Detection of Small Airway Dysfunction Using Specific Airway Conductance*  

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Study objective: To assess the potential utility of specific airway conductance (sGaw) in detecting small airways dysfunction, the postlung-transplant bronchiolitis obliterans syndrome (BOS) was used as a model of small airways dysfunction. BOS is defined as an otherwise unexplained 20% reduction in FEV1. We hypothesized that if sGaw is sensitive to small airways dysfunction, it should decrease before the decline in FEV1.

Design/methods: The pulmonary function test and sGaw measurements of patients who underwent heart-lung or bilateral lung transplantation between May 1981 and January 1993 were reviewed. Patients with and without BOS were identified. A significant decrease in sGaw was defined as a 20% fall from baseline.

Results: Twenty-six BOS and 15 non-BOS patients had at least three sGaw measurements such that trends could be examined. Eleven of the 26 BOS patients (42%) had a significant decrease in sGaw before a 20% decrease in FEV1, as compared to 2 of the 15 non-BOS patients (13%) (p=0.08). In comparison, 12 of the 26 BOS patients (46%) and 4 of the 15 non-BOS patients (27%) had a significant decrease in forced expiratory flow at 25 to 75% of the forced lung volume (FEF25-75) (p=0.32), an accepted test of small airways dysfunction.

Conclusion: sGaw tended to decrease before FEV1 in BOS. The trend in sGaw was similar to the trend in FEF25-75. We conclude that (1) small airways may contribute more to airway conductance than previously thought, and (2) further prospective studies are warranted to better define the relative contribution of small and large airways to sGaw. (CHEST 1997; 111:1533-35)

Key words: airway conductance; bronchiolitis obliterans; lung transplantation; small airways

Abbreviations: BOS = bronchiolitis obliterans syndrome; FEF25-75 = forced expiratory flow at 25 to 75% of the forced lung volume; Raw = airway resistance; sGaw = specific airways conductance

In normal individuals, specific airways conductance (sGaw) (and its inverse, resistance) is thought to primarily reflect the flow-resistive properties of larger airways.1 Recent studies, however, have questioned this belief by demonstrating a greater impact of the peripheral airways on total airway resistance.2-4 Van Brabandt et al4 have shown that the peripheral airways account for 44 to 96% of total airway resistance. In a human postmortem study, Niewoehner and Kleinerman5 demonstrated a significant correlation between mean bronchiolar diameter and inspiratory pulmonary conductance, whereas no such correlation was detected with bronchial diameter. Thus, a reduction in small airway caliber may indeed decrease total airway conductance.

To study the potential association between small airways dysfunction and sGaw, we chose the bronchiolitis obliterans syndrome (BOS) in lung transplant recipients as a model of small airways disease. The BOS is the major limitation to long-term survival in lung transplant recipients.6 The pathologic correlate of BOS is the narrowing and obliteration of terminal and respiratory bronchioles by dense collagenous scar tissue.6 Lung biopsy may miss affected areas, hence, BOS is defined functionally as a persistent and otherwise unexplained 20% fall in FEV1 compared with baseline.7 Since BOS is a disease of the peripheral bronchioles, early detection (ie, detection before a decline in FEV1) would require a test sensitive to abnormalities of the small airways. The forced expiratory flow between 25% and 75% of FVC (FEF25-75)8,9 and the single-breath nitrogen washout test10 (both tests of small airway dysfunction) have already been shown to become abnormal before a decline in FEV1.
In this study, we report the potential utility of sGaw in detecting small airways dysfunction. Pulmonary function and sGaw measurements were reviewed in heart-lung and bilateral lung transplant recipients with and without BOS (1) to assess the utility of sGaw in early detection of BOS, and (2) to compare trends in sGaw to trends in FEF<sub>25-75</sub>, an established early predictor of BOS.

**Materials and Methods**

**Patient Selection**

Patients included in this analysis were those who (1) underwent a heart-lung or bilateral lung transplant at Stanford University Medical Center from May 1981 to January 1993, and (2) had regular pulmonary function tests and at least three sGaw measurements.

**Pulmonary Function Testing**

Airway resistance (Raw) and thoracic gas volume were measured by body plethysmography (Erich Jaeger; Würzburg, Germany). Raw was measured on inspiration during tidal volume breathing. About five to seven maneuvers were performed until three or four nearly identical Raw values were obtained. sGaw was calculated as L/(Raw × thoracic gas volume). The published normal range for sGaw is 0.112 to 0.4 L/s/cm H<sub>2</sub>O/L<sup>11</sup> with a coefficient of variation of 10.2%.<sup>13</sup> The coefficient of variation at our laboratory is 12.3%. In almost all patients, sGaw was measured annually. A few patients had more frequent measurements. Spirometry was performed according to American Thoracic Society guidelines<sup>13</sup> (Collins DS Plus Spirometer; Braintree, Mass). Predicted values for FEF<sub>25-75</sub> were taken from Morris et al.<sup>14</sup> Only FEF<sub>25-75</sub> measurements obtained with sGaw measurements were analyzed. All pulmonary function values used were those obtained in the absence of acute illness or known abnormalities other than BOS.

**Definitions**

BOS was defined as an otherwise unexplained 20% fall in absolute FEV<sub>1</sub> compared with the average of the two highest values in the first 3 to 9 months posttransplant (baseline), that persisted for at least 1 month.<sup>9</sup> A significant decrease in FEF<sub>25-75</sub> and sGaw was defined as a persistent 20% fall compared with the baseline value. Since sGaw measurements were obtained relatively infrequently in many patients, a single reading at a time of clinical stability was considered sufficient to determine a baseline value. At least three measurements, each 4 weeks apart, were required to define a sustained fall in FEF<sub>25-75</sub> or sGaw; a baseline and two subsequent measurements having values below 20% of baseline. In the BOS group, two of the three sGaw measurements must have been obtained prior to the 20% fall in FEV<sub>1</sub>.

**Statistics**

The two-tailed t test was used to compare sGaw values before and after the development of BOS. Fisher's Exact Test was utilized to compare BOS to the non-BOS group with respect to the number of patients who sustained a fall in sGaw or FEF<sub>25-75</sub>.

**Results**

A total of 113 heart-lung and bilateral lung transplants were performed during the study period. Forty-six met the inclusion criteria. There were 26 BOS and 15 non-BOS patients. Five patients had bronchiolitis obliterans detected on surveillance transbronchial biopsy specimen without an abnormal FEV<sub>1</sub> and were excluded from further analysis. The profiles of the BOS and non-BOS patients are given in Table 1. Seventy-three percent of the patients in the BOS group had biopsy specimens demonstrating the pathologic changes of bronchiolitis obliterans either at the time of the 20% fall in FEV<sub>1</sub> or afterwards.

The mean baseline sGaw in the 26 BOS patients was 0.22 (SD 0.10) L/s/cm H<sub>2</sub>O/L. This value decreased to a mean of 0.10 (SD 0.08) L/s/cm H<sub>2</sub>O/L in 18 patients who had sGaw measurements after the onset of BOS (p=0.0001). Hence, in the BOS group, sGaw decreased significantly once FEV<sub>1</sub> had decreased by 20%.

**sGaw Values Before the Development of BOS**

In the 26 BOS patients, there was a sustained fall in sGaw in 11 (42%) patients at a median interval of 252 days (range, 26 to 1,091 days) prior to the 20% drop in FEV<sub>1</sub>. In the 15 non-BOS patients, 2 (13%) had a drop in sGaw from baseline (p=0.08). Hence, there was a tendency for sGaw to decrease before the fall in FEV<sub>1</sub> with the onset of BOS.

FEF<sub>25-75</sub> measurements obtained at the same time as the sGaw values revealed that 12 of the 26 BOS patients (46%) had a sustained fall in FEF<sub>25-75</sub> at a median interval of 367 days (range, 93 to 3,003 days) before the 20% decrease in FEV<sub>1</sub>. In the 15 non-BOS patients, 4 (27%) experienced such a drop.

| Table 1—Profile of BOS and Non-BOS Patients* |
|----------------|----------------|---------------|
|                | BOS (n=26)     | Non-BOS (n=15) |
| Age, y, median (range) | 33 (16-52) | 32 (26-49)  |
| Sex, % female | 46 | 60          |
| Follow-Up, d, median (range) | 1,588 (443-4,096) | 2,126 (1,138-4,461) |
| Baseline sGaw, L/s/cm H<sub>2</sub>O/L, mean (SD) | 0.22 (0.10) | 0.21 (0.07) |
| Diagnosis, n | CF | 5 | 5 |
|              | PPH | 9 | 6 |
|              | CHD | 9 | 4 |
|              | COPD | 3 | — |

*CF=cystic fibrosis; PPH=primary pulmonary hypertension; CHD=congenital heart disease.
would have rendered such calculations any significance drop in FEV1, although neither reached statistical significance (Fig 1).

**DISCUSSION**

Our data revealed that sGaw tended to decrease before FEV1 in patients who subsequently developed BOS. Although the results did not reach statistical significance, the trend in sGaw was similar to the trend in FEF25-75, a test already established as an early detector of BOS. Two patients in the non-BOS group had a drop in sGaw and we cannot exclude the possibility of future development of BOS in these patients. The median interval between a decrease in sGaw and a decrease in FEV1 was 252 days, while the corresponding interval between a decrease in FEF25-75 and FEV1 was 367 days. In comparison, Patterson et al reported a 4-month average interval between a decrease in FEF25-75 to 70% of predicted and a 20% decrease in FEV1.

We did not attempt to calculate sensitivity or specificity values since our goal was not to establish a new test for the detection of BOS, but to lend credence to the theory that small airways contribute more to sGaw than previously appreciated. Furthermore, the limited number of subjects and sGaw measurements, as well as the exclusion of patients with any illness or abnormality other than BOS, would have rendered such calculations uninterpretable. Even if the ability of sGaw to detect BOS is verified prospectively, technical issues will likely prevent its widespread acceptance over simpler tests such as FEF25-75.

Our study has shown that sGaw may be more sensitive to small airways dysfunction than previously believed. Further prospective and physiologic studies are needed to define the relative contributions of small and large airways to airway conductance better. Hopefully, such studies will further our understanding of the flow-resistive properties of the lungs.

**REFERENCES**


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![Figure 1](image-url) Percentage of patients with BOS who developed a 20% decline in sGaw or FEF25-75 prior to a decline in FEV1, compared with percentage of patients in the non-BOS group who developed a decrease in sGaw or FEF25-75.