responsible for this separation: levels of threonine (and/or lactate), alanine, carnitine, acetylcarnitine, and trimethylamine-N-oxide were suggested to be increased in the exacerbated condition, whereas levels of acetate, citrate, malonate, hippurate, dimethylglycine, and phenylacetylglutamine seemed to be decreased compared with the stable condition (Fig 2, *B*).

During exacerbations, urine revealed increased levels of aldehydes and alkanes, as well as alterations in a number of nonvolatile metabolites.

As for limitations and strengths of this study, diet and current treatment might interfere with the urine metabolomic profile. No food restriction was made. Despite all patients having a similar initial dose of methylprednisolone (approximately 80 mg/d), this remains a confounding factor. Further studies with a larger population are necessary to confirm these findings.

The use of 2 high-throughput techniques used in this study provides complementary information, enhancing the current understanding of the metabolic pathways affected (see the Results and discussion, Limitations and strengths section, in this article's Online Repository at www.jacionline.org).

Alkanes and aldehydes, end products of the peroxidation of unsaturated fats, can be formed during inflammation. Their levels were found to be increased during exacerbation, suggesting a high level of oxidative stress compared with the stable state (see the Results and discussion, Data interpretation section, in this article's Online Repository at www.jacionline.org).

Carnitine and acetylcarnitine can be linked to increased oxidative burden because they play an essential role in the transport of fatty acids into mitochondria for oxidation. These metabolites are critically altered in asthmatic patients.[2] Moreover, changes in metabolites, such as citrate and alanine, suggest a disturbance of the tricarboxylic acid cycle, whereas altered levels of trimethylamine-N-oxide, hippurate, and phenylacetylglutamine might be related to diet.

Urine is an easily accessible and information-rich biofluid. Our preliminary data show that urine metabolomics might provide important information on the patients' oxidative stress status. They also show promise in asthma management. This would suggest that research on metabolomic signatures in a broader group of asthmatic patients, including different phenotypes and disease presentation, might be valuable.

In conclusion, urinary metabolic composition was highly altered during exacerbation compared with that seen in the stable state. GC × GC-TOFMS– and ^{1}H-NMR–based methodologies allowed complementary information to be retrieved. In spite of the limited number of cases considered, the present results suggest that oxidative stress is a fundamental factor in asthma exacerbation.

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Disclosure of potential conflict of interest: J. Bousquet is a board member for Actelion, Almirall, Meda, Merck, MSD, Novartis, Sanofi Aventis, Takeda, Teva, and Uriach; is a member of the board of directors for Stallergenes; and has received lecture and travel fees from Almirall, AstraZeneca, Chiesi, GlaxoSmithKline, Meda, Merck, MSD, Novartis, OM Pharma, Sanofi Aventis, Schering-Plough, Takeda, Teva, and Uriach. T. Bom has received consultancy fees from Lab Vitoria, has received lecture fees from GlaxoSmithKline and MSD, has received payment for development of educational presentations from Thermo Scientific, and has received travel fees from Boehringer Ingelheim. The rest of the authors declare that they have no relevant conflicts of interest.

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Unsuspected mild emphysema in nonsmoking patients with chronic asthma with persistent airway obstruction

To the Editor:

We have previously demonstrated that reversible loss of lung elastic recoil is a significant contributing factor in limiting maximal expiratory airflow in acute asthma.[1] We[2] and others[3-7] have also reported chronic loss of lung elastic recoil in clinically stable, nonsmoking, adult patients with moderate-to-severe asthma with persistent expiratory airflow limitation that may be partially reversible with treatment. The mechanism(s) responsible for the loss of lung elastic recoil in acute[1] and chronic asthma[2-7] remains unknown, especially with normal diffusing capacity and normal or only mild parenchymal attenuation of lung density on high-resolution thin-section lung computed tomography (CT) at full inspiration.[2] Here, in a prospective study, we investigated the potential pathophysiologic mechanism(s) limiting maximal expiratory airflow ($V\text{max}_{E}$) after optimal clinical improvement. Our hypothesis is that undiagnosed diffuse breakdown of lung tissue leading to mild, diffuse emphysema may be responsible for both the loss of lung elastic recoil and persistent expiratory airflow limitation.

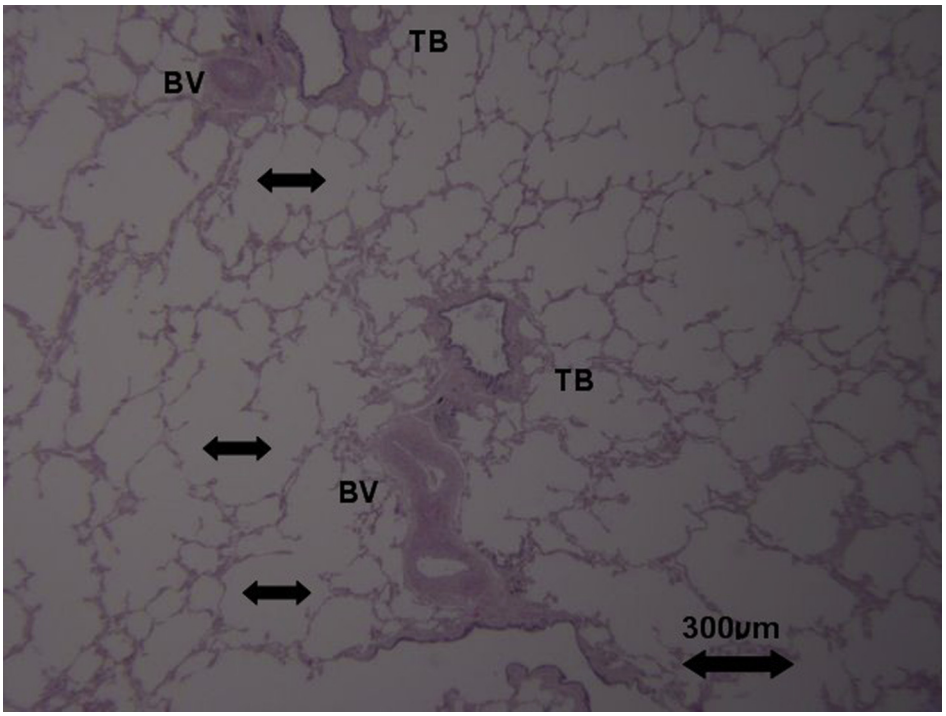

FIG 1. Microscopic section right-upper lobe (×4) in case 9, a 72-year-old woman with lifelong asthma who never smoked. There is mild centrilobular emphysema with irregularly enlarged air spaces and fractured alveolar septa *(see arrows)*. Alcian blue/PAS stain as shown demonstrated mucin in lumen of terminal bronchioles *(TB)* with predominantly recruited neutrophils seen on higher magnification with the CD 15 stain. Sections from left-lower lobe were similar. *BV*, Blood vessel; *PAS*, periodic acid–Schiff.

Ten adult patients with with near-lifelong asthma who had never smoked were followed for 5 to 22 years in a tertiary referral asthma clinic directed by A.F.G. Therapy included inhaled beclomethasone equivalent (inhaled coticosteroid) (≤0.4 mg/day), inhaled short- and long-acting β_2 agonist and muscarinic antagonist, oral leukotriene receptor blocker, and tapering but not maintenance oral corticosteroid. Studies included lung function, elastic recoil, and high-resolution thin-section (1 mm) lung CT at full inspiration using a helical 64-slice multidetector row CT (Model Sensation 64, Siemens, Malvern, Pa). Voxel quantification of less than −950 HU consistent with hyperinflation/emphysema was determined by using Apollo software and 1.0 mm reconstruction slice thickness and kernel B75f at Vida Diagnostics, Inc (Cupertino, Calif, and Coralville, Iowa; vidadiagnostics.com). Serum alpha$_1$ antitrypsin levels were normal, there was no known exposure to inhaled toxic agents and/or second-hand smoke, and none had chronic bronchitis. All 10 patients with asthma had experienced acute exacerbations in the past requiring hospitalization(s) and 3 had been intubated and required short-term mechanical ventilation. Three of the 10 patients with asthma who died unrelated to acute asthma had autopsies, with formalin-fixed lungs inflated to 15 cmH_2O. A control case included an 82-year-old woman with chronic asthma on inhaled coticosteroid + long-acting β_2 agonist who never smoked and had normal spirometry, lung CT, and voxel quantification. She died unrelated to asthma and was autopsied. Within the previous 2 years of study, all patients with asthma satisfied the spirometric criteria for at least partial reversibility, with increase in FEV_1 of more than 200 cc and 12% following 270 μg aerosolized albuterol sulfate via spacer chamber when off all long-acting and short-acting β_2 agonist and muscarinic antagonist metered dose inhaler for 24 and 6 hours, respectively. The Asthma Control Test was used for quantitation of clinical status.[8] Tissue sections were stained with hematoxylin-eosin and also with Alcian blue/periodic acid–Schiff for mucin and CD15 for neutrophils. Results obtained in the present study have not been previously published. All the patients with asthma studied gave informed consent for participation. This study was approved by the Western Institutional Review Board, Olympia, Wa, with NCT registration 00576069.

Results (Fig 1; see Table E1 and Fig E1 in this article's Online Repository at www.jacionline.org) in 10 adult patients (age 52 ± 14 years) with asthma (5 women) revealed total blood eosinophil levels of 206 (131-260) cells/μL (median, 1-3 interquartile range) and serum IgE level of 280 (31-500) kμ/L. The Asthma Control Test score ranged from 16 to 19. Thurlbeck lung CT emphysema score[2] ranged from 0 to 10 with none/trivial (8 cases) emphysema and was 15 and 20 with mild emphysema (2 cases). Lung CT voxel quantification was consistent with insignificant hyperinflation and/or emphysema (<10% lung voxel ≤−950 HU). Fig E1, *A*, demonstrates loss of static lung elastic recoil pressure ($Pst_{(l)}$) in all patients with asthma despite optimal clinical status. Fig E1, *B*, indicates that reduction in both $Pst_{(l)}$ and airway conductance (Gus) had a near-equal contribution to the decrease in $V\max_E$ at 90% predicted total lung capacity. In 3 autopsied cases, transaxial *macroscopic* section of formalin-fixed inflated lungs revealed normal/trivial emphysema in 1 and borderline mild centrilobular emphysema in 2 cases. However, *microscopic* examination revealed diffuse, mild centrilobular emphysema in all cases with upper-lobe predominance (see Fig 1, case 9). Intra-alveolar chord diameter in areas of normal lung parenchyma was 300 μm or less, whereas