Does increased baseline ventilation heterogeneity following chest wall strapping predispose to airway hyperresponsiveness?

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AIRWAY HYPERRESPONSIVENESS (AHR) is a characteristic feature of asthma, being defined as exaggerated bronchoconstriction in response to low-dose stimulation of airway smooth muscle (ASM), i.e., airways that narrow too easily and too much to stimuli (33). Although the presence of AHR has many important clinical correlates, including an increased risk of exacerbation (20) and increased decline in lung function (5), the pathophysiological mechanisms leading to AHR are not fully understood. Recently, it has been reported that baseline ventilation heterogeneity correlates with the severity of AHR in asthma (13, 15), an association that is independent of airway inflammation. This association has led to the speculation that increased baseline ventilation heterogeneity may be a mechanism that could lead to AHR. Since many disease processes in asthma could lead to uneven ventilation distribution, such as airway remodeling or reductions in elastic recoil, a role for ventilation heterogeneity in AHR could include the effects of many abnormalities of asthma. However, it is unknown whether increased baseline ventilation heterogeneity predisposes to AHR or whether the association reflects common pathophysiology.

Results of one computational modeling study suggest a potential pathway by which increased baseline ventilation heterogeneity could predispose to AHR. Venegas et al. (28) used a lung model in which airway narrowing in one region could influence narrowing in a nearby region via parenchymal tethering. The model predicted that ASM contraction with the addition of small, random heterogeneities in airway caliber would lead to airway instability during bronchoconstriction, such that excessive airway narrowing would occur, resulting in regional airway closure. Increased baseline ventilation heterogeneity may provide sufficient airway instability, so as to allow this phenomenon to be initiated once bronchoconstriction occurs. While cross-sectional associations between baseline ventilation heterogeneity and AHR support this theory, further evidence is necessary to determine if this is a causal pathway. An intervention that increased baseline ventilation heterogeneity, which in turn correlated with subsequent changes in AHR, would provide such supportive evidence of causality.

In healthy subjects, reducing end-expiratory volume by voluntarily breathing below functional residual capacity (FRC) (9) or with chest wall strapping (CWS) increases baseline ventilation heterogeneity (4, 27). Similarly, reducing end-expiratory volume in healthy subjects increases airway responsiveness whether done voluntarily (12) or with CWS (26, 31). A reduction in end-expiratory lung volume will reduce lung elastic recoil and the forces opposing ASM shortening, thus potentially increasing airway responsiveness (12). However, it is unknown whether the increase in baseline ventilation heterogeneity with reduced end-expiratory lung volume correlates with the increase in airway responsiveness and whether this is independent of the effect of lung volume. An intervention such as CWS in healthy subjects allows investigation of a causal pathway between baseline ventilation heterogeneity and airway responsiveness in the absence of disease pathology.

We hypothesized that increasing baseline ventilation heterogeneity by reducing end-expiratory lung volume would increase airway responsiveness. The aim of the present study was to determine whether the increase in ventilation heterogeneity with CWS correlates with the increase in airway responsiveness, measured by the fall in forced expiratory volume in 1 s (FEV₁).
METHODOLOGY

**Subjects.** Male subjects were recruited from the staff and students of the University of Sydney and the Woolcock Institute of Medical Research and through the research volunteer database at the Woolcock Institute of Medical Research. Subject recruitment was limited to men simply because of the greater convenience in strapping of the chest wall. Subjects had no history or symptoms consistent with asthma. All subjects were lifelong nonsmokers and had no other respiratory or cardiac disease. All subjects were free from upper respiratory tract infection in the 4 wk prior to participation. The study was approved by the University of Sydney’s Human Research Ethics Committee, and all subjects gave written informed consent.

**Study design.** Subjects attended the laboratory on two visits. During the control session, baseline spirometry and body plethysmography were determined before ventilation heterogeneity was measured by multiple-breath N2 washout (MBNW). Subjects then underwent a high-dose methacholine challenge test, with spirometric measurements made after each dose. On a separated day, baseline spirometry and body plethysmography were measured before placement of an elastic corset on the subject. The top of the corset was placed on the xiphoid process of the sternum and covered the majority of the abdomen. This position was chosen to restrict the movement of the diaphragm and chest wall. Spirometry and body plethysmography measurements were repeated, and the rest of the protocol was carried out as described for the control session. Study visits were performed at the same time of day, <1 wk apart, and baseline FEV1 was repeatable between study visits to within 10% for all subjects.

**Body plethysmography.** Lung volumes were measured using a constant-volume body plethysmograph that was calibrated daily (Medisoft BodyBox 5500, Medisoft, Sorries, Belgium). At least three reproducible measurements were obtained, according to American Thoracic Society/European Respiratory Society criteria (32), from which the average total lung capacity (TLC) and FRC were selected. Values are reported as percentage of predicted values (8).

**Methacholine challenge.** High-dose methacholine challenges (MP Biomedicals, Santa Ana, CA) were performed using a KoKo dosimeter (PDS Instrumentation, Louisville, KY) in a dose range of 0.79–200 μmol (3). Spirometry was measured according to American Thoracic Society/European Respiratory Society criteria (1), and forced vital capacity (FVC) maneuvers were sustained for ≥6 s and until a plateau in the expiratory volume trace was observed. Baseline measurements are reported as percent predicted (14). The response to methacholine was measured as the percent fall in FEV1 at each dose step of the challenge. AHR was defined as a provocative dose causing a 20% fall in FEV1 of >6.1 μmol of methacholine.

**MBNW.** The MBNW test was carried out as described previously (13). Briefly, subjects breathed 100% O2 at a tidal volume of 1–1.3 liters, until end-tidal N2 concentration dropped to 1/40th of the starting alveolar N2 concentration. Lung clearance index (LCI), as a measure of global ventilation heterogeneity reflecting small- and large-airway ventilation heterogeneity (29), was calculated as the number of lung turnovers (cumulative expired volume divided by FRC) required to reduce the end-tidal N2 concentration to 1/40th of the starting alveolar N2 concentration. Analysis of the MBNW trace also allows for ventilation heterogeneity to be partitioned into two distinct distal airway regions defined by their mode of gas transport (30): (1) ventilation heterogeneity due to an inequality in convective flows between lung regions due to differences in pressure-volume characteristics (Scond) (22) and (2) ventilation heterogeneity due to the interaction between diffusion and convection gas transport, independent of convective gas flow, (Sacin) (23). Increases in Sacin arise due to an increase in the asymmetry in lung structure at the level of the airway tree where the magnitude of convective gas transport is comparable to the magnitude of diffusive gas transport. Since Sacin is due to diffusion-dependent ventilation heterogeneity, it is a more distal measure of ventilation heterogeneity than Scond. Each test comprised three washouts, from which mean values of Scond, Sacin, and LCI were calculated.

**Data analysis.** The data were analyzed using Analyse-It for Microsoft Excel (Analyse-It Software, Leeds, UK). The response to methacholine was measured as the percent fall in FEV1, and the reported values were calculated at the highest dose common to both protocols. Paired comparisons of baseline lung function and the response to methacholine between control and CWS protocols were made using paired Student’s t-tests. Normality was tested using the Shapiro-Wilk test. Correlations were assessed using Pearson coefficients. Forward step-wise multiple regression analyses were used to assess the determinants of the change in response to methacholine due to CWS. Summary data are presented as mean ± 95% confidence interval unless otherwise stated. P < 0.05 was regarded as statistically significant.

RESULTS

Data were obtained from 13 healthy subjects. The mean age of the subject group was 29 ± 4.5 yr, mean height was 1.79 ± 0.03 m, and mean body mass index was 23.1 ± 2.2 kg/m². In 11 of the 13 subjects, responsiveness to methacholine at the screening visit was normal; the other 2 subjects had asymptomatic AHR. The median maximum dose (interquartile range) of methacholine administered during the control challenge was 200 μmol (38.5–200).

**Effect of CWS on baseline lung function.** Table 1 reports the baseline spirometric and lung volume measurements for control and CWS protocols. Compared with control, CWS caused a small reduction in TLC (P = 0.02) but did not affect residual volume (RV) (P = 0.5). In addition, CWS decreased FRC by 15.6 ± 2.7% (P < 0.0001), so that expiratory reserve volume (ERV) decreased by a mean of 0.53 ± 0.14 liter (P < 0.0001). At baseline, CWS produced a small decrease in FEV1 (P = 0.001) and FVC (P = 0.07) but did not alter FEV1/FVC (P = 0.49). CWS increased overall baseline ventilation heterogeneity, measured by a mean increase in LCI of 0.51 ± 0.26 lung turnovers (P = 0.002; Fig. 1A). However, there was no effect...

Table 1. Baseline lung function data during control and CWS protocols

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Control</th>
<th>CWS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, %predicted</td>
<td>96.0 ± 8.0</td>
<td>94.2 ± 8.4</td>
<td>0.001</td>
</tr>
<tr>
<td>FVC, %predicted</td>
<td>102.6 ± 5.9</td>
<td>99.8 ± 6.3</td>
<td>0.07</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.76 ± 0.04</td>
<td>0.77 ± 0.04</td>
<td>0.49</td>
</tr>
<tr>
<td>TLC</td>
<td>7.59 ± 0.5</td>
<td>7.40 ± 0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>%predicted</td>
<td>105.1 ± 6.5</td>
<td>102.4 ± 6.2</td>
<td>0.015</td>
</tr>
<tr>
<td>FRC</td>
<td>4.03 ± 0.4</td>
<td>3.42 ± 0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>%predicted</td>
<td>119.0 ± 10.6</td>
<td>101.1 ± 10.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ERV, liters</td>
<td>2.08 ± 0.19</td>
<td>1.43 ± 0.17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV</td>
<td>1.95 ± 0.3</td>
<td>2.00 ± 0.3</td>
<td>0.59</td>
</tr>
<tr>
<td>%predicted</td>
<td>109.8 ± 13.5</td>
<td>113.1 ± 15.2</td>
<td>0.51</td>
</tr>
<tr>
<td>Sacin, I/l</td>
<td>0.077 ± 0.01</td>
<td>0.080 ± 0.03</td>
<td>0.6</td>
</tr>
<tr>
<td>Scond, I/l</td>
<td>0.025 ± 0.005</td>
<td>0.028 ± 0.005</td>
<td>0.4</td>
</tr>
<tr>
<td>LCI, turnovers</td>
<td>7.52 ± 0.3</td>
<td>8.02 ± 0.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Fall in FEV1, %</td>
<td>13.7 ± 2.5</td>
<td>23.3 ± 6.1</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Values are means ± 95% confidence interval, unless otherwise indicated. CWS, chest wall strapping; FEV1, forced expiratory volume in 1 s; TLC, total lung capacity; FRC, functional residual capacity; ERV, expiratory reserve volume; RV, residual volume; Scond, convection-dependent ventilation heterogeneity; Sacin, diffusion-convection-dependent ventilation heterogeneity; LCI, lung clearance index.
of CWS on ventilation heterogeneity, measured by Scond ($P = 0.4$) or Sacin ($P = 0.6$; Fig. 1, B and C).

**Effect of CWS on airway response to methacholine.** CWS increased the response to methacholine, measured as the percent fall in FEV$_1$ at the highest common dose ($13.7 \pm 2.5\%$ vs. $23.1 \pm 6.1\%, P = 0.006$). Increased response to methacholine with CWS correlated with the percent decrease in FRC ($r = 0.63, P = 0.02; \text{Fig. 2A}$) and the increase in Sacin ($r = 0.59, P = 0.03; \text{Fig. 2B}$), but not with changes in Scond ($r = -0.08, P = 0.8$) or LCI ($r = 0.31, P = 0.30$). In multiple regression analysis, the effect of CWS on Sacin and FRC were significant independent predictors of the overall increase in response, measured by the percent fall in FEV$_1$ ($r^2_{adj} = 0.46, F = 6.03, P = 0.02$). The reduction in FRC explained 34% of the adjusted variance and the change in Sacin an additional 12%. There was no correlation between the percent decrease in FRC with CWS and changes in Sacin, Scond, or LCI with CWS ($P = 0.2, 0.2,$ and $0.8$, respectively).

**Change in Sacin with CWS.** Although the increase in response to methacholine correlated with the increase in Sacin after CWS, there was no mean effect of CWS on Sacin, suggesting that CWS increased Sacin in some subjects and decreased it in others. To determine the consequences of such a differential effect on Sacin, we undertook a post hoc analysis by dividing subjects into those in whom CWS had decreased Sacin ($\Delta \text{Sacin}_{\text{dec}}$) and those in whom CWS had increased Sacin ($\Delta \text{Sacin}_{\text{inc}}$) (Table 2).

In the $\Delta \text{Sacin}_{\text{inc}}$ group, CWS decreased baseline FEV$_1$ ($P = 0.006$), with a trend toward a decrease in FVC ($P = 0.06$), but did not alter FEV$_1$/FVC ($P = 0.1$). In the $\Delta \text{Sacin}_{\text{dec}}$ group, CWS had no effect on baseline spirometry. There was no difference between groups in the effect of CWS on LCI ($P = 0.5$), Scond ($P = 0.5$), FRC ($P = 0.24$), or ERV ($P = 0.2$). However, there was a correlation between the absolute reduction in ERV due to CWS and the effect on Sacin ($r_p = 0.56, P = 0.04$).

The response to methacholine increased significantly in the $\Delta \text{Sacin}_{\text{inc}}$ group ($16.3 \pm 10.8\%$ fall in FEV$_1$, $P = 0.03$) but not in the $\Delta \text{Sacin}_{\text{dec}}$ group ($5.4 \pm 5.4\%$ fall in FEV$_1$, $P = 0.09$).

**DISCUSSION**

The effect of CWS was to decrease end-expiratory lung volume, as measured by reductions in FRC and ERV, increase in global measures of ventilation heterogeneity (LCI), and response to methacholine. The increase in airway response in the presence of a reduction in end-expiratory volume was independently predicted by the change in FRC and the change in Sacin. These findings suggest that the increase in Sacin made an additional contribution to the increased response to methacholine that was independent of the effect of the reducers.

![Fig. 1. Comparison of difference parameters of ventilation heterogeneity measured by multiple-breath N$_2$ washout between control and corset protocols. A: lung clearance index (LCI). B: convection-dependent ventilation heterogeneity (Scond). C: diffusion-convection-dependent ventilation heterogeneity (Sacin). **$P < 0.01$.](http://jap.physiology.org/content/doi/10.1152/japplphysiol.01582.2011/fig/1)

![Fig. 2. Correlations between the effect of chest wall strapping (CWS) on the response to methacholine and the decrease in functional residual capacity (FRC) (A) and the effect of CWS on Sacin (B). FEV$_1$, forced expiratory volume in 1 s.](http://jap.physiology.org/content/doi/10.1152/japplphysiol.01582.2011/fig/2)
tion in end-expiratory lung volume on airway responsiveness. This finding implies that ventilation heterogeneity may directly contribute to increased airway responsiveness.

The increase in airway responsiveness with CWS was independently predicted by the effect of CWS on Sacin and on FRC. Pellegrino et al. (24) induced similar changes in end-expiratory lung volume with CWS placed on three different thoracic regions. The increase in response was independent of the position of the CWS. However, the position of the CWS is known to affect the change in ventilation heterogeneity, as measured by single-breath washout (4). Pellegrino et al. (24) therefore concluded that the increase in response with CWS was independent of changes in ventilation heterogeneity. Findings in the present study are consistent with the conclusion of Pellegrino et al., since the increase in response to methacholine was independently associated with changes in FRC, but not with changes in LCI or Scord. This independent contribution of FRC most likely reflects the reduction in lung elastic recoil, equivalent to \( \sim 2-3 \, \text{cmH}_{2}\text{O} \) when reduced by 500 ml (12), which would promote increased ASM shortening during bronchoconstriction. However, we also found that the increase in response was independently related to the change in Sacin, suggesting that increased ventilation heterogeneity in the presence of reduced lung volume made a contribution to the increase in AHR that was independent of the direct effect of the reduction in end-expiratory lung volume.

Although there was no mean change in Sacin with CWS in the present study, Sacin was increased by CWS in some subjects but decreased in others (Fig. 1C). Interestingly, when the groups were divided on the basis of the effect of CWS on Sacin, the response to methacholine was increased only in those in whom CWS caused an increase in Sacin, despite no difference in the percent fall in FRC between the groups. Although there was no association between the effect of CWS on FRC and Sacin, the effect of CWS on Sacin was partially explained by the reduction in ERV \( (r_p = 0.56, P = 0.04) \). This suggests that the effect of CWS on ventilation heterogeneity was not due to the reduction in end-expiratory volume per se but, rather, the extent to which end-expiratory volume approached RV. Reducing end-expiratory lung volume to within 300 ml of closing capacity (CC) with CWS increases the phase III slope of single-breath \( N_2 \) washout (4), consistent with an increase in Sacin. Furthermore, ventilation heterogeneity dramatically increases in healthy subjects once end-expiratory lung volume reaches CC (9). Taken together, the association between Sacin and the response to methacholine appears to be due to the encroachment of FRC on CC, where the onset of airway closure begins to affect Sacin. Our finding that ventilation heterogeneity can improve as FRC decreases is consistent with previous findings (9, 10). Since closed airways do not contribute to the measurement of Sacin, the most likely explanation for this airway closure in previously poorly ventilated lung regions. Given that the percent fall in FRC was not different between the two subgroups, closure of poorly ventilated airways may be determined by factors other than the magnitude of reduction in FRC.

The present study suggests that increases in baseline ventilation heterogeneity increase airway responsiveness. Cross-sectional studies have shown an association between baseline ventilation heterogeneity and the severity of AHR in asthma (13, 15) but could not determine whether this association reflected a causal pathway. In the present study, changes in Sacin at baseline due to CWS correlated with the increase in response to methacholine. Importantly, this association in healthy subjects is independent of disease pathology. This suggests that changes in Sacin, independent of any specific disease pathology, are sufficient to increase AHR. While the exact anatomic site corresponding to the increase in Sacin is unknown, modeling of multiple-breath washout tests using inert gases suggests that, in normal, healthy subjects, Sacin reflects ventilation heterogeneity arising in intra-acinar airways (28). Nonetheless, Sacin reflects ventilation heterogeneity in airways where gas transport occurs via diffusion, so that it is a measure of the most distal airways. LCI is a global measure sensitive to changes in ventilation heterogeneity in small localized or large regional levels (29). In the present study, the changes in LCI most likely reflect an exaggeration of the apical-basal ventilation gradient resulting from the position of the CWS around the abdomen. Importantly, changes in LCI were not related to changes in AHR. Therefore, the association between changes in Sacin and AHR suggests that small-airway ventilation heterogeneity between localized airway regions at baseline is a determinant of AHR. These localized regions of heterogeneity may predispose to the formation of localized clusters of airway closure following methacholine, as predicted by computational modeling (28). Since increased phase III slope of single-breath \( N_2 \) washout is associated with increased heterogeneity of the elastic properties of the lung (2), it is possible that CWS reduces elastic recoil, which increases Sacin. This in turn may predispose to increased airway narrowing during bronchoconstriction and, thus, increased AHR. The severity of AHR is determined by Scord in younger asthmatic patients (13) and by Sacin in elderly asthmatic patients (15). Aging reduces elastic recoil (7) and increases ventilation heterogeneity (19). Since changes in Sacin appear sufficient to increase AHR, even in healthy subjects, it may be that the change in pathophysiological mechanisms of AHR in elderly asthma patients is not due to an increase in asthma disease pathology per se but, rather, the combined effects of asthma and aging.

The elastic CWS in the present study reduced end-expiratory lung volume, with little effect on other lung volumes, so that the results may have implications for the effect of obesity on

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Table 2. Change in lung function parameters due to CWS in subjects in whom Sacin increased and in those in whom Sacin decreased with CWS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( \Delta \text{Sacin}_{\text{inc}} (n = 5) )</th>
<th>( \Delta \text{Sacin}_{\text{dec}} (n = 8) )</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRC, %</td>
<td>(-17.7 \pm 3.5^*)</td>
<td>(-14.3 \pm 3.7^*)</td>
<td>0.2</td>
</tr>
<tr>
<td>ERV, ml</td>
<td>(-645 \pm 270^*)</td>
<td>(-452 \pm 140^*)</td>
<td>0.2</td>
</tr>
<tr>
<td>Baseline FEV(_1), liters</td>
<td>(-0.13 \pm 0.08^*)</td>
<td>(-0.06 \pm 0.07)</td>
<td>0.2</td>
</tr>
<tr>
<td>Baseline FVC, liters</td>
<td>(-0.35 \pm 0.27)</td>
<td>(-0.04 \pm 0.14)</td>
<td>0.04</td>
</tr>
<tr>
<td>Baseline FEV(_1)/FVC</td>
<td>(0.02 \pm 0.02)</td>
<td>(-0.005 \pm 0.01)</td>
<td>0.04</td>
</tr>
<tr>
<td>LCI, turnovers</td>
<td>(0.62 \pm 0.45)</td>
<td>(0.44 \pm 0.43^*)</td>
<td>0.5</td>
</tr>
<tr>
<td>Scord, l/l</td>
<td>(0.005 \pm 0.005)</td>
<td>(0.001 \pm 0.007)</td>
<td>0.5</td>
</tr>
<tr>
<td>Sacin, l/l</td>
<td>(0.021 \pm 0.01^*)</td>
<td>(-0.008 \pm 0.003^*)</td>
<td>0.04</td>
</tr>
<tr>
<td>%Fall in FEV(_1)</td>
<td>(16.3 \pm 10.8^*)</td>
<td>(5.4 \pm 5.4)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Values are means ± 95% confidence interval. All data were calculated as values during CWS protocol minus values during control protocol, \( \Delta \text{Sacin}_{\text{inc}} \), subjects in whom Sacin increased; \( \Delta \text{Sacin}_{\text{dec}} \), subjects in whom Sacin decreased. *\( P < 0.05 \) for effect of CWS vs. control within group.
asthma. The magnitude of the changes in lung volumes with CWS were consistent with the changes observed in mild-to-moderate obesity, including a slightly reduced TLC, a normal RV, and a ~500-ml reduction in FRC (18). CWS has consistently shown to increase airway responsiveness in healthy subjects; however, evidence of an effect of obesity on airway responsiveness is weak and inconsistent in subjects with asthma (21) and without asthma (25). The present study suggests that a reduction in end-expiratory volume as seen in obesity should lead to AHR, independent of whether obesity, per se, does (17) or does not (16) alter ventilation heterogeneity. We previously reported that increased body mass index is associated with a protective effect against the severity of AHR (6). In the present study, only in the group with increased Sacin was the response to methacholine increased, despite similar reductions in FRC. Therefore, it may be that the distinction between the effect of CWS and obesity on AHR is due to dissimilar effects on Sacin. However, the effect of obesity on Sacin is unknown and needs to be ascertained before we can speculate on the role of ventilation heterogeneity on AHR in obesity.

In the present study, the increase in the response to methacholine due to CWS was independently predicted by the reduction in FRC and the increase in Sacin. Therefore, the increase in airway responsiveness with CWS was due to an increase in diffusion-convection-dependent ventilation heterogeneity in the presence of reduced end-expiratory lung volume, as well as a direct effect of the reduction in lung volume. This suggests that changes in ventilation heterogeneity are sufficient to increase airway responsiveness, even without airway pathology. These results provide further evidence of the potential importance of peripheral airway abnormalities in AHR, particularly in elderly asthmatic patients, in whom elastic recoil is reduced.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.G.C., N.B., and C.M.S. are responsible for conception and design of the study; D.G.C. and K.R.H. performed the experiments; D.G.C. and K.R.H. analyzed the data; D.G.C., N.B., K.R.H., G.G.K., and C.M.S. interpreted the results of the experiments; D.G.C. prepared the figures; D.G.C. drafted the manuscript; D.G.C., N.B., K.R.H., G.G.K., and C.M.S. edited and revised the manuscript; D.G.C., N.B., K.R.H., G.G.K., and C.M.S. approved the final version of the manuscript.

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