

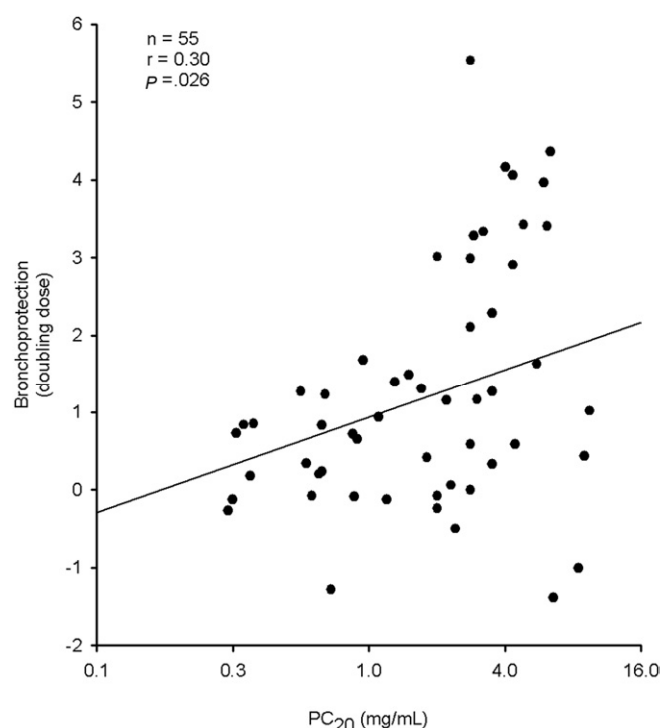


Fig. 1. Deep inhalation bronchoprotection vs baseline (tidal breathing) methacholine provocation concentration that caused a decrease in forced expiratory volume in 1 second of 20% (PC_{20}). Bronchoprotection is defined as the doubling dose difference in PC_{20} between the 2 methods (dosimeter minus tidal breathing).

We believe the importance of this bronchoprotective effect is often overlooked. Our data² demonstrate that a quarter of asthmatic patients with a positive tidal breathing methacholine test result have negative dosimeter test results. This number approaches 50% of patients when addressing those with mild to borderline airway hyperresponsiveness (ie, PC_{20} of 1–16 mg/mL). This is the range most positive diagnostic methacholine challenge results would be expected to occur. The major value of methacholine challenge is the high diagnostic sensitivity and high negative pre-

dictive value,⁴ providing that symptoms are clinically current⁵ (ie, within the past day or two). We would also like to add the additional caveat that the methacholine should be inhaled by submaximal inhalations to preserve the diagnostic sensitivity. The dosimeter method can be adequately and easily performed using submaximal inhalations.⁶

In summary, the important bronchoprotective effect of inhaling methacholine by total lung capacity inhalations does not depend on baseline FEV_1 but rather depends on baseline (tidal breathing) PC_{20} . We recommend that diagnostic methacholine challenges, performed by either method,¹ be performed without deep total lung capacity inhalations.

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The use of the peroxisome proliferator-activated receptors γ agonist rosiglitazone to treat airway hyperreactivity

Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear hormone receptors with multiple functions. PPAR- γ is found at highest concentrations in adipose tissue and is also expressed in the lung epithelium, submucosa, and airway smooth muscle. Expression appears to be upregulated in response to inflammation and is greater in patients with asthma versus people without asthma.¹

Murine studies have shown PPAR- γ receptors to possibly play an inhibitory role in asthma, because administration of PPAR- γ agonists decreased airway inflammation via direct effects on a number of key cells, including smooth muscle, epithelium, eosinophils, and lymphocytes.^{2–5}

Hashimoto and Nakahara⁶ reported on 2 patients who had improvements in asthma symptoms and forced expiratory volume in 1 second (FEV_1) when treated with PPAR- γ agonists for diabetes.⁶ To

further examine the potential benefits of PPAR- γ agonists in asthma, we studied the change in airway hyperreactivity after serial methacholine challenges in patients with asthma.

Thirty-two steroid-naïve healthy adults older than 18 years of age with physician-diagnosed mild-to-moderate persistent asthma were enrolled. All participants provided written informed consent, and the study was approved by the Institutional Review Board of Creighton University, Omaha, Nebraska. Inclusion criteria were FEV_1 of 60% or more and methacholine of concentration causing a 20% decline in FEV_1 (PC_{20}) no greater than 10 mg/mL. Patients were excluded if they were active smokers or if they had respiratory tract infections within 2 weeks of screening.

All eligible subjects received rosiglitazone 4 mg by mouth daily for 8 weeks, followed by 8 mg by mouth daily for an additional 4 weeks. Subjects had a methacholine challenge preceded by measurement of exhaled nitric oxide (NO) at baseline (visit 1) and weeks 4 (visit 2), 8 (visit 3), and 12 (visit 4). Bronchoprovocation challenge with methacholine (Provocho-

Disclosures: Authors have nothing to disclose.

Funding Sources: Health Future Foundation of Creighton University

line; Roche, Nutley, New Jersey) was conducted according to manufacturer's recommendations, using a 5-breath dosimeter (KokoDigiDoser; nSpire Health, Longmont, Colorado).⁷ Methacholine challenge was continued until there was more than 20% reduction in FEV₁ or the 25 mg/mL methacholine concentration had been administered. Results are reported as PC₂₀, concentration causing a 20% decline in FEV₁.

Of the 16 patients enrolled, 10 were female and 6 were male, with a mean age of 34 years (age range, 19–58). Thirteen self-reported allergic rhinitis, and 2 had an upper respiratory infection during the study, which was treated with antibiotics. No patients required systemic prednisone therapy during the trial. For methacholine challenge, missing data were observed within 4 patients. One patient was noncompliant and was discharged from the study, and another withdrew because of new-onset hypertension. No missing data were observed within the remaining 14 patients for both FEV₁ and exhaled NO.

Linear mixed models were estimated separately for PC₂₀, FEV₁, and fractional exhaled of nitric oxide (FENO) to evaluate unconditional mean differences across the 4 measurements while accounting for residual dependency and missing data.⁸ Initially, alternative covariance structures were fit to identify the most parsimonious variance–covariance structure. Nested models were compared via likelihood ratio test ($-2\Delta LL$), whereas non-nested models were compared via Akaike's Information Criteria-corrected. All analyses were performed using the PROC MIXED procedure within SAS v. 9.2 (SAS Institute, Cary, North Carolina) using restricted maximum likelihood estimation and the Satterthwaite approximation for denominator degrees of freedom; $P < .05$ was used to indicate statistical significance. Finally, total R^2 was calculated as the squared Pearson's correlation between the observed and model-predicted outcome.⁸

For comparison purposes, an unstructured R-matrix-only model was estimated initially. For PC₂₀, the Huynh-Feldt (ie, sphericity) structure did not fit significantly worse than the unstructured model, whereas the compound symmetry structure was identified for both FEV₁ and FENO. Attempts to estimate a random intercept in the G-matrix were nonpositive definite for all outcomes. Using these covariance structures, results of saturated means models indicated a statistically significant omnibus effect within PC₂₀ ($F_{3,36.7} = 3.03$, $P = .042$; $R^2 = .11$), with a statistically significant mean difference between baseline and week 12 ($M_{diff} = 4.90$, $SE = 1.67$, $P = .006$). No statistically significant omnibus effects were indicated within FEV₁ ($F_{3,39} = 1.17$, $P = .33$; $R^2 = .46$) or FENO ($F_{3,39} = 1.39$, $P = .26$; $R^2 = .15$).

To our knowledge, this is the first study to examine the feasibility of using the PPAR- γ agonist rosiglitazone in the treatment of asthma. Our hypothesis was supported by the data showing that airway hyperreactivity, assessed by methacholine responsiveness, decreased after 12 weeks of rosiglitazone therapy (Fig 1). In a previous study conducted with inhaled mometasone, we found that the PC₂₀ improvement was greater and occurred by 2 to 8 weeks of treatment.⁹ A possible reason for this difference could be the potential differences in the putative mechanisms by which corticosteroids and PPAR- γ agonists work. However, PPAR- γ agonists and corticosteroids both inhibit important transcription factors, with the former inhibiting gene expression by binding to AP1 or co-activators.^{10,11}

Secondary outcomes included exhaled nitric oxide and FEV₁. Based on our previous data, exhaled NO measurement appeared to be a marker of rapid and transient decline in inflammation with mometasone.⁹ Such a decline was not observed with rosiglitazone. Similarly, we found that FEV₁ improved after mometasone treatment⁹ but not with rosiglitazone. Postbronchodilator reversibility was not an inclusion criterion for enrollment, and this may account for the nonsignificant differences in FEV₁.

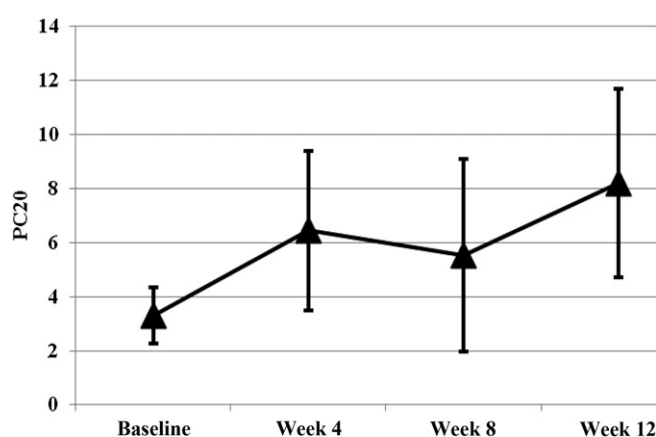


Fig. 1. Estimated means and 95% confidence intervals for PC₂₀ measurements.

Among the potential shortcomings of this feasibility study are the small sample size, dropouts, and lack of placebo control arm.

The external validity and applicability of these findings need to be confirmed by larger double-blind placebo-controlled trials with PPAR agonists in a variety of patients with asthma. The safety of rosiglitazone was acceptable in our study; however, a higher frequency of cardiovascular events has been noted in patients with NYHA class I or II heart failure treated with thiazolidinediones, and this may restrict its use to special populations.

Acknowledgments

The authors thank the study coordinators who assisted in the patient visits and Francisco Romero and Dr. Paul Turner for statistical support.

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Delayed-onset cold anaphylaxis after hymenoptera sting

Cold contact urticaria (CCU) is characterized by urticarial wheals and/or angioedema typically appearing in the exposed areas within minutes of contact with cold air, liquids, or objects. Serious anaphylactic reactions may occur during aquatic activities.^{1–4} Most cases of CCU are primary, but secondary CCU has been reported.^{5–8} We describe a patient who acquired CCU 12 days after a wasp sting.

A previously well, 68-year-old woman who was an avid swimmer experienced a local reaction to a wasp sting. She was stung on her right wrist and developed a local swelling that extended to the midupper arm. Twelve days later, she developed pruritus of her palms and soles and urticaria on her extremities after swimming for a few minutes in an outdoor swimming pool. Before this sting, the patient had no CCU symptoms and became symptomatic on the first swim she took. On the second swim, she developed generalized pruritus within seconds of entering the water. She exited the pool having developed generalized urticaria and immediately experienced lightheadedness, palpitations, vomiting, and diarrhea, with no oropharyngeal involvement. After taking 50 mg of diphenhydramine, she fell asleep, and 2 hours later her symptoms resolved. She avoided swimming thereafter but continued to develop urticaria after contact with cold objects. Her history was remarkable for previous large local reactions to stings. The patient was taking no medications and had no family history of CCU. Her physical examination findings were unremarkable. A 5-minute cold stimulation test (CST) on the volar forearm measured at 10 minutes after removal of a frozen vial demonstrated a wheal-and-flare response, with the largest diameters of 22 mm for the wheal and 40 mm for the flare. The results of sequential intradermal tests to venom extracts (Hollister Stier, Montreal, Quebec, Canada) were positive

for honey bee (wheal of 8 mm and flare of 12 mm) and wasp (wheal of 10 mm and flare of 25 mm) at a concentration of 0.1 $\mu\text{g/mL}$, white faced hornet (wheal of 12 mm and flare of 35 mm), yellow hornet (wheal of 14 mm and flare of 40 mm), and yellow jacket (wheal of 12 mm and flare of 30 mm) at a concentration of 1.0 $\mu\text{g/mL}$. The results of laboratory investigations, including complete blood cell count with differential, erythrocyte sedimentation rate, C-reactive protein, hepatitis B and C serologic tests, anti-streptolysin O titer, antinuclear antibody, rheumatoid factor, complement levels, cryoglobulin, cold agglutinin, serum protein electrophoresis, quantitative immunoglobulins, peripheral blood flow cytometry, thyroid-stimulating hormone, and thyroid autoantibodies, were either within normal limits or negative. The patient was advised to avoid cold exposure and aquatic activities. She was prescribed cetirizine, 10 mg daily, for prophylaxis of CCU symptoms and supplied with epinephrine autoinjectors. She was offered venom desensitization therapy, which she declined. During the subsequent 12 months, she remained asymptomatic and gradually resumed swimming at water temperatures of 20°C to 22°C. No interim stings occurred. A subsequent 5-minute CST while the patient was not taking antihistamines revealed a decreased response (wheal of 22 mm and flare of 27 mm), but she still experienced pruritus when handling cold objects. At 24 months, she was able to swim at water temperatures of 17°C to 18°C. Two months later she acquired another sting and within 2 weeks developed systemic urticaria when swimming at water temperatures of 17°C to 18°C. A subsequent 5-minute CST, 6 weeks after the sting, revealed a worsened response (wheal of 33 mm and flare of 52 mm) (Fig 1).

Our case report demonstrates a 68-year-old woman who acquired CCU 12 days after a wasp sting, which contrasts with the

Disclosures: Authors have nothing to disclose.



Fig. 1. Yearly ice cube test results of wheal-and-flare reaction after application of a frozen water-filled vial for 5 minutes and traced at 10 minutes after removal (inner circle indicates the wheal; outer circle indicates the flare). The picture demonstrates the ice cube test procedure on October 5, 2010.