A PRIMATE MODEL OF BYSSINOSIS: PULMONARY CHANGES FOLLOWING INHALATION OF COTTON DUST EXTRACT

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Abstract

Pulmonary function values were determined in cynomolgus monkeys following acute bronchial challenge to cotton dust extracts and following 3 months subchronic exposure to cotton dust extracts. Monkeys reacted acutely and chronically with significant changes in pulmonary mechanics and ventilatory performance affecting both large and small airways. This is the first study that has provided clues to understanding the relationship between the acute byssinotic reaction and chronic byssinosis. This study also suggests that the monkey is ideally suited for long term longitudinal studies of byssinosis because of its similarities to man, and longevity. In addition, the ability to measure and compare pulmonary function parameters, immunologic and pharmacologic reactions by the same techniques used in man is unique to the monkey model and necessary to clinically equate the adverse affects of inhaling cotton dusts and extracts.

Introduction

The development and use in our laboratory of sensitive in vitro bioassays to study chemotaxis, histamine release and smooth muscle constriction, has resulted in several potential etiopathogenic avenues in need of in vivo study in a suitable animal model. In the last 5 years we have explored the possibility of using the rat, guinea pig, rabbit, hamster and monkey to develop an animal model of the acute byssinotic reaction. The monkey because of its similarity to man, i.e., physiologic, pharmacologic, immunologic and pathologic likeness, is obviously the most suitable. A successful animal model should provide the basis for an understanding of the relationship between the acute byssinotic reaction and chronic disease which cannot be investigated by in vitro bioassay. Also, the monkey, because of its lifespan, is the most feasible for long term longitudinal studies of chronic byssinosis.

Our studies were designed to assess immunologic, physiologic, pharmacologic and pathologic changes from baseline to 3½ months post-exposure to cotton dust extracts (CDE). In this study, pulmonary function changes in a primate animal model of byssinosis following bronchial challenge to CDE are reported. The monkey reacts both acutely and chronically to weekly exposures of CDE. The majority of monkeys exhibit immediate increased airway resistance or decreased flow when challenged to CDE. Six of eight animals demonstrate acute (2 hour) delayed reactions with greater than 200% change from baseline for resistance or 80% change from baseline for $FeF_{50\%}$. Interestingly, the subchronic study showed dramatic and interesting changes in pulmonary mechanics and ventilatory performance affecting both large and small airways. Some monkeys become hyperreactive, others tolerant and several remained non-reactive. This is the first study that has provided insight into the pathogenesis of the relationship between the acute byssinotic reaction and chronic byssinosis.

Materials and Methods

Pulmonary Function Analysis

Eight male cynomolgus monkeys (Macaca fasicularis) were randomly selected for this study. All monkeys were maintained in primate quarters at the NIOSH facility in Cincinnati, Ohio for more than one year prior to selection and had undergone routine evaluation for TB and parasites. All were young and in excellent health. The weights ranged from 4.5 to 6.0 kilograms. Each animal served as his own control for all studies described. Prior to bronchial challenges, each monkey was anesthetized with a mixture of ketamine and xylazine. They were then transorally intubated with a Magil cuffed endotracheal tube of maximum diameter, 20 or 22 french with the aid of laryngoscope. The monkey was then placed ventral side up in a variable pressure plethismograph respirator. An esophageal balloon was then placed into the lower third of the esophagus and adjusted to produce the greatest transpulmonary pressure. The esophageal and static mouth pressures were sensed with a Statham TC131 Differential Pressure Transducer. Flow at the mouth was measured by a Rudolph Pediatric Model Pneumotachograph with differential pressure obtained by a Validyne DP45 Transducer. Volume was obtained by electrical integration of flow signal using a variable timed constant with appropriate sensitivity for tidal breathing or for maximum expiratory maneuvers. The pneumotach system had been tested for frequency response, and showed a flat response up through 40 Hertz, which has been shown to be more than adequate for testing animals of this size. Pulmonary mechanics were measured by the methods described by Frank, Mead and Ferris, (1). Dynamic lung volume and flows were obtained as described by Moorman et. al.(2) and all signals were displayed on an Electronic for Medicine DR12 Recorder. Sampling and computations were performed automatically with the Telemed Computer System.

Bronchoprovocation Challenges

Bronchoprovocation challenges were performed in anesthetized monkeys to assess specific airway responsiveness. The endotracheal tube was inserted and challenges were performed by nebulizing the solution of interest with a Bird micronebulizer (output 0.065 ml/min) with positive pressure ventilation and respiration controlled by a Bird Mark 7 respirator. End inspiratory pressure was set at 20 cm H_2O. Challenges were performed with a 30 breath exposure to CDE (0.01 g/ml) and a 30 breath exposure to acetyl-B-methycholine chloride (10 g/ml). All challenges were performed in buffered saline vehicles. The response following 30 breaths of CDE or methacholine was compared to baseline (30 breaths of saline). The experimental design for the exposure studies is seen in Table I.

Cotton Dust Extract Preparation

"Standard" West Texas cotton dust (38-75 µm particle size) generously supplied to us by Dr. Robert Jacobs of Cotton, Incorporated, Raleigh, NC, was collected under controlled growing, harvest and drying conditions and then subjected to particle sizing, elemental analysis, endotoxin, microbial and fungal analysis and assessment of biological activity by numerous investigators in this country.

Cotton dust extract was prepared by immersing 1 g of "Standard" West Texas cotton dust in 25 ml pyrogen free water. The suspension was stirred for 1 hour at 4°C, clarified by centrifugation at 10,000g for 10 minutes at 4°C and filtered through a 0.45 um filter. Extracts were lyophilized and stored at -70°C. Extracts for bronchoprovocation were prepared at a final concentration of 0.01 g of crude dust per 1 ml saline (pH 6.96).

Sub-Chronic (3 month) Cotton Dust Exposures

Monkeys were anesthetized, intubated and exposed twice weekly to 30 breaths of CDE (0.01 g/ml) for 12 weeks.

Pre-Post Exposure Pulmonary Function Analysis

Baseline pulmonary function, as well as post provocation pulmonary function analysis were performed by the method of Moorman, et al. (2). Basically, an anesthetized animal was fitted with the endotracheal tube and the external pressure rapidly changed to allow forced maneuvers. Mechanical parameters were evaluated at tidal breathing. The

pulmonary function variables studied were average respiratory rate, pulmonary flow resistance, pulmonary compliance, peak expiratory flow rate, forced expiratory volume in 0.5 sec corrected for forced vital capacity, forced expiratory flow at 50%, 25% and 10% of vital capacity. These parameters were obtained at baseline (immediate and 2 hours after initial bronchial challenge to 0.01 g/ml of CDE) and post challenge, i.e., 3 months of twice weekly bronchial challenge followed by a 2 week rest period then rechallenged and pulmonary function tested immediately and at 2 hours post bronchial challenge.

Statistical Analysis of Results

Prior to the onset of exposures, all animals were evaluated for pulmonary function concentration-responses to CDE and methacholine bronchoprovocation. At the end of the 3 month exposure regimen (and after a 2 week refractory period), these same parameters were reevaluated. Differences in dose responses were analyzed using paired multiple comparisons. For each of the dependent variables paired (before-after exposure) multiple comparisons were evaluated using the non-parametric method of Kruskal-Wallace. To prove the experimental hypothesis, one would expect significantly greater post exposure dose responses to methacholine and CDE. In addition, clinical objective criteria were established to compare individual pre-and post-pulmonary function values.

Results

Individual evaluation of each animal revealed important responses that were not apparent in average group data (not shown). Some monkeys clearly demonstrated clincally important increased responsiveness while others demonstrated decreased responsiveness. Two of eight monkeys were non-responsive. The observation that some individual responses increased while others decreased dramatically lead us to employ an alternate approach which correctly described and compared the physiological responses.

An objective clinical criteria was established enabling us to identify significant responders from non-responders at each time/test period. In addition, it provided a basis for categorizing the incidence of responders in each time test period. The critical clinical criteria for placement into the responder category was either a) a 200% of base value increase in resistance or b) a decrease to 80% of base value for forced expiratory flow rates. With this criteria uniformly applied to all monkeys, pulmonary function data placed 4 (C1, 16, 30, 33) of 8 monkeys in the resistance "responder" category following pre-exposure bronchial challenge (Tables II and V). At the end of the 14 week exposure period, 2 (C1,16) of 8 monkeys continued to be placed in the "responder" category and in fact became hyperresponders while 2 of the initial responders (C30,33) had become resistant tolerant (Tables II and V). The 2 monkeys categorized as responders pre and post exposure (C1, 16) also demonstrated increased methacholine challenge responsiveness (not shown). Based upon their increased responsiveness, we termed these animals as "hyperreactive". Two monkeys (C11, 23) did not show clinically significant resistance change but did react markedly (C23--186%; C11--185% change from baseline) and became increasingly tolerant following the 3 months of exposure (Tables II and V).

Table III shows 5 (C1,11,24,30,33) of 8 animals respond acutely at 2 hrs with significant change in small airways ($FeF_{10\%}$). Four animals (C1,11,16,23) demonstrate clinically significant post-exposure changes in small airways at 14 wks. In fact, the hyperresponders (C1,16) show the greatest decrement in small airways, 57% and 27%, respectively. Three animals that were pre-exposure responders (C24,30,33) became small airway tolerant.

Four (C1,11,24,30) of eight monkeys exhibited clinically significant changes in large airway flow ($FeF_{50\%}$) at 2 hrs on initial bronchial challenge to cotton dust (Table IV). Only 1 (C11-68%) in 8 demonstrated significant large airway flow change when tested immediately after challenge to CDE (Table V). C1 and C16 exhibited large airway change of 70% and 87% on initial exposure at 2 hrs (Table IV) and at 14 wks post-exposure at 2 hrs demonstrated severe large airway involvement, C1-66% and C16-48%, respectively (Tables IV and V). Interestingly, animals C11,24 and 30 with clinically significant changes at 2 hrs pre-exposure became large airways tolerant (Table IV).

Table V shows individual resistance and flow ($FeF_{50\%}$) responses pre-and post-exposure. Resistance values (R) are shown over large airway responses $FeF_{50\%}$. Initial challenge with CDE resulted in 6 of 8 animals with increased immediate pulmonary resistance change (116-160%) (C1,11,16,23,30,33) (Table V), although none met the clinically objective criteria of 200% increase for R_L or 80% decrease of baseline for $FeF_{50-10\%}$ with one exception. The exception (C11) exhibited immediate and significant large airway decrement in $FeF_{50\%}$(68%). Another animal (C30) showed close but not clinically significant large airway changes (84%). Both of these animals (C11,30) showed clinically significant changes at 2 hrs (48% and 60% decrement in $FeF_{50\%}$ respectively: Tables IV and V. Following 12 wks of bronchial challenge, a 2 wk vacation and rechallenge at 2 hrs, immediate pulmonary function analysis at 14 wks revealed essentially no reactive animals. Four (C11,24,30,33) of six animals (C1,11,16,24,30,33) that initially had clinically significant changes in R or $FeF_{50-10\%}$ developed tolerance to CDE challenge at 3½ months (Table V).

Two animals became hyperresponders with significant changes in all 3 categories, i.e. resistance, large airways and small airways. Two animals (C17,23) were nonresponders initially and at 14 wks.

As an indicator of general health and severity of experimental treatment, pre-exposure body weights were compared to post-exposure weights. No significant differences were found. The pre-exposure weights were; mean 5,128 gms ± 471, range 4,550 to 6,073 and the post-exposure weights were; mean 5,289 gms ± 536, range 4,530 to 6,284. Each monkey generally demonstrated a 100-200 gm weight increase during the study.

Discussion

The objectives of this study were to describe and compare the acute bronchial challenge response in naive monkeys exposed to CDE and the acute response following subchronic exposure. The weekly exposures were selected to be sufficient to produce a moderate pulmonary response. These episodes of bronchoconstrictions potentially reoccurred twice weekly for 3 months. Interestingly, half of the monkeys demonstrating a pre-exposure acute response became tolerant to the CDE challenge following subchronic exposure. Additionally, this tolerance was specific for CDE as the methacholine responsiveness demonstrated an apparent increase post-exposure.

Two of the eight monkeys demonstrating a significant pre-exposure response became considerably more responsive following the subchronic exposure. These differences in resulting responsiveness provide an excellent opportunity to correlate individual physiologic response with the qualitative and quantitative assessment of pharmacologic and immunologic mediators which will be reported elsewhere.

The immediate (10 min) challenge response was studied to detect possible allergic (Type I) response; however, few dramatic immediate responses were noted. The naive monkeys generally demonstrated a slight increase (120-130% of baseline value) in resistance with a very slight decrease in flow performance (2-3%). On the other hand the responses at 2 hrs for resistance and flow were greatly increased indicating that some time was required to develop significant and notable changes in resistance and flow. These findings tend to deemphasize the importance of the acclaimed acute histamine release response and place more importance on mediators that result in delayed and prolonged effects on the lung.

Our animal studies published recently have added further credence to our previous studies that these mediators ($PGF_2\alpha$, TXA_2, leukotrienes and 5-HT) play the major role in the acute byssinotic reaction (3-10). All of the arachidonic acid metabolites can be synthesized and released from various cells that are recruited in alveoli following cotton dust inhalation (PMNs, macrophages, etc.). 5-HT appears

to be the major endogenous smooth muscle constrictor in cotton dust (3,8). This was discovered in our laboratory by blocking in vitro smooth muscle contractions with methysergide; residual contractions were successfully blocked by indomethacin and led to further studies which showed cotton bract and dust caused release of $PGF_2\alpha$, and thromboxanes from animal and human blood cells and platelets. Thus both in vitro and in vivo studies in our laboratory have shown the importance of these mediators and defined their role and target cells (3-7,9,10).

Important data regarding the human parameters of the byssinotic reaction was provided by the classical studies of Bouhuys, namely 1) the acute byssinotic response is marked by shortness of breath and chest tightness and can be elicited not only by cotton dust, but also by a 10 minute aerosol inhalation of aqueous dust extracts (11,12); 2) healthy people exposed for the first time to dust or dust extract respond as severely as long term workers after a single exposure to dust extract (11,13); and 3) the response upon returning to the work environment is notable on the first day following a weekend and even more pronounced following 2 or more weeks' absence from work (14). Nitrogen washout curves were interpreted as reflecting reversible small airways obstruction in cardroom workers exposed to dust on Mondays following a weekend away from the work environment (11). Furthermore, the decreased expiratory flow at small lung volumes seen in the acute byssinotic reaction are compatible with narrowing of small airways (13,15,16). Increased total pulmonary resistance has been reported suggesting that large airways may also be involved (17).

A recent study by Beck et al. (18) has demonstrated chronic pulmonary effects of cotton dust exposure in workers using many of the same forced expiratory flow and volume test employed in our monkey animal model. In nonsmokers, significant lower lung functions were noted when the observed minus the predicted values were evaluated. The group mean values also did not distinguish the exposed from controls. Both cotton dust exposure and smoking were found to impair lung function additively; however, cotton dust tended to affect large airways, whereas smoking affected small airways. In our studies of the flow response, both large and small airways showed clinically significant changes.

The most severe reaction encountered in man is not the absence from the work environment over a weekend, but a return to work after a prolonged layoff of several weeks. Parkes (19) quotes Greenhow (20) as offering the first clear description of the symptom pattern now usually associated with byssinosis "namely, that of late onset asthma worse at the beginning of the work week than at the end, and an increased severity of symptoms on the first day at work after a longer period of absence than a weekend."

Our results reveal that the monkey reacts to inhalation of cotton dust extracts similar to man, i.e., following exposure a variable pattern is seen; some react and others fail to react. Tolerance in the human has not been studied but may correlate with what has been described as the survivor population in the cotton industry.

Our studies in monkeys demonstrate dramatic changes following 3 months of CDE inhalation exposures in monkeys. The hyperresponder and tolerant state observed in exposed monkeys is the first indication of the mechanism that relates the acute response to chronic exposure and may provide an explanation as to how a "survivor population" manifests itself in the cotton mill industry. Additionally, and probably of equal importance is that some monkeys like some humans do not react to cotton dust or extracts. Furthermore, this study implies that dust is not necessary, and like Bouhuys classical studies suggested, the etiological agent is contained in water soluble extracts (15).

The monkey appears to be an excellent animal model for byssinosis offering many advantages, primarily relating to the direct application of the same diagnostic procedures that are used in humans. Individual responses of tolerance and hyperreactivity are demonstrated as probably occurs in cotton mill workers. The important issue of whether chronic cotton dust exposure leads to chronic disease should be addressed by long-term inhalation exposures in the monkey animal model where periodic bronchoprovocation challenge responses could be evaluated over time. An endpoint in such a study would be the development of irreversible obstructive lung disease consistent with emphysema. The monkey has already been shown to be a sensitive model for chronic obstructive lung disease in a number of 2-year inhalation studies with coal dust, silica and polyurethane foam (2,21,22).

Acknowledgements

The authors are grateful to John Clark, Camille Whitener, Cynthia O'Dell and E. Hope Geer for technical assistance and Marla Warren for secretarial assistance.

This study was supported in part by funds from Cotton, Inc., the American Lung Association of South Carolina, and The Cotton Foundation. Additional support by way of cooperative participation and resource utilization has come from the Division of Biomedical and Behavioral Science of the National Institute of Occupational Safety and Health.

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Table I. Experimental Design

Pre-Exposure Design

Baseline bronchial challenge with methacholine
Baseline bronchial challenge with CDE
Baseline pulmonary function (10 min and 2 hrs)

↓

Exposure Phase

Twice weekly exposure of monkeys to 30 breaths CDE (0.01 g/ml) for 12 weeks

↓ (2 weeks)

Post-Exposure Phase

Post-exposure CDE bronchial challenge
Post-exposure pulmonary function (10 min and 2 hrs)
Post-exposure methacholine bronchial challenge

TABLE II
CLINICAL EVALUATION OF
INDIVIDUAL PULMONARY FUNCTION (RESISTANCE)

Acute Pharmacologic Responders - Pre-Exposure (2 hr)

	Δ%	Actual Values (ml/sec)
C1	360	9.86 - 35.52
C16	215	8.52 - 18.32
C30	204	8.41 - 17.23
C33	205	6.10 - 12.54

Hyperresponders - Post Exposure (2 hr)

	Δ%	Actual Values (ml/sec)
C1	522	9.92 - 51.82
C16	249	6.39 - 15.91

Pre-Exposure Responders Becoming Tolerant - Post-Exposure

	Pre-Exposure (2 hr)		Post Exposure (2 hr)	
	Δ%	Actual Values (ml/sec)	Δ%	Actual Values (ml/sec)
C33	205	6.10 - 12.54	80	8.05 - 6.51
C30	204	8.41 - 17.23	121	8.63 - 10.46
C23	186	7.12 - 13.30	100	7.13 - 7.20
C11	185	11.42 - 21.18	154	7.55 - 11.69

TABLE III
CLINICAL EVALUATION OF
INDIVIDUAL PULMONARY FUNCTION (FLOW)
FeF 10%

Acute Pharmacologic Responders - Pre-Exposure (2 hr)

	Δ%	Actual Values (ml/sec)
C1	78	129 - 101
C30	52	106 - 55
C33	64	158 - 101
C11	24	146 - 35
C24	71	129 - 91

Hyperresponders - Post-Exposure (2 hr)

	Δ%	Actual Values (ml/sec)
C1	57	190 - 109
C11	73	86 - 63
C16	27	329 - 89
C23	72	317 - 228

Pre-Exposure Responders Becoming Tolerant - Post-Exposure

	Pre-Exposure (2 hr)		Post Exposure (2 hr)	
	Δ%	Actual Values (ml/sec)	Δ%	Actual Values (ml/sec)
C30	52	106 - 55	160	65 - 104
C33	64	158 - 101	109	127 - 139
C24	71	129 - 91	119	139 - 165

TABLE IV
CLINICAL EVALUATION OF
INDIVIDUAL PULMONARY FUNCTION (FLOW)
FeF 50%

Acute Pharmacologic Responders - Pre-Exposure (2 hr)

	Δ%	Actual Values (ml/sec)
C1	70	1455 - 1017
C30	60	895 - 578
C11	48	1333 - 639
C24	70	1039 - 730

Hyperresponders - Post-Exposure (2 hr)

	Δ%	Actual Values (ml/sec)
C1	66	1407 - 925
C16	48	1633 - 798

Pre-Exposure Responders Becoming Tolerant - Post-Exposure

	Pre-Exposure (2 hr)		Post Exposure (2 hr)	
	Δ%	Actual Values (ml/sec)	Δ%	Actual Values (ml/sec)
C30	60	895 - 578	81	755 - 612
C11	48	1333 - 639	96	890 - 856
C24	70	1039 - 730	105	1076 - 1127

Table V
Individual Resistance and Flow Responses FeF_{50} (1)

	Pre-Exposure				Post-Exposure				Clinical Category
	Base — Immed.(10')		Base — 2 hrs		Base — Immed.(10')		Base — 2 hrs		
C1	142		360	▲	149		522	▲ *	Hyperresponder
	95		70	▼	97		66	▼ *	
C11	114		185		106		154		
	68	▼	48	▼	108		96	T	Flow tolerant
C16	116		215	▲	99		248	▲ *	Hyperresponder
	102		87		92		48	▼ *	
C17	104		144		99		151		Non-responder
	100		82		110		96		
C23	152		186		100		100		Non-responder
	99		90		98		91		
C24	101		116		118		100		
	96		70	▼	115		105	T	Flow tolerant
C30	160		205	▲	107		121	T	Resistance and
	84		60	▼	97		81	T	Flow tolerant
C33	135		205	▲	83		80	T	Resistance tolerant
	102		89		99		90		

▲▼ = Clinically significant change, i.e. "responder". (200% ▲ R or 80% of base for FeF)
* = Increased
T = Tolerant

(1) $\frac{R}{FeF_{50}}$ · percent of baseline

Price: $25.00

COTTON DUST

Proceedings of the Eighth Cotton Dust Research Conference
Beltwide Cotton Production Research Conferences
Atlanta, Georgia, January 9-10, 1984

Sponsored by
National Cotton Council
and
The Cotton Foundation

P. J. Wakelyn, National Cotton Council
and R. R. Jacobs, Cotton Incorporated, Editors

Proceedings published by:
National Cotton Council, Memphis,TN and
Cotton Incorporated, Raleigh, NC 1984

Library of Congress Cataloging in Publication Data

Cotton Dust Research Conference (8th : 1984 : Atlanta, Ga.)
Cotton dust.

Bibliographies: p.
1. Cotton dust--Toxicology--Congresses. 2. Byssinosis --Congresses. 3. Cotton manufacturer--Hygienic aspects-- Congresses. 4. Cotton manufacture--Dust control-- Congresses. 5. Cotton dust--Composition--Congresses. I. Wakelyn, P.J. (Phillip J.), 1940- . II. Jacobs, R. R. (Robert R.), 1948- . III. National Cotton Council of America. IV. Cotton Foundation (Memphis, Tenn.). V. Title.
RA1242.C82C68 1984 616.2'44 84-8268
ISBN 0-9613408-0-0

PRINTED IN THE UNITED STATES OF AMERICA