

The Respiratory Inflammatory Response to the Swine Confinement Building Environment

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Abstract

Swine confinement facility workers often develop respiratory problems secondary to their work, including acute bronchitis, the asthma-like syndrome, exacerbation of asthma, chronic bronchitis and mucous membrane irritation syndrome. Organic dust toxic syndrome is seen in these workers as well. Swine confinement barns are characterized by the presence of multiple factors that can cause respiratory tract and systemic inflammation symptoms, including dust, endotoxin and ammonia. Investigators have found evidence of inflammation characterized by increased numbers of neutrophils, macrophages and to a lesser degree, lymphocytes in both naïve subjects and swine confinement building workers. Interestingly, this inflammation is most pronounced in subjects with no prior exposure to this environment. This finding raises the question of whether or not tolerance to endotoxin or other substances in this environment is induced after repeated exposures. There is still a great need for implementation of feasible interventions for reduction of the risk of having symptomatic respiratory disease as a result of working in a swine confinement facility.

Introduction

Increasing numbers of pigs are raised indoors in confinement buildings in the United States, in Europe and elsewhere. This method of raising pigs has economic advantages, primarily by reducing labor costs, and has become common practice during the past 20 years. On large farms, caring for the pigs housed in this type of facility, which is known as a swine confinement facility, is a full-time occupation for the owners and/or employees of the farm. It has been estimated that in the U.S., 250,000 people work in swine confinement facilities. These persons include workers responsible for the daily care of the animals, veterinarians and individuals that perform specialized operations such as cleaning the barns.

It has been known for over 20 years that exposure to the confinement barn environment can cause acute and chronic respiratory symptoms in many of the workers who care for the hogs (1-3). The majority of the complaints fall into the category of airway disease. The symptoms either represent an asthma-like syndrome, bronchitis, or exacerbation of pre-existing asthma (4). The respiratory problems associated with hog confinement facilities are a common reason for workers to seek medical attention and benefits through the workers' compensation system or for them to take legal action against employers (5). Also, a large but poorly documented number of people leave the industry because they have developed respiratory complaints secondary to

working in the swine confinement building environment.

Recent research has led to a better understanding of causative agents in this complex environment as well as the mechanisms by which they act. This work is very important because it will likely lead to the development of methods by which the key exposures can be monitored and controlled. Important findings include the observation that high endotoxin levels in this environment are associated with the presence of respiratory complaints in the workers. Laboratory research has shown that endotoxin is a potent stimulus for eliciting inflammatory responses in the respiratory tract (6-9). In addition, it has been found that low level endotoxin exposure induces tolerance to subsequent endotoxin challenges (10,11).

Swine confinement workers have evidence of lower respiratory tract inflammation that is consistent with an irritant response (12, 13). Interestingly, swine confinement building workers have fewer inflammatory cells in their upper and lower respiratory tract than do naïve subjects after an acute exposure to the swine confinement facility environment. The observation that hog farmers have a low prevalence of sensitization to occupational and domestic allergens also of note (14). It is possible that chronic, low level endotoxin exposure down regulates the inflammatory response in the airway of swine confinement workers secondary to the tolerance phenomenon.

Interventions such as use of respirators and spraying of canola oil to reduce dust has been shown to reduce evidence of upper respiratory tract inflammation and a cross-shift drop in pulmonary function. Unfortunately, compliance with respirator use is not high in the swine confinement worker population. There is a need for cost effective innovations that reduce the levels of the substances in this environment that cause respiratory tract inflammation.

Swine Confinement Building Environment

The swine confinement building is a very complex environment (15). The air in these buildings is characterized by the presence of a large variety of gases as well as high levels of dust. Approximately 160 different gases have been identified in the ambient air of confinement barns. While many of these gases contribute to the odor associated with swine production, most are present only in trace amounts and have not been linked to respiratory illness in workers. A small number of gases have been found to contribute to human respiratory illness, including ammonia, hydrogen sulfide, carbon dioxide and methane.

The acute and chronic airway symptoms experienced by the workers have been linked to ammonia levels, but not to hydrogen sulfide, carbon dioxide or methane levels. Ammonia is released into the air of swine confinement building from the breakdown of urea in the urine of the animals. Ammonia levels in the air of swine confinement barns rarely reach the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 25 ppm. However, it was recently reported that there is an association between ammonia levels exceeding 7.5 ppm and a decrement in FEV1 in swine confinement workers (16). Other investigators have made similar observations (17). Reasons for this apparent lowering of the threshold of response in workers is the presence of multiple agents in the environment of these

facilities that are additive or possibly multiplicative in their effects. Ammonia levels often exceed 7.5 ppm, especially in poorly managed buildings, when ventilation is decreased in cold weather or secondary to ventilation system malfunction. However, higher ammonia levels are often found together with increased endotoxin and total dust levels. It is likely that the multiple exposures in these facilities lowers the threshold limit for health effects from any one toxic exposure.

The hog confinement barn can be a dusty environment, with total dust levels ranging from 1.9 to 30.0 mg/m³ having been reported (15, 18-20). The dust is heterogeneous, with feed particles and swine fecal material being the most prevalent substance by weight. Other components of the dust include swine dander, molds, insect parts and mineral ash. The dust particles include 5-50 % in the respirable range. There is evidence that total dust levels should be kept under 2.5 mg/m³ (18). Research by a number of investigators has shown that high levels of dust increases the risk for respiratory disease (16, 18, 21). Also, dust particles adsorb ammonia, allowing the ammonia to travel deep into the respiratory tract.

Finally, the dust is rich in endotoxin (16-18,21). Both values for total dust and endotoxin often exceed the ACGIH TLV-TWA level for organic dust of 10 mg/m³ and for endotoxin of 10 ng/m³. Endotoxin, a potent inflammatory agent, is a component of the cell membrane of Gram negative bacteria. It can be found in large amounts in this environment due to the number of coliform bacteria present in the animal waste. High endotoxin levels have been found in hog dust in several studies. It appears to be an independent risk factor for lung disease in swine confinement workers (21, 22).

Respiratory and Systemic Responses to the Swine Confinement Facility Environment

Lower Respiratory Tract Inflammation

Those working for two or more hours daily for more than six years are at greatest risk for developing chronic respiratory symptoms (16). The chronic respiratory complaints of animal confinement workers resemble those of other types of workers exposed to organic dusts such as cotton dust. At a recent consensus conference the term "asthma-like syndrome" was given to the airway disorder characterized by cough, chest tightness, dyspnea and wheezing without airway obstruction on pulmonary function testing which is commonly seen in animal confinement workers (23). Some workers with this problem have mild airway obstruction. This syndrome is most pronounced after return to work after a weekend or vacation, much like byssinosis. Symptoms occur in about 25% of workers and are associated with the number of hours worked per day. After being first identified in swine veterinarians, it was recognized that the asthma-like syndrome also occurs commonly in a more chronic form in subjects who provide daily care for the pigs in confinement barns (1, 24-26). Cross-shift decrements in FEV₁, FVC and FEF₂₅₋₇₅ have been identified and found to correlate with endotoxin exposure in the workplace and with follow-up time (22).

The natural history of the asthma-like syndrome is not well documented at this time. However, it is known that acute symptoms can develop within days of starting to work in this environment.

More commonly, early respiratory complaints develop after several months of employment in a swine confinement facility. It is well known within the industry that some workers leave this environment because of respiratory symptoms within weeks or months of employment. Thus, one must take the healthy worker effect into consideration when interpreting data on persons who have been employed in this industry for more than several months. Unfortunately, there is no quantitative information published about attrition in the hog industry secondary to respiratory symptoms.

Important unanswered questions concerning the asthma-like syndrome include whether or not it can progress to severe, irreversible airway disease over a lifetime of work in this setting. This outcome can occur in asthma but as yet there is little evidence that it is to be expected in swine confinement workers with the asthma-like syndrome. Only a small group of workers has been described which developed severe obstructive airways disease (27). It is possible that workers leave the industry as they begin to become symptomatic, thus protecting themselves from further insult. Alternatively, there may be a process that serves to limit the inflammatory response in the respiratory tract that could otherwise lead to chronic airway obstruction.

The asthma-like syndrome must be distinguished from asthma. It is of note that there is little evidence that work in hog confinement buildings can cause asthma (4). The airway inflammation seen in hog confinement workers is characterized by the presence of increased numbers of neutrophils and macrophages, not eosinophils (Table 1). Persons who suffer from underlying asthma may be at risk of experiencing exacerbations of this disorder secondary to work in swine confinement buildings. This problem is not yet well understood.

Chronic bronchitis is a common complaint in swine confinement workers (4,23). It has been estimated that 25% of workers commonly complain of the cough and sputum production characteristic of this disorder. A large number of the workers have intermittent symptoms suggesting the presence of acute bronchitis. Bronchitis symptoms are also linked to duration of work in the hog confinement barns and likely represent a variation in the spectrum of or a different stage in the progression of irritant responses to endotoxin, dust and ammonia in the environment. It not known if repeated episodes of acute bronchitis eventually leads to chronic bronchitis. Also, there is overlap in the symptoms of chronic bronchitis with an acute exacerbation and those of the asthma-like syndrome. Symptoms are more common in workers who also smoke cigarettes and the effects of cigarettes. This work environment and cigarette smoke exposure appear to be additive in terms of risk for developing bronchitis. Severe airway obstruction related to chronic bronchitis appears to occur only in swine confinement workers who also smoke cigarettes (27).

The symptoms of the asthma-like syndrome and chronic bronchitis are similar to one another. Most investigators who study swine confinement workers have considered workers with these disorders as one group of symptomatic workers. A number of non-invasive and minimally invasive techniques have been applied to study the lower respiratory tract. Methacholine challenge testing has demonstrated an enhanced airway response to inhalation of methacholine (12, 28). Bronchoscopy with bronchoalveolar lavage were conducted in a comparative study of both symptomatic and asymptomatic subjects working in swine confinement buildings (12). Findings include visible evidence of airways inflammation on bronchial wall biopsy in both

symptomatic and asymptomatic subjects despite normal spirometric and bronchoalveolar lavage findings. Lung volumes were notable for the presence of increased residual volumes in that study. Another group of investigators found lymphocytes and neutrophils to be increased in swine confinement workers, but not eosinophils (29). They also saw evidence of macrophage activation in the subjects. A normal cell profile with the exception of a slight increase in the number of macrophages has also been identified by use of induced sputum to assess the lower respiratory tract of swine confinement workers (13). A group of Swedish investigators has also published data on bronchoalveolar lavage in swine confinement workers (30). They also found that the number of neutrophils was increased compared to a control group, but found that the macrophage and lymphocyte numbers were in the normal range (Table 1).

Normal volunteers without previous exposure to this environment develop cough, dyspnea, nasal stuffiness, headache, fever and chills, malaise, nausea and eye irritation after exposure lasting several hours. (20, 31-33). Such an exposure has also been shown to induce airway hyperresponsiveness in normal in healthy subjects (31-34). Bronchoalveolar lavage done in naïve subjects exposed to the swine confinement facility environment by Larsson and colleagues revealed the presence of greatly increased numbers of neutrophils compared to a reference group of office workers (Table 1). There was a smaller but still significant increase in the number of macrophages, eosinophils and lymphocytes in the naïve subjects reported in this study. Neutrophils, lymphocytes and macrophages were also increased in a recent study (34). Another group found a two-fold increase in numbers of lymphocytes in the lower respiratory tract in response to acute swine dust inhalation (35). This increase was explained in part by increased numbers of activated T-lymphocytes. The white blood cell count was also increased to between 10 and $15 \times 10^9/L$.

Acute exposure of healthy, nonatopic volunteers to the swine confinement barn environment also has been shown to cause a significant reduction in peak expiratory flow rates and FEV1 (20, 32, 34). A transient increase in bronchial reactivity in these subjects has also been shown in a number of studies.

Analysis of the lavage fluid revealed the presence of several inflammatory cytokines and chemokines in increased amounts within 24 hours of a hog confinement exposure including interleukin 8, interleukin-6, and interleukin-1 alpha and beta (20,34) . These mediators have been shown to participate in recruitment of neutrophils and other inflammatory cells to the lower respiratory tract as well as to peripheral blood and in causing the fever and constitutional symptoms seen in these subjects. The mediators of inflammation likely also help cause the respiratory symptoms observed.

Organic Dust Toxic Syndrome

Organic dust toxic syndrome (ODTS) is a febrile illness characterized by malaise, myalgias, chest tightness, headache and nausea after exposure to large amounts of organic dust (36). Symptoms appear 4-8 hours after exposure occurs and can last for several days. Prior sensitization is not required. During the acute illness laboratory findings include a leukocytosis with a predominance of neutrophils and a left shift, a finding ODTS shares with acute

hypersensitivity pneumonitis. However, ODTS is characterized by an unremarkable chest X-ray, normal arterial blood gases and normal pulmonary function tests. It is however associated with a profound neutrophil influx to the lower respiratory tract, as demonstrated by bronchoalveolar lavage. The symptoms of ODTS are self-limiting but may have respiratory sequelae in terms of risk for having chronic bronchitis (37).

ODTS was originally described after silo-unloading but has subsequently been identified after a variety of exposures to organic dust (38). It is likely that endotoxin exposure is the cause of the signs and symptoms of ODTS because they can be reproduced by experimental endotoxin exposure (8). Episodes of ODTS are reported in 6.4 to 34% of hog farmers (39-41). It is not known if having had ODTS while working in the hog barn increases risk for developing airway disease while working in that setting.

There is a febrile response to grain dust, another heterogenous substance which is also rich in endotoxin. This response, a form of ODTS, is more likely to appear in new workers or those who have recently spent time away from the workplace (42). It is not yet known if the same temporal pattern is true for persons exposed to the swine confinement building environment.

Upper Respiratory Tract Inflammation

The complex of nasal, eye and throat complaints found in animal confinement workers has been called mucous membrane inflammation syndrome. Nasal symptoms are reported by approximate 50% and sinusitis by approximately 25% of swine confinement workers. Acute changes in the nose after exposure to the hog barn environment have been studied fairly extensively but less is known about acute and chronic pathophysiological changes in the sinuses. Nasal lavage findings in naïve subjects and workers exposed to this environment included increased numbers of neutrophils and increased levels of interleukin-8, interleukin 6. Use of respirators has recently been shown to reduce nasal inflammation as well as the cross-shift reduction in FEV1 (43).

Effects of Single and Repeated Endotoxin Exposure in the Laboratory Setting

Endotoxin exposure in humans has been shown to cause chest tightness and airway irritation in over half of normal naïve subjects (7, 8). Also, approximately half of subjects develop fever. Acute endotoxin exposure is associated with the presence of increased numbers of inflammatory cells in the lower respiratory tract. It has been shown that challenging normal control subjects with endotoxin causes a dose-dependent increase in the numbers of total cells and neutrophils recovered from the lower respiratory tract (7).

Leukocyte recruitment to the lung is a complex phenomenon, which involves endothelial cell activation and expression of endothelial cell-derived adhesion molecules, leukocyte activation and expression of leukocyte-derived adhesion molecules, leuko-endothelial cell adhesion, leukocyte diapedesis and directional leukocyte migration beyond the vascular compartment via chemotactic gradients (44-46). Many of these aspects of leukocyte recruitment have not been extensively studied specifically after endotoxin challenge. The presence of the protein

chemoattractant IL-8 in the airways after endotoxin exposure has been measured. IL-8 has been shown to be present in increased amounts in bronchoalveolar lavage fluid after challenge with endotoxin in normal subjects (7). IL-1 and TNF are important to neutrophil migration to the lung because they can induce production of endothelial adhesion molecules necessary for neutrophil recruitment (45). Interestingly, tolerance to neutrophil recruitment to the airways and the release of IL-1 beta and TNF alpha can be induced by daily challenge with sublethal amounts of endotoxin both in vivo and in vitro (47-49).

The causation of fever after endotoxin challenge has been well studied. Acute exposure to endotoxin is known to cause fever by production of three known endogenous pyrogens, interferon alpha, interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-alpha) from peripheral blood monocytes. IL-6 may also play a role in causing fever after endotoxin challenge. Interestingly, tolerance to the febrile reaction and release of IL-1 beta and TNF alpha can be induced by daily challenge with sublethal amounts of endotoxin both in vivo and in vitro. Pretreatment with TNF itself can also induce endotoxin tolerance (48, 49). The anti-inflammatory protein interleukin 10 appears to play an important role in endotoxin tolerance as well, based on experiments showing upregulation of interleukin 10 production after endotoxin challenge (50).

Much more remains to be learned about endotoxin tolerance in general. In particular, there is still information missing about the application of the concept of endotoxin tolerance to the clinical setting. Little is known about the applicability of the concept of endotoxin tolerance to the human worker who is regularly exposed to endotoxin. Also, we do not know how concurrent exposure to other inflammatory substances such as ammonia affects the response to endotoxin.

Summary and Conclusions

Swine confinement facility workers commonly develop acute airway symptoms and organic dust toxic syndrome as well as the asthma-like syndrome and chronic bronchitis. These problems have a considerable negative effect on the health of the workers and their ability to remain employed in this industry. For these reasons, this environment and its individual components has been studied extensively in recent years. The swine confinement facility environment is characterized by the presence of multiple factors that can cause respiratory tract inflammation as well as systemic symptoms. Features of this environment that appear to cause symptoms in workers include dust, endotoxin and ammonia. Efforts to understand the effects of breathing these substances have included exposing naïve subjects to the environment as well as studying the workers. Findings have included evidence of airways inflammation in both groups. Interestingly, a more pronounced airways inflammatory process is seen in the naïve subjects than in the swine confinement building workers. This process consists of the presence of increased number of neutrophils, macrophages and lymphocytes as well as mediators of inflammation such as chemoattractants. It is possible that workers vary in the intensity of their inflammatory responses to this environment and that the healthy worker effect explains this observation. However, this observation also raises the question of whether or not tolerance to work in this environment is induced after repeated exposures. Tolerance to endotoxin challenge has been described using animal studies and cell culture. It is possible that tolerance to endotoxin, through

down regulation of the production of mediators of inflammation, explains the fact that the workers tested represented those who may have a less profound response to endotoxin or other substances in this environment. If the concept of tolerance to relatively low doses of endotoxin turns out to be relevant to this environment, it should be a factor to be considered in designing interventions to reduce the risk of having symptomatic respiratory disease as a result of working in a swine confinement facility. Also, the relationship between chronic endotoxin exposure in this environment and atopy needs to further explored as does the potential interaction between endotoxin and cigarette smoke.

Table 1: Cells Recovered by Bronchoalveolar Lavage in Swine Confinement Workers, Naïve Subjects Exposed to the Swine Confinement Building Environment and a Reference Group of Office Workers			
Cell Type	Number of Cells Recovered X 106/L		
	Swine Confinement Workers*	Naïve Subjects**	Office Workers*
Neutrophils	4.8	76.1	0.8
Macrophages	96.0	194	80.0
Lymphocytes	8.2	9.4	5.9
Eosinophils	0.2	1.1	0.3
* Larsson et al. (30) ** Larsson et al. (31)			

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