02\% \pm 2.8\%$  vs.  $3.42\% \pm 2.0\%$ ,  $p < 0.0001$ ). Moreover, evaluation of each subject's mean SpCO regression (Figure 1) demonstrated that nearly all subjects had a negative slope (lowering of SpCO) between exacerbation and convalescence. The ROC curve found SpCO determined exacerbation status with very good predictive value (area under the curve (AUC): 0.79, Figure E2 in the Online Repository). A level of 4% correctly classified exacerbation 74.6% of the time with sensitivity of 81.4% and specificity of 67.8% (Table E2 in the Online Repository). There were significant differences in SpCO between the mean exacerbation level, convalescent level, and interestingly, between the convalescent levels of children with prior exacerbation and the ambulatory SICAS-2 population (SICAS-2 SpCO mean=1.44, sd=1.96,  $p < 0.001$  for bivariate comparison to exacerbation and convalescent level; Figure 2).

Our study demonstrates that SpCO reliably differentiates asthma exacerbation versus convalescent state following recovery in children who present to the emergency ward and further discriminates convalescent states from well-controlled asthma without recent exacerbation. The prospective methodology of this study design with repeated measures suggests that transcutaneous carboxyhemoglobin is a potentially important biomarker of asthma exacerbations and may fill a void in personalized monitoring of asthma.

The biologic plausibility of carboxyhemoglobin as a biomarker for asthma control has been well established<sup>2, 3, 6</sup>. Transcutaneous CO-Oximetry has previously been associated with increased Asthma Control Test (ACT) scores in a cross-sectional clinic cohort<sup>8</sup>. However, Naples, et al<sup>9</sup> found that SpCO was not diagnostic for asthma in adults. Our results and those of Naples would suggest that the clinical utility of SpCO is as a measure of asthma activity during exacerbations but not as a diagnostic test for asthma. Potential clinical use will be limited to monitoring of patients at risk for exacerbation, but not in the diagnosis of asthma.

It is important to recognize that our study design identified subjects at the extremes of asthma control – emergency exacerbation and convalescence following intensive treatment. While we identified a clear distinction in the SpCO levels between these states, the design

does not lend itself to determining if the SpCO measurement is a predictive marker in advance of exacerbations or if it can be generalized to ambulatory patients with asthma. Additionally, fundamental differences between the SICAS-2 comparison group and the primary cohort of children presenting with exacerbation may also contribute to differences in SpCO.

Transcutaneous CO-Oximetry is a reliable biomarker of asthma exacerbation in children with asthma. The non-invasive, effort-independent, simple-to-perform measurement makes its application to clinical practice appealing. Further investigation to determine its clinical utility in predicting loss of asthma control above currently available measures is needed.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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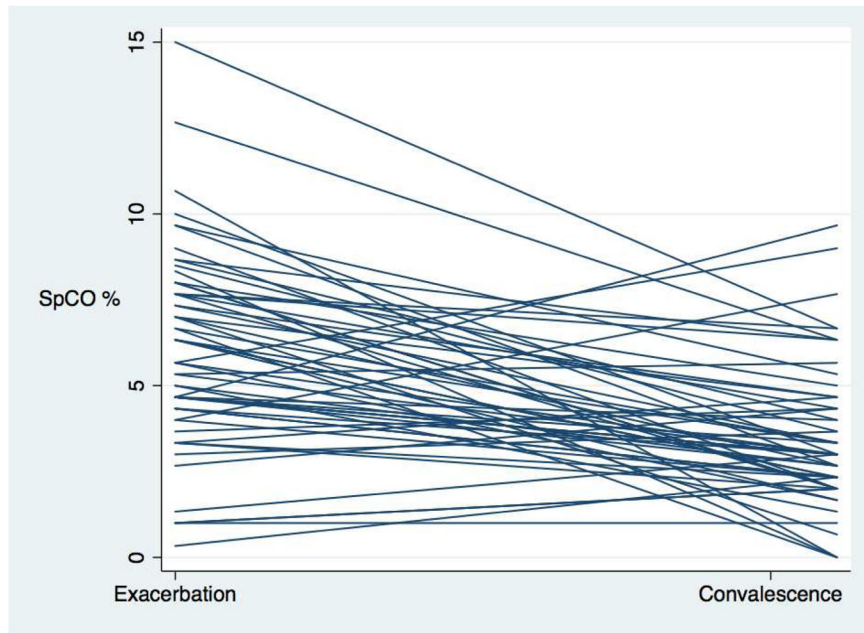
## Abbreviations

SpCO	Peripheral blood carbon monoxide percent saturation of hemoglobin, measured by pulse CO-oximeter
CO	Carbon monoxide

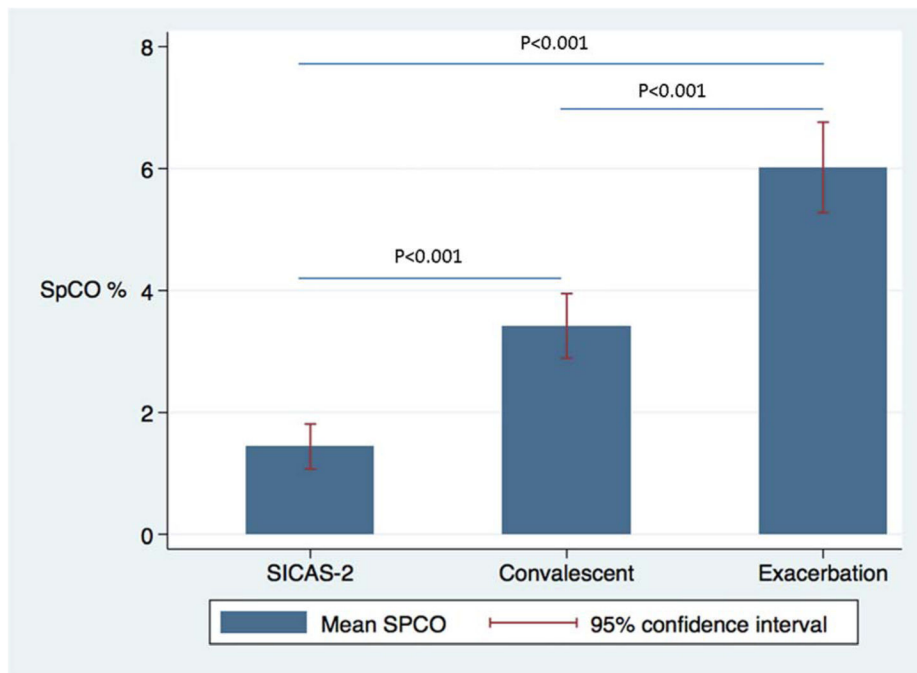
## References

1. Szeffler SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet*. 2008; 372:1065–72. [PubMed: 18805335]
2. Morse D, Choi AM. Heme oxygenase-1: from bench to bedside. *Am J Respir Crit Care Med*. 2005; 172:660–70. [PubMed: 15901614]
3. Brussino L, Badiu I, Sciascia S, Bugiani M, Heffler E, Guida G, et al. Oxidative stress and airway inflammation after allergen challenge evaluated by exhaled breath condensate analysis. *Clin Exp Allergy*. 2010; 40:1642–7. [PubMed: 20726860]
4. Zhang J, Yao X, Yu R, Bai J, Sun Y, Huang M, et al. Exhaled carbon monoxide in asthmatics: a meta-analysis. *Respir Res*. 2010; 11:50. [PubMed: 20433745]
5. Shaoqing Y, Ruxin Z, Yingjian C, Jianqiu C, Yanshen W, Genhong L. A meta-analysis of the association of exhaled carbon monoxide on asthma and allergic rhinitis. *Clin Rev Allergy Immunol*. 2011; 41:67–75. [PubMed: 20094823]

6. Yasuda H, Yamaya M, Yanai M, Ohrui T, Sasaki H. Increased blood carboxyhaemoglobin concentrations in inflammatory pulmonary diseases. *Thorax*. 2002; 57:779–83. [PubMed: 12200522]
7. Kantor DB, Stenquist N, McDonald MC, Schultz BJ, Hauptman M, Smallwood CD, et al. Rhinovirus and serum IgE are associated with acute asthma exacerbation severity in children. *J Allergy Clin Immunol*. 2016; 138:1467–71e9. [PubMed: 27474123]
8. Kurlandsky LE, Anbar RD, Soultan ZN. Elevated Carboxyhemoglobin in Active Asthma and Allergic Rhinitis as Measured by Pulse CO-Oximetry. *Pediatric Allergy, Immunology & Pulmonology*. 2013; 26:35.
9. Naples R, Laskowski D, McCarthy K, Mattox E, Comhair SA, Erzurum SC. Carboxyhemoglobin and methemoglobin in asthma. *Lung*. 2015; 193:183–7. [PubMed: 25680415]



**Figure 1.**  
Spaghetti plot of SpCO by subject



**Figure 2.** Cross-sectional comparison of exacerbation and convalescent levels of SpCO compared to the SICAS-2 pediatric asthma cohort