

## SHORT PAPER

## Caffeine decreases exhaled nitric oxide

C Bruce, D H Yates, P S Thomas

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See end of article for authors' affiliations

Correspondence to:  
Dr P S Thomas, Department  
of Respiratory Medicine,  
Prince of Wales Hospital,  
Randwick, Sydney, NSW  
2031, Australia;  
[paul.thomas@unsw.edu.au](mailto:paul.thomas@unsw.edu.au)

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**Background:** Caffeine is known to inhibit phosphodiesterases, to mobilise intracellular calcium, and to act as an antagonist at adenosine receptors, all of which can potentially alter nitric oxide (NO) production. It was therefore hypothesised that caffeine may alter exhaled NO (eNO) levels.

**Methods:** In a randomised, single blind, crossover manner, 12 normal subjects consumed either (1) coffee and a placebo capsule, (2) decaffeinated coffee and a capsule of 200 mg caffeine, or (3) decaffeinated coffee and a placebo capsule. Serum caffeine levels were measured at baseline and 1 hour later. Exhaled NO levels were also measured at baseline and each hour for 4 hours.

**Results:** A significant percentage fall in mean (SE) eNO from baseline was seen 1 hour after either caffeinated coffee or a caffeine capsule when compared with placebo (13.5 (4.0)%,  $p=0.009$  and 19.0 (3.8)%,  $p=0.001$ , respectively).

**Conclusion:** Caffeine causes a significant decrease in eNO which will need to be considered when designing trials to measure eNO levels. The mechanism may be via adenosine receptor antagonism or by altering levels of cGMP.

Nitric oxide (NO) is generated from L-arginine by constitutive NO synthases (ecNOS and nNOS) and inducible NO synthase (iNOS). It has become apparent that a number of exogenous factors affect levels of exhaled NO. Cigarette smoking and alcohol decrease exhaled NO levels via effects upon constitutive and iNOS, respectively, while asthmatic inflammation and upper respiratory tract infections increase exhaled NO (eNO) via iNOS induction.<sup>1-3</sup>

Caffeine is widely consumed as coffee, tea, and cola. Coffee also contains numerous other substances such as minerals, lipids, proteins, carbohydrates, aliphatic acids, glycosides, and contaminants formed during the roasting process including nitrosamines, heterocyclic amines, and paraffins.<sup>4</sup> In high doses caffeine inhibits phosphodiesterases, leading to elevation of cyclic AMP (cAMP) and cyclic GMP (cGMP) which may be the mechanism for its weak bronchodilatory effect in mild asthmatic subjects. It can also mobilise intracellular calcium stores and, at lower concentrations, caffeine antagonises adenosine receptors ( $A_1$ ,  $A_{2a}$ ).<sup>4</sup> In addition, an increase in intracellular cGMP upregulates ecNOS expression and an increase in intracellular cAMP downregulates it.<sup>5,6</sup> Stimulation of adenosine receptors leads to differential effects, with  $A_{2a}$  receptor stimulation increasing NO generation while  $A_1$  receptor stimulation leads to decreased NO production by endothelial cells.<sup>7</sup> This led us to test the hypothesis that caffeine may have an effect on eNO levels in normal subjects.

## METHODS

## Study sample and protocol

Twelve normal healthy habitual caffeine drinkers (four men) of mean age of 33.2 (9.3) years were recruited to the study. All were non-smoking non-asthmatic subjects with normal spirometric parameters and no recent history of respiratory tract infections. Subjects abstained from dietary methylxanthines for at least 8 hours before the study. The study was approved by the institutional ethics committee and all subjects gave written informed consent.

There were three arms to the study, which were randomised in a single blind, placebo controlled, crossover manner and comprised: (1) coffee 2.4 g with an approximate caffeine content of 100 mg per 200 ml cup (Espresso filtered coffee, Harris Ltd, Sydney) and a matched placebo capsule (Glucodin

(glucose), Boots Healthcare, Australia); (2) decaffeinated coffee (<3 mg caffeine per 200 ml cup, Moccona, Douwe Egberts Joure, Holland) and a capsule of 200 mg caffeine (No Doz, Key Pharmaceuticals, Sydney); or (3) decaffeinated coffee and a placebo capsule. Subjects consumed a further aliquot of the same beverage after the first hour.

At baseline, eNO and serum caffeine levels were measured. Exhaled NO was then measured every hour for 4 hours. Serum caffeine samples were taken 1 hour after caffeine intake to sample peak serum levels of caffeine.

## Measurement of exhaled NO

Exhaled NO was measured by chemiluminescence (Model 2107, Dasibi Environmental Corporation, Glendale, CA, USA) with subjects exhaling slowly at a flow rate of 5 l/min from total lung capacity over 30-40 s with constant raised oral pressure avoiding nasal contamination, following ERS recommendations.<sup>8</sup> The mean of three successive peak plateau readings was used for analysis. Ambient NO levels were recorded and, if >40 ppb, the analyser was flushed with NO-free gas.

## Measurement of serum caffeine levels

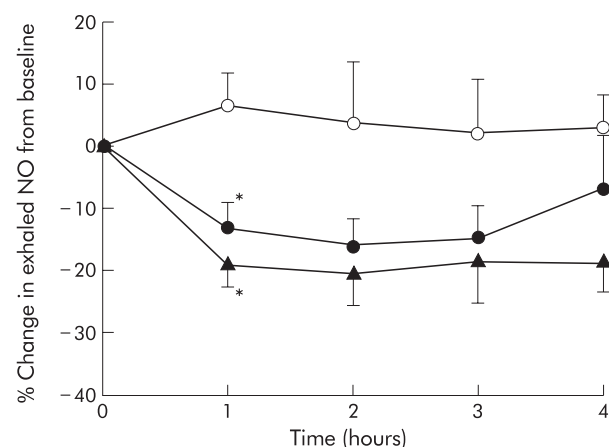
Serum caffeine concentrations taken at baseline and 1 hour were analysed by gas chromatography-mass spectroscopy.

## Spirometric testing

Spirometric tests were performed using a dry wedge spirometer (Vitalograph, UK) to ensure that all subjects had a normal forced expiratory volume in 1 second (FEV<sub>1</sub>).

## Statistical analysis

Exhaled NO values were log transformed to the normal distribution and analysed by two way repeated measures ANOVA to compare the differences between the three treatment groups over time. Exhaled NO levels were expressed as mean (SE) parts per billion (ppb) and changes in exhaled NO displayed as mean (SE) % change from baseline. Serum caffeine levels were reported as mean (SE) mg/l and analysed by paired *t* test. Significance was taken as  $p<0.05$ , with post hoc Bonferroni corrected paired *t* test applied to significant ANOVA results.



**Figure 1** Percentage change in exhaled NO compared with the baseline value (0) at 1, 2, 3, and 4 hours after administration of decaffeinated coffee and placebo (open circles, mean (SE) baseline value 9.9 (2.4) ppb), coffee and placebo (closed circles, mean (SE) baseline value 11.6 (2.3) ppb), or decaffeinated coffee and 200 mg caffeine (triangles, mean (SE) baseline value 12.3 (2.6) ppb) in 11 normal subjects. \* $p < 0.05$ .

## RESULTS

### Subjects

Eleven of the 12 subjects completed the study; one subject was withdrawn because of a respiratory tract infection.

### Exhaled NO

Baseline eNO results were not significantly different between the study days in any of the three phases. After coffee or caffeine consumption there was a significant decrease in eNO levels compared with placebo ( $p = 0.008$ , two way ANOVA). Mean eNO levels decreased significantly in the first hour after coffee or caffeine consumption compared with the placebo phase and caused a mean percentage fall of 13.5 (4.0)% and 19.0 (3.8)% ( $p = 0.009$  and  $p = 0.001$  respectively, post hoc  $t$  tests, fig 1). Mean eNO levels during the coffee and caffeine phase remained consistently lower than baseline levels during the following 3 hours, although the difference was not statistically significant.

### Serum caffeine levels

Baseline serum caffeine levels did not differ significantly between study days. The mean (SE) serum caffeine level changed after 1 hour during the three phases: (1) caffeinated coffee and placebo from 0.6 (1.3) mg/l to 2.8 (0.8) mg/l,  $p = 0.002$ ; (2) decaffeinated coffee and caffeine from 0.6 (1.2) mg/l to 3.7 (0.9) mg/l,  $p = 0.003$ ; (3) decaffeinated coffee and placebo from 0.5 (1.3) mg/l to 0.4 (0.3) mg/l,  $p = 0.21$ . No relationship was found between serum caffeine levels and change in eNO.

## DISCUSSION

This study shows that caffeine significantly decreases eNO levels, either as 200 mg caffeine or as coffee with an average caffeine content of 100 mg. There are many other additional components of coffee, but none have a known mechanism which would cause NO to fall. The mechanism for this reduction in eNO is not certain, but it is known that at doses similar to those used in our study caffeine antagonises adenosine receptors. At higher concentrations caffeine causes inhibition of the breakdown of cAMP and cGMP, but it may also inhibit guanylate cyclase.<sup>5,6,9</sup>

Adenosine enhances NO production from endothelial cells through adenosine  $A_{2a}$  receptors, while adenosine  $A_1$  receptors decrease it.<sup>7</sup> Thus, caffeine could antagonise  $A_{2a}$  receptors if

these are active in airway epithelium, reducing the generation of NO.<sup>7</sup> If caffeine acts by adenosine receptor antagonism, then  $A_1$  receptors are less likely to be involved. Direct airway AMP challenge has also been associated with a fall in eNO, but this was interpreted as being related to airway bronchoconstriction.<sup>10</sup>

An alternative mechanism by which caffeine could alter NO generation is through the inhibition of the phosphodiesterases and hence the breakdown of the secondary messengers cGMP and cAMP. However, theophylline inhibits soluble guanylate cyclase thus reducing the formation of cGMP, so the effects of caffeine on cGMP may be mixed.<sup>5,9</sup> Cyclic GMP upregulates eNOS generation while cAMP may downregulate it,<sup>5,6</sup> but these effects are at the level of protein translation which would not be expected to be seen for some hours. It would appear therefore that the immediate effect of caffeine observed in this study is more compatible with a reduction in cGMP via inhibition of soluble guanylate cyclase.<sup>9</sup>

Spirometric tests were not performed so as not to alter the levels of eNO spuriously, as some reports have suggested a fall in eNO after repeated spirometry alone.<sup>11</sup> Silkoff *et al* measured exhaled NO both after repeated spirometric testing and  $\beta_2$  adrenergic agonist inhalation in asthmatic and normal subjects and found that spirometric testing decreased eNO levels while the  $\beta_2$  agonist increased them.<sup>11</sup> Others have reported that eNO levels are reduced shortly after bronchoconstriction to direct and indirect stimuli in subjects with asthma, and suggested that eNO levels can be modulated by bronchial tone.<sup>10</sup> The first measurement after intervention was at the end of the first hour, which was at the time when previous studies have indicated that eNO is no longer significantly different from baseline. In addition, the control phase of the experimental design indicates that the effects on eNO are due to caffeine and not to repeated spirometric tests (fig 1).

Decaffeinated coffee had no effect on eNO levels, suggesting that caffeine is the principal agent causing the decrease in eNO. Caffeine is associated with a brief reduction in eNO levels over 4 hours in normal subjects, which suggests that it should be withheld for at least this time period before taking measurements in normal and probably in asthmatic subjects; however, this latter group was not assessed in this study.

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### Authors' affiliations

**C Bruce, P S Thomas**, Faculty of Medicine, UNSW and Department of Respiratory Medicine, Prince of Wales Hospital, Sydney, NSW 2031, Australia  
**D H Yates**, Royal North Shore Hospital, Sydney, Australia

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## SHORT PAPER

# Freeze fracture study of airway epithelium from patients with primary ciliary dyskinesia

C H Thai, T M Gambling, J L Carson

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See end of article for authors' affiliations

Correspondence to:  
Dr C H Thai, The University of North Carolina at Chapel Hill, EPA Human Studies Facility, CB #7310, 104 Mason Farm Road, Chapel Hill, NC 27599, USA; thai@email.unc.edu

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**Background:** The airway cilia of patients with primary ciliary dyskinesia (PCD) exhibit several anomalies when studied by transmission electron microscopy, but little is known about the ultrastructural organisation of ciliary membranes in these patients. Freeze fracture replication of airway epithelium from patients with PCD provides a means of achieving high resolution views of cell membrane structure. Ciliary necklaces are a specialised structural feature of ciliary membranes thought to serve as a timing mechanism for ciliary beat, and their characterisation in the cilia of patients with PCD may contribute new insights into the pathophysiology of this syndrome.

**Methods:** The nasal epithelium of three patients with PCD was freeze fractured and replicated with platinum and carbon shadowing. The resultant preparations were examined by transmission electron microscopy and the ciliary necklaces were compared with similar preparations of nasal biopsy specimens from normal healthy subjects.

**Results:** The ciliary necklaces of the three patients with PCD were normal with no overt differences from those of healthy individuals.

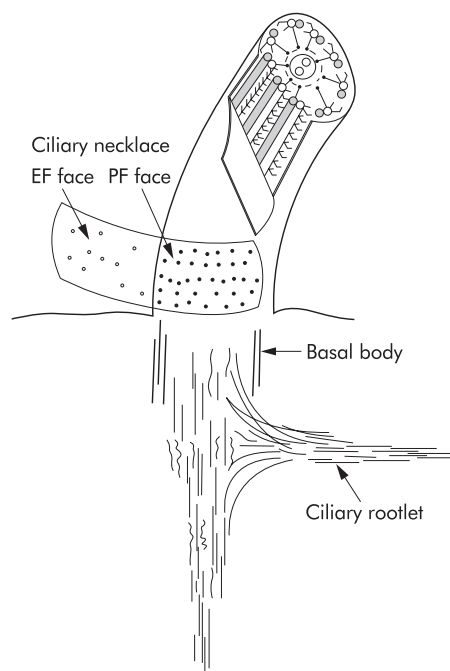
**Conclusions:** The defective ciliary motility observed in patients with PCD does not appear to result from membrane dysfunction associated with overt disorganisation of ciliary necklace structure.

Sections of airway cilia from patients with primary ciliary dyskinesia (PCD) exhibit several anomalies when viewed by transmission electron microscopy.<sup>1–3</sup> However, little is known about the ultrastructural organisation of ciliary membranes in these individuals. PCD is a rare genetic disorder characterised by hereditary structural defects in the cilia which affects one in 20 000 individuals.<sup>4</sup> It was initially described by Siewert in 1904 as a triad of symptoms characterised by situs inversus, sinusitis, and bronchiectasis.<sup>5</sup> At present PCD is characterised clinically by recurrent sinopulmonary infection, bronchiectasis, subfertility, and situs inversus<sup>4</sup> and confirmed by laboratory documentation of ciliary dyskinesia and ultrastructural defects.

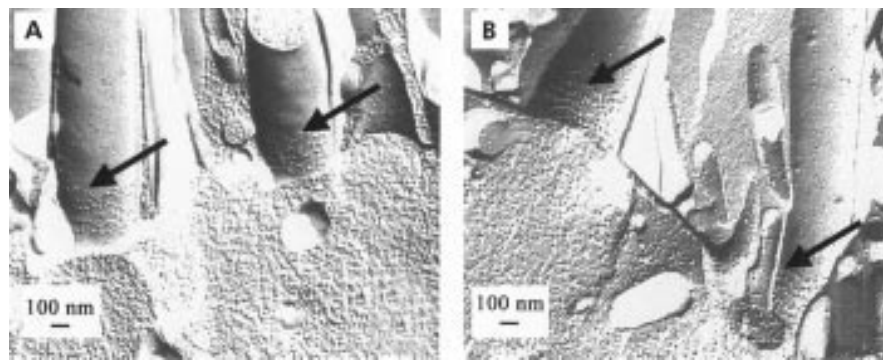
A normal cilium exhibits a core axoneme comprising nine peripheral doublets of microtubules surrounding a central pair of microtubules. The orientation of the central microtubular pair reflects the coordinated movement of the cilia. There are also several microtubule associated proteins (MAPs) which play important structural and functional roles. Dynein arms were among the first MAPs identified.<sup>6</sup> Outer dynein arms are thought to regulate beat frequency and inner arms to regulate beat waveform.<sup>6</sup> Radial spokes comprise another type of MAP that connect each doublet to the central microtubular pair.

Among the ultrastructural abnormalities observed in the cilia of patients with PCD are absent or reduced inner and outer dynein arms,<sup>1</sup> absent radial spokes,<sup>2</sup> an absent central microtubular pair replaced by a peripheral microtubule doublet (transposition),<sup>3</sup> and ciliary aplasia with defects in ciliary orientation.<sup>7</sup>

The ciliary necklace is a complex of particles found at the base of each cilium (fig 1). The particles are generally arranged



**Figure 1** Diagram of a normal cilium illustrating the EF face and PF face in the region of the ciliary necklace. Note the location of the strands at the base of the cilium and the lower density of particles in the EF face.



**Figure 2** Transmission electron micrograph of freeze fracture preparation of airway epithelium from nasal biopsy specimens showing that ciliary necklaces (arrows) from (A) healthy controls and (B) patients with PCD are comparable in appearance. The necklaces consist of 4–5 evenly spaced strands of particles and no disruption of this pattern is evident in the preparation of epithelium from the patient with PCD.

in scalloped rows about 30 nm apart with each scallop corresponding to a peripheral microtubule.<sup>8</sup> The number of necklace strands varies among species, with 4–6 strands usually present in human cilia.<sup>8</sup> The ciliary necklace has been proposed as a membrane component that functions in energy transduction or timing of ciliary beat.<sup>8</sup>

Nasal biopsy specimens from three well documented patients with PCD were freeze fractured to study the ultrastructural organisation of the ciliary membrane. To our knowledge, this is the first report characterising ciliary necklace organisation in the airway epithelium of patients with PCD.

## METHODS

Samples of nasal epithelium from three clinically and laboratory documented patients with PCD were obtained under direct vision by gentle curettage of the inferior nasal turbinate. The specimens were fixed immediately in 2% paraformaldehyde/2% glutaraldehyde/0.5% tannic acid or 2% paraformaldehyde/2% glutaraldehyde in 0.1 M phosphate buffer, pH 7.2. Following fixation, the samples were rinsed for 1 hour in 0.1 M phosphate buffer containing 0.2 M sucrose and then incubated in 0.1 M phosphate buffer containing 25% glycerol. Samples were mounted between double replica specimen mounts, frozen in liquid nitrogen cooled freon, and stored in liquid nitrogen until processed.

Freeze fracture was performed in a Balzers BAF 400T unit at a stage temperature of  $-100^{\circ}\text{C}$ . The fractured samples were shadowed by platinum and carbon evaporation from an angle of  $30^{\circ}$  and carbon evaporation from  $90^{\circ}$ . The replicas were cleaned in 5% sodium dichromate in 50% sulfuric acid and rinsed in several washes of distilled water. They were retrieved on copper grids and viewed in a Zeiss EM 900 transmission electron microscope at an accelerating voltage of 50 kV.

Both patients and volunteers gave informed consent before participating in the study under a protocol approved by an institutional review board on the protection of the rights of human subjects.

## RESULTS

Electron microscopic examination of the freeze fracture preparations revealed that the ciliary necklaces present in the cilia of biopsy specimens from patients with PCD were comparable in organisation to those of normal healthy volunteers (fig 2). The ciliary necklaces of both patients and healthy volunteers usually consisted of five rows of particles, extending distally from the base of each cilium approximately  $0.25\text{ }\mu\text{m}$ . No deviation in this arrangement was seen in the epithelial cilia preparations from patients with PCD.

Previous studies from this laboratory have shown that disruption of the ciliary necklaces is evident in mycoplasma

infection and following in vivo exposure to sulfur dioxide, both of which contribute to ciliary dysfunction.<sup>9 10</sup>

## DISCUSSION

The suggestion that ciliary necklaces function as a timing device for ciliary beat is appropriate as ciliostasis has been observed in studies where the ciliary necklaces appear to be disorganised.<sup>9 10</sup> Generally characterised in normal subjects by rows of membrane associated particles, this is the first study of ciliary necklace organisation in patients with PCD.

An early report by Lessner *et al*<sup>11</sup> studied the distribution of intramembrane particles (IMPs) on different fracture faces of cilia from patients with PCD but did not provide any specific characteristics of ciliary necklace organisation in these subjects. They found a higher density of IMPs on the EF faces than on the PF faces of cilia of patients with PCD, a pattern which contrasts with the distribution seen in normal subjects. They further concluded that the higher IMP density on the EF face was probably due to a defective microtubular system in these patients.<sup>11</sup>

In this study we have shown that ciliary necklaces present in preparations of nasal epithelial tissue from three patients with PCD appear to have normal ultrastructural organisation. Abnormal organisation of the ciliary necklace particles has been previously reported with experimental *Mycoplasma pneumoniae* infection<sup>9</sup> and experimental exposure to sulfur dioxide exposure.<sup>10</sup> In the mycoplasma study only remnants of the necklaces remained or the necklaces were completely absent in infected tissues.<sup>9</sup> Following exposure to sulfur dioxide, remnants of the necklaces were also observed at the bases of the cilia in addition to distal displacement of the particles along the ciliary membrane.<sup>10</sup> The ciliary necklaces of patients with PCD lacked these abnormalities, so we conclude that the ciliostasis and other irregularities of ciliary motility seen in patients with PCD are not directly associated with structural abnormalities of the ciliary necklace.

The functional decrements in ciliary activity and mucociliary clearance associated with upper respiratory infection and/or irritant exposure, together with the observed anomalies of ciliary necklace organisation, suggest a significant role for necklace proteins in maintaining normal mucociliary function. Because of this link between structure and function, it is plausible to hypothesise that necklace organisation may have a role in the pathophysiology of PCD, but our findings suggest that a direct structure/function anomaly does not occur.

This study provides the first characterisation of ciliary necklace organisation of epithelial cells from patients with PCD. Although organisation of the ciliary necklace in patients with PCD was found to be the same as that of healthy volunteers, this does not preclude membrane or membrane-axoneme dysfunction in the pathophysiology of PCD.



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## Authors' affiliations

**C H Thai, J L Carson**, Department of Cell Biology and Anatomy, The University of North Carolina at Chapel Hill, NC 27599, USA  
**T M Gambling, J L Carson**, Department of Pediatrics, The University of North Carolina at Chapel Hill

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