Laryngeal Dysfunction in Chronic Cough

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Statement of Originality

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Acknowledgement of Authorship

I hereby certify that this thesis is in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a signed statement from each co-author, attesting to contribution of each author to each of the publications contained in this thesis.
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List of Abbreviations
(listed in order of appearance in document)

VCD=vocal cord dysfunction*

PVFM=paradoxical vocal fold movement*

CC=chronic cough

EAHR=extrathoracic airway hyperresponsiveness

ADP=anatomic diagnostic protocol

PNDS=post nasal drip syndrome

GORD=gastroesophageal reflux disease

NAEB=nonasthmatic eosinophilic bronchitis

ACE=angiotensin conversion enzyme

UACS=upper airways cough syndrome

ENT=ear nose throat

LOS=lower oesophageal sphincter

OSA=obstructive sleep apnoea

CPAP=continuous positive airway pressure

HAD=hospital anxiety and depression

STAI=state trait anxiety inventory
CCEI=crown crisp experimental index
RARs=rapidly adapting receptors
URTI=upper respiratory tract infection
RSV=respiratory syncytial virus
SARS=severe acute respiratory syndrome
CIC=chronic idiopathic cough
PCR=polymerase chain reaction
WTC=world trade centre
PCBs=polychlorinated biphenyls
SLN=superior laryngeal nerve
RLN=recurrent laryngeal nerve
PVVN=post viral vagal neuropathy
URI=upper respiratory infection
HSN1=heredity sensory neuropathy-1
SPTLC1=serine palmitoyltransferase-1
TRP= transient receptor potential
TRPV1= transient receptor potential, vanilloid-1
TRPA1= transient receptor potential, ankyriol-1
CGRP = calcitonin gene related peptide

ACCP = American college of chest physicians

LPR = laryngopharyngeal reflux

QOL = quality of life

CQLQ = cough-specific quality of life questionnaire

SHR = sensory hyperreactivity

MCS = multiple chemical sensitivity

PKC = protein kinase C

C2 = capsaicin dose inducing 2 coughs

C5 = capsaicin dose inducing 5 coughs

UTC = urge-to-cough

CICADA = cough in children and adults: diagnosis and assessment

PFT = pulmonary function testing

SPLI = speech language pathology intervention

BtxA = botulinum toxin type A

FVL = flow volume loop

FOL = fibre optic laryngoscopy

BHR = bronchial hyperresponsiveness
MIF=maximum inspiratory flow

* NB: VCD and PVFM are different terms for the same condition and both are used extensively throughout the literature therefore, they have been used interchangeably throughout this thesis document.
Abstract

Cough is one of the main reasons for seeking medical care in Australia with 11% to 16% of the general population reporting a persistent cough, and 7% describing a cough that is sufficient to interfere with activities of daily living on at least a weekly basis. Patients with chronic cough (CC) frequently report a range of physical symptoms such as musculoskeletal chest pains, sleep disturbance, a hoarse voice, syncope, stress incontinence, rib fractures and vomiting. The psychological impact of cough includes a high prevalence of depressive and anxiety symptoms, as well as worry about serious underlying diseases such as cancer and tuberculosis. Persistent cough can also have an adverse impact on social well being leading to difficulty in relationships, avoidance of public places, and disruption of employment.

Refractory cough refers to persistent cough that does not respond to usual medical treatment. Idiopathic chronic cough refers to cough that cannot be diagnosed even after a thorough systematic investigation has been conducted. Laryngeal dysfunction includes conditions such as vocal cord dysfunction (VCD) also known as paradoxical vocal fold movement (PVFM), and sensory laryngeal neuropathy. The relationship between laryngeal dysfunction and refractory and idiopathic cough is poorly characterised. This thesis addresses the significance of laryngeal dysfunction in CC by characterising the disorder, investigating potential mechanisms and assessing viable treatments. It also looks at the prevalence and mechanism of CC in adults and its association with upper airway hyperresponsiveness after respiratory infection.
The primary findings of this thesis are:

1. Laryngeal dysfunction presenting as PVFM and EAHR commonly occurs in CC. Fifty-six percent of participants have laryngeal dysfunction presenting as paradoxical vocal fold movement.

2. Individuals with CC and PVFM have increased extrathoracic airway hyperresponsiveness (EAHR) compared to individuals with CC alone and healthy controls.

3. Laryngeal dysfunction with CC is associated with quality of life impairment and sensory hyperreactivity of the cough reflex.

4. Laryngeal hypersensitivity may be a common mechanism in CC.

5. Successful treatment for CC with speech language pathology intervention leads to improvements in laryngeal dysfunction manifest as PVFM and EAHR.

6. Speech language pathology intervention for refractory and idiopathic CC leads to improvement in cough through reduced laryngeal irritation resulting in decreased cough sensitivity, decreased urge to cough and an increased cough threshold.

7. When compared to placebo, gabapentin effectively decreases cough frequency and increases quality of life in people with refractory or idiopathic CC. The likely mechanism for this is that gabapentin inhibits release of excitatory neurotransmitters at supraspinal sites.

8. EAHR is a feature of postinfectious cough.

9. Postinfectious cough due to H1N1 2009 influenza has similar characteristics to other postinfectious cough and is associated with cough reflex hypersensitivity.