Title: Higher cough flow is associated with lower risk of pneumonia in acute stroke

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To the Editor

Abstract

There is little available evidence to demonstrate how cough strength mediates the risk of aspiration-related pneumonia in acute stroke. Our secondary analysis of trial data indicates that risk of pneumonia reduces with increasing peak cough flow (PCF) of voluntary cough (OR 0.994 for each 1 L/min increase in PCF, 95%CI 0.988-1.0, p=0.035); and to a lesser degree with increasing PCF of reflex cough (OR 0.998 for each 1 L/min increase in PCF, 95%CI 0.992-1.004, p=0.475). These data serve hypothesis generation. Further studies are needed to confirm these findings and validate their clinical utility.

Introduction

Cough is the most immediate defense mechanism against aspiration.[1] It is a commonly encountered clinical belief that strong cough offers some protection from aspiration-related pneumonia, although there is little evidence available to support this. Data from our completed trial of respiratory muscle training in acute stroke (ISRCTN40298220) allowed us to examine the association between cough flow and pneumonia risk. We have previously shown that stroke leads to impairment of both voluntary and reflex cough.[2, 3] Here, we present an exploratory secondary analysis of trial data, examining whether higher peak cough flow (PCF) (indicating stronger cough) might be protective against pneumonia in stroke patients with swallowing problems.

Methods

Data from 72 patients were available for this analysis. Study procedures have been detailed previously.[4] Briefly, we recruited adults within 2 weeks of stroke, and excluded patients with significant cardiac/pulmonary disease; neurological conditions other than stroke; orthopaedic conditions affecting respiratory mechanics; inability to cooperate; or signs of pneumonia at enrolment. Swallowing function was described according to standardised bedside swallow assessment.[5] We measured cough flow of volitional and capsaicin-induced reflex cough, using a calibrated pneumotachograph with full face mask.[4] Pneumonia was observed for 4 weeks following baseline assessment and determined from documented medical diagnosis.

Our analysis was hypothesis-driven, assuming the data structure of a longitudinal observational study and examining only the predictor PCF for outcome pneumonia. First, we stratified the sample according to aspiration risk and pneumonia, and conducted group comparison tests. Second, we used logistic regression to examine the association between PCF and outcome pneumonia in the unsafe swallow group. Third, we categorised patients in the unsafe swallow group in 2 groups of high and low voluntary PCF, using a threshold of 400 L/min; and we calculated the odds ratio for outcome pneumonia according to dichotomised PCF. All analyses were conducted using Stata®11.2 statistical software.

Results

Analysis of the sample stratified by aspiration risk showed that PCF of voluntary cough was significantly lower in patients who had unsafe swallow and who developed pneumonia (table

1, online-supplement figures 1 and 2). Full sample characteristics at baseline are given in online-supplement table 2.

Logistic regression showed a statistically significant association between PCF of voluntary cough and pneumonia (OR 0.994 for each 1 L/min increase in PCF, 95%CI 0.988-1.0, p=0.035). The association between PCF of reflex cough and pneumonia was smaller and not statistically significant (OR 0.998 for each 1 L/min increase in PCF, 95%CI 0.992-1.004, p=0.475). Goodness of fit indicators were adequate (Pearson chi-squared and Hosmer-Lemeshow tests, p>0.05). Stata outputs for the logistic regression are given in online-supplement tables 3 and 4.

Categorising patients with unsafe swallow according to a threshold of 400 L/min voluntary PCF resulted in 22 patients in the low PCF category, out of which 9 developed pneumonia; and 11 patients in the high PCF group, out of which 2 developed pneumonia. The risk of pneumonia was approximately three times higher for patients in the low PCF group, although this was not statistically significant (OR 3.12, 95%CI 0.45-35.24). The Stata output is given in online-supplement table 5.

Table 1. Peak cough flow (PCF) according to 4-week incidence of pneumonia in patients with low aspiration risk (safe swallow) and high aspiration risk (unsafe swallow)

	Low aspiration risk (safe swallow)			High aspiration risk (unsafe swallow)		
	No pneumonia (n=37)	Pneumonia (n=2)	p-value*	No pneumonia (n=22)	Pneumonia (n=11)	p-value*
PCF of voluntary cough (L/min)	535 (264)	546 (307)	0.917	448 (244)	252 (130)	0.0053
PCF of reflex cough (L/min)	301 (110)	324 (168)	0.945	276 (124)	231 (100)	0.277

Figures are mean (SD)

*Independent samples t-test with unequal variance (5% alpha, 80% power)

Discussion

Our data lend support to the notion that strong cough protects from aspiration-related pneumonia. This association was stronger for voluntary cough, which leads us to hypothesise that PCF of voluntary cough might serve as a useful predictor of pneumonia risk in acute stroke. Logistic regression showed that each increase in voluntary PCF by 1 L/min reduced the risk of pneumonia by 0.6% (OR 0.994). The equivalent odds ratios for an increase in voluntary PCF by 50 and 100 L/min are approximately 0.73 and 0.53, respectively.

To illustrate how application of a PCF threshold might inform pneumonia risk in clinical practice, we applied an informed, although somewhat arbitrary cut-off of 400 L/min to categorise patients into those with stronger and those with weaker voluntary cough. The small sample size is a limitation to this analysis. Although we maximised statistical precision by examining only one association of interest, which was defined *a priori*, studies with larger sample sizes are required to develop more sophisticated multivariable predictor models, which would also allow adjustment for other known risk factors of post-stroke pneumonia.[6]

Further limitations to this analysis are trial eligibility criteria, which may have introduced selection bias not present in observational studies on consecutive patients. Respiratory muscle training in the intervention group may have affected the incidence of pneumonia, but this is unlikely as the trial showed no effect of these exercises on PCF compared with control patients. Although criteria based, pneumonia was physician diagnosed, but detection bias is unlikely as physicians were masked to allocation and to baseline assessments. Any future study of PCF and pneumonia risk would benefit from robust methods for diagnosing pneumonia.[7] In particular, the potential for diagnosis to be influenced by the diagnosing physician's subjective assessment of cough strength needs to be considered.

Despite limitations, the present analysis provides potentially valuable findings in a little researched field. Measurement of cough flow may provide an objective, device-based method to inform pneumonia risk in stroke patients with unsafe swallow at the bedside. Further studies are needed to confirm these results and validate their clinical application.

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Competing interests: The authors declare no competing interests

Patient consent: All participant gave written informed consent

Ethics approval: UK National Research Ethics Service, South West London Research Ethics Committee 3, reference 10/H0803/32

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Online-supplement Table 2 . Sample characteristics at baseline

		Stratification by aspiration risk		
	Total sample (n=72)	Safe swallow (n=39)	Unsafe swallow (n=33)	p-value[a]
Age (years)	64.6 (14.4)	59.9 (14.0)	70.2 (13.1)	0.0022
Males	42 (58%)[b]	23 (59%)[b]	19 (58%)[b]	0.905
NIHSS score (median, IQR)[c]	8 (5, 12)	6 (5, 10)	9 (7, 14)	0.0002
Pre-morbid NEADL score (median, IQR)[d]	60 (46, 63)	60 (54, 63)	57 (35, 63)	0.203
Stroke Type				
Ischemic	65 (90%)	38 (97%)	27 (82%)	0.089
Haemorrhagic	7 (10%)	1 (3%)	6 (18%)	0.089
Stroke Side				
Left	26 (36%)	16 (41%)	10 (30%)	0.393
Right	45 (62%)	22 (56%)	23 (70%)	0.393
Bilateral	1 (1%)	1 (3%)	-	0.393
Stroke Site				

Cortical	33 (46%)	17 (44%)	16 (48%)	0.578
Subcortical	31 (43%)	19 (49%)	12 (36%)	0.578
Brainstem/cerebellar	8 (11%)	3 (8%)	5 (15%)	0.578
Current smoker	18 (25%)	10 (26%)	8 (24%)	0.891
Forced spirometry				
FVC (L)	2.2 (1.0)	2.6 (0.9)	1.8 (1.0)	0.0008
FEV_1 (L)	1.8 (0.8)	2.0 (0.8)	1.5 (0.8)	0.0071
FEV_1/FVC ratio	0.82 (0.14)	0.79 (0.14)	0.85 (0.14)	0.0743
PEF (L/min)	240 (138)	274 (146)	199 (118)	0.0070
Maximal mouth pressures				
PEmax (cmH_2O)	59 (34)	71 (35)	40.5 (25)	0.0005
PImax (cmH_2O)	43 (29)	53 (30)	31 (23)	0.0013
Maximal voluntary cough				

PCF (L/min)	465 (258)	535 (262)	383 (230)	0.011
PIF (L/min)	134 (73)	146 (80)	119 (61)	0.109
CVE (L)	1.3 (0.7)	1.5 (0.7)	1.1 (0.7)	0.042
CVI (L)	1.6 (0.8)	1.8 (0.7)	1.3 (0.8)	0.011
CVAC (L/s/s)	166 (113)	194 (119)	134 (99)	0.024
GCT (s)	0.24 (0.2)	0.26 (0.2)	0.21 (0.1)	O.223
Capsaicin-induced involuntary cough				
PCF (L/min)	283 (114)	303 (110)	260 (116)	0.126
PIF (L/min)	88 (44)	98 (51)	77 (32)	0.046
CVE (L)	0.7 (0.4)	0.7 (0.4)	0.6 (0.3)	0.406
CVI (L)	1.2 (0.6)	1.3 (0.7)	1.0 (0.5)	0.024
CVAC (L/s/s)	114 (50)	124 (49)	102 (50)	0.073
GCT (s)	0.20 (0.1)	0.19 (0.1)	0.22 (0.1)	0.345
Pneumonia within 4 weeks of baseline	13 (18%)	2 (5%)	11 (33%)	0.004

assessment

Figures are mean (SD) and frequency (%), unless stated otherwise

[a]Independent samples t-test or Mann-Whitney U test for continuous data, Chi squared or Fisher's exact test for categorical data (5% alpha, 80% power)

[b]Percentages are percentages of column totals

[c]NIHSS, National Institutes of Health Stroke Scale: score range 0-34, higher score indicates more severe stroke, score <5 predicts favourable clinical outcome

[d]NEADL, Nottingham Extended Activities of Daily Living questionnaire: score range 0-66, higher score indicates greater independence in activities of daily living

CVAC, cough volume acceleration; CVE, cough volume expired; CVI, cough volume inspired; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; GCT, glottis compression time; PCF, cough flow; PEF, peak expiratory flow; PEmax, maximal expiratory mouth pressure; PIF, peak inspiratory flow; PImax, maximal inspiratory mouth pressure

Online-supplement Table 3. Logistic regression and goodness-of-fit tests: outcome pneumonia and predictor PCF of voluntary cough at baseline in 33 patients with unsafe swallow

```
. logistic RegPneu4Weeks VCPEFRbaseline if Swallowsafety1safe2unsafe==2

Logistic regression                             Number of obs   =         33
                                                LR chi2(1)      =       7.24
                                                Prob > chi2     =     0.0071
Log likelihood = -17.386481                     Pseudo R2       =     0.1723

------------------------------------------------------------------------------
RegPneu4We~s | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
VCPEFRbase~e |   .9936175   .0030242    -2.10   0.035     .9877078    .9995626
------------------------------------------------------------------------------

.
. logit

Logistic regression                             Number of obs   =         33
                                                LR chi2(1)      =       7.24
                                                Prob > chi2     =     0.0071
Log likelihood = -17.386481                     Pseudo R2       =     0.1723

------------------------------------------------------------------------------
RegPneu4We~s |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
VCPEFRbase~e |  -.0064029   .0030437    -2.10   0.035    -.0123684   -.0004375
       _cons |   1.413704   .9745368     1.45   0.147    -.4963532    3.323761
------------------------------------------------------------------------------

.
. estat gof

Logistic model for RegPneu4Weeks, goodness-of-fit test

       number of observations =        33
 number of covariate patterns =        33
             Pearson chi2(31) =        29.47
                  Prob > chi2 =         0.5447

.
. estat gof, group(10)

Logistic model for RegPneu4Weeks, goodness-of-fit test

  (Table collapsed on quantiles of estimated probabilities)

       number of observations =        33
             number of groups =        10
     Hosmer-Lemeshow chi2(8) =         1.96
                  Prob > chi2 =         0.9823
```

Online-supplement Table 4. Logistic regression and goodness-of-fit tests: outcome pneumonia and predictor PCF of reflex cough at baseline in 33 patients with unsafe swallow

```
. logistic RegPneu4Weeks RCPEFRbaseline if Swallowsafety1safe2unsafe==2

Logistic regression                             Number of obs   =         33
                                                LR chi2(1)      =       0.53
                                                Prob > chi2     =     0.4663
Log likelihood = -20.739546                     Pseudo R2       =     0.0126

------------------------------------------------------------------------------
RegPneu4We~s | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
RCPEFRbase~e |   .9977293   .0031731    -0.71   0.475     .9915294    1.003968
------------------------------------------------------------------------------

.
. logit

Logistic regression                             Number of obs   =         33
                                                LR chi2(1)      =       0.53
                                                Prob > chi2     =     0.4663
Log likelihood = -20.739546                     Pseudo R2       =     0.0126

------------------------------------------------------------------------------
RegPneu4We~s |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
RCPEFRbase~e |  -.0022733   .0031804    -0.71   0.475    -.0085067    .0039602
       _cons |  -.1326467   .8517719    -0.16   0.876    -1.802089    1.536795
------------------------------------------------------------------------------

.
. estat gof

Logistic model for RegPneu4Weeks, goodness-of-fit test

       number of observations =        33
 number of covariate patterns =        33
             Pearson chi2(31) =        32.78
                  Prob > chi2 =         0.3798

.
. estat gof, group(10)

Logistic model for RegPneu4Weeks, goodness-of-fit test

  (Table collapsed on quantiles of estimated probabilities)

       number of observations =        33
             number of groups =        10
     Hosmer-Lemeshow chi2(8) =         7.25
                  Prob > chi2 =         0.5097

.
```

Online-supplement Table 5. Odds ratio: outcome pneumonia (cases) and risk factor voluntary PCF ≤400 L/min (exposed) in 33 patients with unsafe swallow

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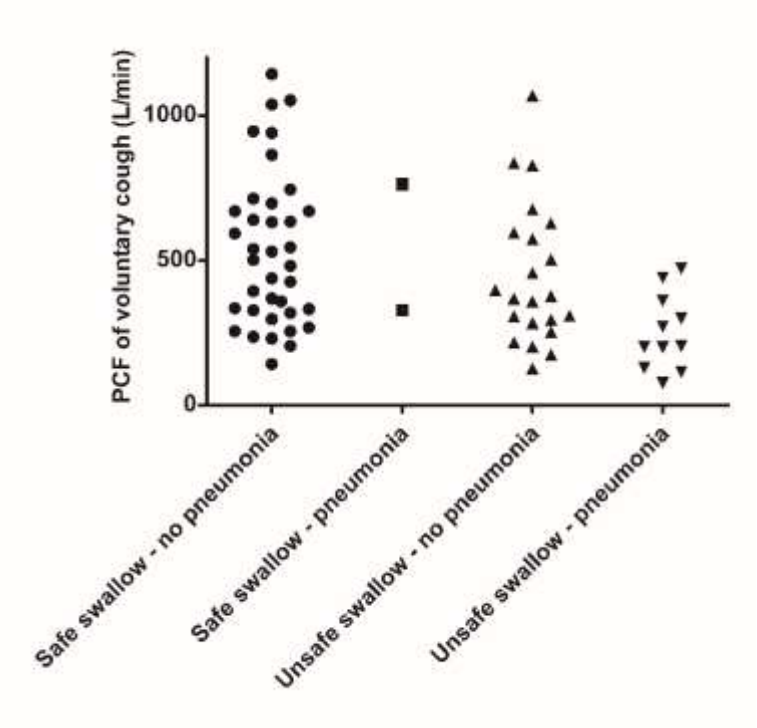
. cc RegPneu4Weeks Cat2_400_VCPEFR if Swallowsafety1safe2unsafe==2
```

	Exposed	Unexposed	Total	Proportion Exposed	
Cases	9	2	11	0.8182	
Controls	13	9	22	0.5909	
Total	22	11	33	0.6667	
	Point estimate		[95% Conf.	Interval]	
Odds ratio	3.115385		.4543444	35.24562	(exact)
Attr. frac. ex.	.6790123		-1.200974	.9716277	(exact)
Attr. frac. pop	.5555556				

chi2(1) = 1.70 Pr>chi2 = 0.1917

Online-supplement Figure 1. Peak cough flow (PCF) of maximal voluntary cough according to swallow safety and pneumonia status (each data point represents one patient, n=72)



Online-supplement Figure 2. Peak cough flow (PCF) of reflex cough according to swallow safety and pneumonia status (each data point represents one patient, n=69)