



ENDOGENOUS ATRIAL NATRIURETIC FACTOR AND AIRWAY CONTROL

By

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SCIENCE

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Dedicated to my parents - Pat and Frankie,
my wife Gill
and children Emma, Claire and Sammy.

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SUMMARY

This thesis describes two experiments investigating the role of endogenous ANF in the modulation of airway calibre and bronchial hyperresponsiveness in humans under normal physiological conditions.

The first study was designed to re-examine the diurnal variation of ANF reported in humans, to test for differences between asthmatic and control subjects and to determine whether spontaneous variations in airway calibre coincided with variations in ANF.

No circadian pattern in ANF levels was found in either an asthmatic or a control group, and there was no difference between the groups. The ANF levels within individuals were remarkably constant through the day.

The second study was designed to test whether an increase in endogenous ANF causes a decrease in histamine bronchial responsiveness or increase in airway calibre. Elevation of ANF levels in asthmatic subjects was attempted using immersion in water to promote central pooling of blood thereby increasing right atrial pressure and stimulating ANF release. Rather than rely entirely on detection of the ANF, cyclic GMP, as a longer lasting marker of ANF, was also monitored.

Atrial natriuretic factor increases attributable to immersion were minimal, but considerably larger changes were seen in cGMP levels. However, changes in bronchial responsiveness were variable and no significant effect of ANF or of cGMP was detected. Immersion was associated with a slight decrease in airway calibre.

The data showed a trend towards reduced bronchial responsiveness following immersion. It is suggested that a stronger stimulus to ANF release, inhibition of ANF degradation and a more sensitive index of bronchial responsiveness used with a well characterised study group may be necessary to show a significant effect of endogenous ANF.

The overall conclusions from the studies described in this thesis are:

- (i) That ANF variations do not account for major changes seen in asthma, i.e. diurnal variation of airway calibre and increased bronchial responsiveness;
- (ii) diurnal variation of ANF did not occur in this group of controls and asthmatics; and
- (iii) a 70% increase in circulating cGMP does not alter bronchial hyperresponsiveness.

DECLARATION

I declare that this thesis contains no material which has been accepted for the award of any degree or diploma in any university, and to the best of my knowledge contains no material previously published by another person, except where due reference is made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Sean David Robert Homan

PUBLICATIONS

The following is a list of publications that have arisen from this work.

HOMAN SDR, RUFFIN RE, MENADUE M, OLIVER J. Diurnal variation of atrial natriuretic factor (ANF) in asthmatics and controls. Proceedings of the Thoracic Society of Australia and New Zealand, Annual Scientific Conference, April 1992.

HOMAN SDR, RUFFIN RE, MENADUE M, OLIVER J. Head out of water immersion increases atrial natriuretic factor and cyclic guanosine monophosphate with minor change in bronchial responsiveness. Proceedings of the Thoracic Society of Australia and New Zealand, Annual Scientific Conference, April 1993.

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ABBREVIATIONS

The following abbreviations have been used in this thesis.

$\beta 2$	Bronchodilator - inhaled $\beta 2$ agonist
ADH	Anti-diuretic hormone
ANF	Atrial natriuretic factor
BHR	Bronchial hyperresponsiveness
BR	Bronchial responsiveness
Cdyn	Dynamic compliance
cGMP	Cyclic guanosine monophosphate
CI	Ninety five percent confidence intervals
CV	Coefficient of variation
EDTA	Ethylenediaminetetra-acetic acid di-sodium salt
FEV _{1.0}	The volume of air expired during the first second of forced expiration from total lung capacity.
FVC	Forced vital capacity.
HB	Heated box - the control intervention.
HIT	Histamine inhalation test
HOWI	Head-out-water-immersion
NEP	Neutral endopeptidase
PD ₂₀ H	Cumulative dose of histamine causing a fall in FEV _{1.0} of 20%.
PRN	As required
RIA	Radio-immuno assay
Rrs	Resistance of the respiratory system
SD	Standard deviation
SEM	Standard error of the mean
SM	Smooth muscle