

Airway Injury in Swine Confinement Workers

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■ **Objective:** To determine whether work-related respiratory symptoms are indicative of underlying lung disease among swine confinement workers and, if so, to identify whether respiratory changes were more indicative of airway or of interstitial lung injury.

■ **Design:** Nested case-control study within a population-based longitudinal study.

■ **Setting:** University hospital.

■ **Participants:** Study participants were randomly selected from a group of 207 swine confinement workers followed longitudinally. Of these, 43 workers with respiratory symptoms were identified, and 31 were randomly selected for inclusion in this study. Three control groups (swine confinement workers, neighbor farmers, and blue collar workers) without work-related respiratory symptoms were frequency-matched by age, sex, and smoking status to the symptomatic swine confinement workers.

■ **Measurements:** Spirometry and lung volumes, diffusing capacity of carbon monoxide, chest radiograph, methacholine airway challenge, and bronchoalveolar lavage were done. An endobronchial biopsy was done in the last 27 participants evaluated.

■ **Results:** Although spirometric measures of airflow were similar between the symptomatic swine confinement workers and the three control groups, swine confinement cases were found to have significant elevations in residual volume (126.5 ± 28.2 L) when compared to swine confinement controls (115.4 ± 38.4 L; $P \leq 0.05$), neighborhood farmer controls (101.1 ± 29.4 L; $P \leq 0.005$), and blue collar controls (106.4 ± 30.4 L; $P \leq 0.05$). Swine confinement cases also had an enhanced airway response to inhaled methacholine and had thickening of the epithelial basement membrane of the lobar bronchi. No parenchymal injury was observed in the swine confinement cases.

■ **Conclusions:** Our findings suggest that swine confinement workers who have work-related respiratory symptoms are at risk for airway, but not parenchymal, lung injury, and that spirometry may not accurately reflect the extent of airway injury.

Approximately 75% of swine produced in the United States are raised in confinement buildings. These confinement buildings (Figure 1) are self-contained structures that are fully enclosed and that usually have minimally effective ventilation systems. Swine are housed in individual pens, are fed through an automatic feeding system that generates respirable grain dust, and stand on a slotted floor so that their urine and feces can collect in a manure pit directly under the confinement unit. Swine confinement operators grind grain, check on the nutritional and health status of the hogs, and maintain and clean the equipment in the confinement unit.

Swine confinement operators appear to be at increased risk for developing symptoms and signs suggestive of asthma and bronchitis (1-5) that are related to specific exposures in the confinement buildings (6, 7). Importantly, swine confinement operators have statistically significant decrements in airflow across a work shift (6), and one report (5) suggests that swine confinement operators have restrictive physiology when compared to rural nonfarming control subjects. Thus, routine measures of airflow (that is, spirometry) do not appear to adequately clarify the physiologic correlate of the work-related symptoms in these workers. Moreover, the finding of restrictive physiology in swine confinement operators (5) suggests that these workers may have parenchymal, as well as airway, injury to their lungs.

To further characterize the clinical relevance of work-related respiratory symptoms in swine confinement operators, we compared symptomatic swine confinement operators to three asymptomatic control groups—swine confinement operators, neighborhood farmers, and blue collar workers—to determine whether these work-related respiratory symptoms were indicative of airway or parenchymal lung injury.

Methods

This investigation was designed as a nested case-control study within a larger, population-based, longitudinal study. Cases and controls were systematically selected from the ongoing longitudinal study so that results from the case-control study could be generalized to subjects in the longitudinal investigation. The population-based, longitudinal cohort was established in 1984 and consisted of a random sample of all swine confinement operators in Eastern Iowa that was stratified by geographic locale. After the 207 swine confinement operators were selected, 158 neighborhood farmers were matched by geographic locale to the group of swine confinement operators. For neighborhood farmers, no swine confinement exposure was permitted to have occurred for 5 years before beginning the study. A referent cohort of 150 blue collar workers was established from small industries (computer service, an electronics plant, and the postal service) in or near Iowa City where employees worked in nondusty, irritant-free jobs. For blue collar workers, work in farming must have ended 5 years before the study.

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Swine Confinement Cases

Of the 207 swine confinement operators, 43 met the case definition of work-related respiratory symptoms; they experienced chest tightness or difficulty breathing on returning to work (2 days after last exposure), frequent episodes of either chest tightness or dyspnea while working in a confinement building or at least two delayed constitutional symptoms (fever, chills, muscle aches, weakness, cough, chest tightness, or dyspnea) occurring 2 to 6 hours after exposure to dust in a confinement building. Thirty-one swine confinement operators were randomly selected from eligible swine confinement cases of whom 9 (29%) had chest tightness or difficulty breathing after returning to work, 17 (55%) had frequent episodes of chest tightness or dyspnea while working in a confinement building, and 17 (55%) had delayed constitutional symptoms several hours after exposure to dust.

Control Subjects

Subjects who did not fit the case definition were selected from each of the three cohorts: swine confinement operators, neighborhood farmers, and blue collar workers. For each cohort, controls were randomly selected from the appropriate age (using 10-year intervals), sex, and smoking status (never, former, or current) strata, such that each control group had a similar number of subjects because the cases and the frequency distribution of age, sex, and smoking status was also similar across the four study groups.

Noninvasive Testing

All participants had chest radiographs that were clinically interpreted by a staff radiologist who was blinded to the exposure history of our study subjects. Pulmonary function tests were done according to standard protocols and the American Thoracic Society guidelines (8). Standard spirometry and a single-breath diffusing capacity test were done using a Medical Graphics 1070 system (St. Paul, Minnesota) and lung volume was measured using a body plethysmography Medical Graphics 1085 system. The predicted normal values used were those of Morris and colleagues (9) for spirometry; Goldman and Becklake (10), for lung volumes; and Van Ganse and associates (11), for diffusing capacity.

Methacholine Aerosol Challenge

A methacholine aerosol challenge was done according to the procedure outlined by the American Academy of Allergy Committee on Standardization of Bronchoprovocation (12). The provocation dose (PD) producing a 10% decrease in the forced expiratory volume in 1 s (FEV_1) ($PD_{10} FEV_1$) was calculated by linear interpolation (12). In addition, the slope of the dose-response curve for methacholine was calculated by dividing the percent decline in FEV_1 by the cumulative dose of methacholine. The slope of the dose-response curve for meth-

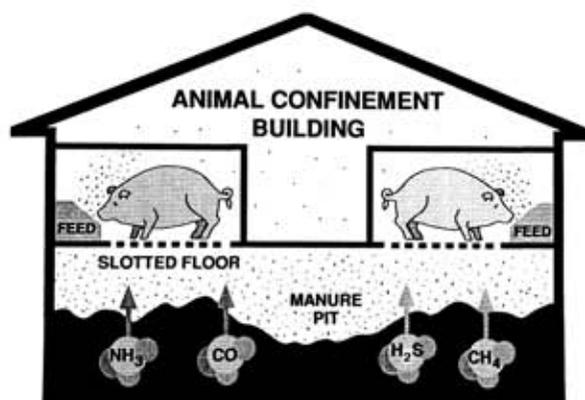


Figure 1. A cross-sectional view of a swine confinement building. The hogs are raised in enclosed pens directly above a manure pit. Note the gases (NH_3 , CO , H_2S , and CH_4) and dusts (manure and grain) present in the confinement building. The confinement workers would spend most of their time between the individual pens with direct access to the hogs and associated equipment. CH_4 = methane; CO = carbon monoxide; H_2S = hydrogen sulfide; NH_3 = ammonia.

acholine has been shown to correlate nearly perfectly ($r > 0.99$; $P = 0.001$) with the $PD_{20} FEV_1$ among asthmatic patients (13) and also permits the quantitative evaluation of the non-specific airway reactivity among all participants (nonasthmatic and asthmatic persons).

Bronchoalveolar Lavage and Endobronchial Biopsy

Bronchoscopic examination and lavage were done on all study subjects by using our standard method (14). Endobronchial biopsies were done on the last 27 study participants evaluated under this protocol. In all instances, two endobronchial biopsies of the right upper, right lower lobe carina were obtained using the flexible bronchoscope and a 3-mm alligator forceps. The biopsy material was immediately placed in a 10% formalin solution and embedded in paraffin. Twenty serial 4- μ m sections of each specimen were stained with hematoxylin and eosin (18 slides) or using Giemsa methods (2 slides) and examined by the same pathologist in a blinded fashion. For each specimen, the presence of squamous metaplasia, endobronchial edema or scarring, and denuded epithelia was noted. In addition, the width of the basement membrane was measured and the quantity of inflammatory cells (per high power field) within the epithelium and in the adjacent subepithelial tissues were estimated by averaging five representative microscopic fields.

Table 1. Demographic, Clinical Characteristics, and Farming History of All Study Subjects*

Characteristic	Swine Confinement Cases (n = 31)	Swine Confinement Controls (n = 34)	Neighborhood Farmer Controls (n = 31)	Blue Collar Controls (n = 32)
Age, y	37.7 \pm 10.0	39.4 \pm 10.4	37.5 \pm 10.4	36.1 \pm 7.9
Male, n (%)	28 (90)	30 (88)	28 (90)	29 (91)
Female, n (%)	3 (10)	4 (12)	3 (10)	3 (9)
Smoking history, n (%)				
Never	17 (55)	21 (62)	18 (58)	16 (50)
Former	6 (19)	8 (24)	5 (16)	7 (22)
Current	8 (26)	5 (15)	8 (26)	9 (28)
Pack-years of cigarette smoking	6.6 \pm 14.1	5.3 \pm 11.9	5.9 \pm 12.8	15.8 \pm 23.2
History of swine confinement work, n (%)	31 (100)	34 (100)	5 (17)	2 (6)
Confinement, y	12.2 \pm 12.6	10.6 \pm 4.4	3.5 \pm 13.3	0.1 \pm 0.4
History of farming work, n (%)	31 (100)	34 (100)	31 (100)	6 (19)
Farming, y	18.3 \pm 10.4	20.4 \pm 9.8	19.1 \pm 9.9	0.3 \pm 0.6

* Values in the table are expressed as the mean \pm SD for continuous variables and as n (%) for categorical variables.

Statistical Analysis

Univariate comparisons were made to determine whether demographic or clinical variables differed among symptomatic swine confinement operators and the three control groups. Because each of these control groups were frequency matched to the cases by age (in decades), sex, and smoking status, comparisons of symptoms and clinical outcomes were made while using multivariate techniques (either linear or logistic regression) to control for each of these potentially influential factors (15). Although the data presented in the tables represent the "raw" values, the tests to assess statistical significance have, in all cases, controlled for age (in decades), sex, and smoking status. Of note, the age, sex, and smoking status adjusted statistical comparisons were quantitatively similar to the crude differences and in none of the comparisons did any of the matching variables prove statistically significant.

Results

The demographic characteristics and work histories of our study subjects are presented in Table 1. By virtue of the study design, the age, sex, and smoking status of the four study group were all quite similar. Of note, over 50% of each study group had never smoked. However, the blue collar controls had a more intense smoking history (that is, more pack-years) than the other study groups. Very few of the neighborhood farmers and blue collar workers had ever worked in the confinement setting (Table 1). The neighborhood farmers had a similar length of farming compared with the confinement operators, but the blue collar referent group had a minimal (and remote) farming history.

Table 2 shows that swine confinement cases had far more work-related symptoms and chronic respiratory complaints than did study participants in our three control groups. Given our case definition, these results were also expected. It was evident, however, that some of our swine confinement controls and neighborhood farmer controls had respiratory symptoms. We did not administer a work-related symptom questionnaire to our blue collar controls.

Spirometric measures of airflow were similar between

swine confinement cases and each of the three control groups (Table 3). Interestingly, when compared with each of the control groups, swine confinement cases tended to trap air as evidenced by the significant elevation in residual volume (Table 3). Although the total lung capacity (TLC) was significantly higher in swine confinement cases when compared with blue collar controls, this was entirely due to the high residual volume among swine confinement cases. Importantly, no differences were noted in gas exchange (diffusing capacity of carbon monoxide or in alveolar-arterial difference in partial pressure of oxygen) between swine confinement cases and any of the three control groups.

When compared with the three control groups, swine confinement cases tended to have an enhanced airway response to methacholine, a nonspecific bronchoconstrictor (Table 4). Significantly more swine confinement cases (48%; $P \leq 0.05$) had at least a 20% decline in FEV₁ when challenged with methacholine than did swine confinement controls (27%), neighborhood farmer controls (19%), or blue collar controls (28%). In general, swine confinement cases required a lower dose of methacholine to result in a 10% decline in FEV₁ (PD₁₀ FEV₁) and had more loss in FEV₁ for each unit dose of methacholine (dose-response slope). However, these differences were not statistically different when swine confinement cases were compared with each of the three control groups.

None of our study participants (cases or controls) had evidence of acute lung disease, chronic interstitial changes, or pulmonary emphysema identified on the chest radiograph. The bronchoalveolar lavage (BAL) cellularity was similar across all study groups, and there was no evidence of alveolitis in the swine confinement cases. Swine confinement cases had a normal cellular profile with a mean of 84% macrophages, 9% lymphocytes, 6% neutrophils, and less than 1% eosinophils. The BAL cell profile was similar in each of the control groups. The slight increase in the neutrophil content

Table 2. Respiratory Symptoms by Study Group

Symptom	Swine Confinement Cases (n = 31)	Swine Confinement Controls (n = 34)	Neighborhood Farmer Controls (n = 31)	Blue Collar Controls (n = 32)
Work-related, %				
Cough	82	32*	31*	NA†
Phlegm	52	13*	8*	NA
Chest tightness	55	12*	0*	NA
Dyspnea	48	16‡	0*	NA
Fatigue	52	10*	19‡	NA
Myalgias	33	10‡	39	NA
Arthralgias	22	7‡	15	NA
Headache	41	19	8‡	NA
Chronic symptoms, %				
Cough	36	9‡	10‡	9‡
Phlegm	52	15*	10*	6*
Wheeze	74	24*	37*	41*
Dyspnea	13	3	10	16

* $P \leq 0.005$. Swine confinement cases compared with each of the three control groups. All comparisons are controlled for age, sex, and smoking status.

† NA = not asked.

‡ $P \leq 0.05$. Swine confinement cases compared with each of the three control groups. All comparisons are controlled for age, sex, and smoking status.

Table 3. Comparison of Pulmonary Function between Symptomatic Swine Confinement Workers and Each of the Three Control Groups*

Variable	Swine Confinement Cases (n = 31)	Swine Confinement Controls (n = 34)	Neighborhood Farmer Controls (n = 31)	Blue Collar Controls (n = 32)
FEV ₁	105.8 ± 16.4	107.4 ± 14.1	112.0 ± 12.3	105.0 ± 16.6
FVC	107.3 ± 12.4	107.3 ± 12.6	111.3 ± 12.8	103.8 ± 12.8
FEV ₁ /FVC ratio	74.6 ± 7.6	76.3 ± 7.9	76.6 ± 7.3	78.1 ± 8.0
TLC	120.4 ± 13.8	118.0 ± 14.4	115.0 ± 13.9	111.4 ± 11.3†
RV	126.5 ± 28.2	115.4 ± 38.4†	101.1 ± 29.4‡	106.4 ± 30.4†
DL _{CO}	113.0 ± 12.8	112.9 ± 14.9	116.5 ± 13.7	108.6 ± 14.7
PA-a O ₂ difference	15.4 ± 16.7	13.0 ± 14.9	13.8 ± 12.2	13.9 ± 12.5

* Pulmonary function values are expressed as the percent predicted (mean ± SD) except for the FEV₁/FVC ratio and the A-a O₂ difference, which are expressed as absolute values. All comparisons are controlled for age, sex, and smoking status. *P* values were computed by comparing the swine confinement cases to each of the three control groups. FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; TLC = total lung capacity; RV = residual volume; DL_{CO} = diffusing capacity of carbon monoxide; PA-a O₂ difference = alveolar-arterial difference in partial pressure of oxygen.

† *P* ≤ 0.05.

‡ *P* ≤ 0.005.

was probably caused by the relatively wide diameter (5.9 mm) of the bronchoscope used for these lavages and clearly was not associated with either respiratory symptoms or work in a swine confinement operation.

The results of the endobronchial biopsies are shown in Table 5. Whereas inflammatory cells in both the epithelium and the subepithelial region were similar in each of the study groups, swine confinement cases had thickening of the basement membrane of the lobar bronchi when compared with either neighborhood farmers (*P* = 0.02) or blue collar workers (*P* = 0.04), but not when compared with swine confinement controls (*P* > 0.2). In addition, no difference was noted in the presence or extent of squamous metaplasia, endobronchial edema or scarring, or denuded epithelia between swine confinement cases and any of our control groups (data not shown).

Discussion

Our results suggest that swine confinement operators who have work-related respiratory symptoms appear not to have parenchymal lung injury but do have airway injury manifested by air trapping, an enhanced airway response to methacholine, and thickening of the basement membrane on endobronchial biopsy. Our findings support epidemiologic observations that swine confinement work is associated with asthma and bronchitis and indicate that respiratory symptoms that occur in asso-

ciation with these exposures appear to be indicative of injury limited to the airways.

Our findings suggest that symptomatic swine confinement operators have evidence of early airway injury that may not be readily apparent using spirometric measures of lung function. Although symptomatic swine confinement operators had normal spirometric measures of airflow, they tended to trap air and have increased airway reactivity when compared with each of our control groups. Moreover, endobronchial biopsies identified thickening of the basement membrane of the airway epithelia among symptomatic workers. Such thickening of the basement membrane has been shown to be an early (16) and consistent (16-20) histologic feature of asthma. The absence of inflammatory cells in the stratified epithelia and subepithelial region of the lobar bronchi was not unexpected because these histologic findings are not uniformly present in asthmatic patients (16-20). Thickening of the bronchial wall may, in and of itself, place the airway smooth muscle at a mechanical disadvantage and predispose to bronchospasm (21).

Our findings suggest that inhaled agents in the confinement setting that cause work-related changes in lung function (6, 7) may also result in other manifestations of airway injury, such as air trapping, enhanced response to methacholine, and airway inflammation. Several potential airway pathogens present in the swine confinement environment could account for the development of

Table 4. Comparison of Airway Response to Inhaled Methacholine between Swine Confinement Cases and Each of the Three Control Groups*

Variable	Swine Confinement Cases (n = 31)	Swine Confinement Controls (n = 34)	Neighborhood Farmer Controls (n = 31)	Blue Collar Controls (n = 32)
≥ 20% decline in FEV ₁ , n (%)	15 (48.4)	9 (26.5)†	6 (19.4)†	9 (28.1)†
PD ₁₀ FEV ₁	45.3 ± 54.1	71.1 ± 57.8	80.3 ± 67.7	71.0 ± 59.0
Dose-response slope	6.3 ± 16.9	1.4 ± 2.5	0.8 ± 1.4	2.4 ± 8.9

* For all comparisons, swine confinement cases were individually compared with each of the asymptomatic control groups: swine confinement workers, neighborhood farmers, and blue collar workers. *P* values were calculated using multivariate models while controlling for age, sex, and smoking status. FEV₁ = forced expiratory volume in 1 second; PD₁₀ FEV₁ = provocative dose of methacholine to cause a 10% drop in FEV₁.

† *P* ≤ 0.05.

Table 5. Comparison of the Endobronchial Biopsy between Swine Confinement Cases and Each of the Three Control Groups*

Biopsy Result	Swine Confinement Cases (n = 5)	Swine Confinement Controls (n = 6)	Neighborhood Farmer Controls (n = 8)	Blue Collar Controls (n = 8)
Stratified epithelium infiltration				
Neutrophils	1.6 ± 2.1	1.3 ± 2.4	0.3 ± 0.7	2.3 ± 4.8
Eosinophils	1.2 ± 1.3	1.2 ± 1.6	1.5 ± 1.4	1.3 ± 1.8
Submucosal infiltration				
Neutrophils	1.6 ± 1.1	2.8 ± 3.9	1.3 ± 1.3	3.6 ± 8.7
Eosinophils	6.4 ± 7.7	4.2 ± 2.9	4.0 ± 5.0	4.4 ± 5.7
Mast cells	1.8 ± 1.8	2.7 ± 3.2	2.4 ± 2.3	1.5 ± 1.7
Basement membrane thickness, (μm)	14.4 ± 2.6	11.3 ± 8.0	8.3 ± 5.2†	8.8 ± 4.1†

* Values in the table are expressed as the mean ± SD. For all comparisons, swine confinement cases were individually compared with each of the asymptomatic control groups: swine confinement workers, neighborhood farmers, and blue collar workers. *P* values were calculated using multivariate models while controlling for age, sex, and smoking status.

† *P* ≤ 0.05.

airway disease (1, 22-24). The level of total dust ranges from 5.0 to 7.5 mg/m³, and the respirable fraction of dust appears to range from 7% to 30% of the total dust content. Bacteria and fungi heavily contaminate these dusts, and endotoxin appears to be concentrated in the respirable fraction of these dusts (24). Inhaled endotoxin has been shown to stimulate airflow obstruction in asthmatic (25) and normal study (26) subjects. Moreover, recent studies suggest that among those exposed to cotton dust (27-29), respirable levels of endotoxin are more predictive of respiratory impairment (symptoms and airflow obstruction) than are concentrations of airborne dust. A similar relationship has been observed in other environments, such as poultry houses (30), where exposure to complex organic dusts is thought to initiate a response in the airways that is characterized by acute and immediate airflow obstruction. Whether endotoxin is related to the development of other manifestations of airway disease (air trapping and hyperreactive airways) remains unknown. Because these dusts also contain ammonia (22-24), the dust particle may actually act as a vehicle to bring ammonia (which would normally solubilize in the upper airway) in contact with the epithelia of the smaller, more distal airways. Clearly, ammonia can have profound and lasting effects on airway epithelium (31). If direct contact is made with epithelium of the smaller airways, ammonia may help cause airway disease in confinement workers. Alternatively, grain dust, the principal component of swine confinement dust, can stimulate macrophages to release chemotactic factors that recruit neutrophils and other inflammatory cells to the site of particle deposition (32).

Although the animal confinement unit is a relatively new advance in agriculture (within the past 15 to 20 years), it is becoming increasingly clear that exposures within these units can cause airway disease and that interventions are needed to diminish dust exposure in these facilities. Ideally, ventilation systems and comprehensive methods to decrease dust levels would be engineered into these structures. However, routine cleaning of the confinement unit, use of dust masks, and proper management of manure pits, would improve the working conditions in these confinement units. Our findings indicate that further attention must be placed on new approaches to the exposures and their dose-response relationship with measures of airway injury to guide prevention and treatment of acute airway disease

among swine confinement and other agricultural workers.

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