

Treatment of mild persistent asthma by cutaneous electronic stimulation

To the Editors:

The Global Initiative for Asthma (GINA) has emphasised the importance of assessing control in response to treatment in grading asthma severity [1]. However, many asthma patients are inadequately controlled despite conventional treatment. GINA also recognises a potential role for complementary medicine in asthma management [1]. Fenzian™ (Eumedic Ltd, Hungerford, UK) is a device that provides low current cutaneous electronic stimulation (CES) and is Food and Drug Administration licensed under the category of minimal risk (Device # 21 FR 882.5890) for biofeedback and treatment of pain. Biofeedback might influence bronchial smooth muscle constriction or perception of asthma control. We examined the hypothesis that CES, added to conventional treatment over 6 weeks, improves asthma control, pulmonary function, symptoms and reliance on rescue bronchodilator therapy in patients with persistent asthma.

In total, 20 subjects were recruited (nine males and 11 females), aged 18–65 yrs with a clinical history of mild-to-moderate persistent asthma for ≥ 3 months [2] and forced expiratory volume in 1 s (FEV₁) between 50% of predicted and the lower

limit of normal [3]. They reported using short-acting bronchodilator therapy on ≥ 4 days in 2 weeks. Their treatment regimen was otherwise stable consisting of bronchodilators alone or in combination with inhaled corticosteroids. None had evidence of recent respiratory tract infection. The study was approved by the Institutional Review Board (Human Subjects Protection Committee) of the University of California (Los Angeles, CA, USA) and each subject gave written informed consent.

The design was a single-blind, parallel-group study with two baseline visits, 4 weeks apart to ensure clinical stability. Subjects were randomised 1:1 to active or sham treatment consisting of 14 sessions over 6 weeks using a Fenzian™ device or an identical but inactivated device. We endeavoured to eliminate treatment and assessment bias. The study personnel who performed the assessments, including pulmonary function tests and administration of questionnaires, were

TABLE 1 Baseline characteristics of the subjects

	Sham	Fenzian™
Age yrs	45.4 ± 15.8	46.8 ± 14.8
Height m	1.70 ± 0.14	1.70 ± 0.05
Weight kg	79.3 ± 16.8	80.4 ± 15.8
FEV ₁ [#] L	2.32 ± 0.7	2.35 ± 0.5
FEV ₁ % reference [†]	70.8 ± 10.7	72.8 ± 9.5
PostBD FEV ₁ L	2.56 ± 0.8	2.67 ± 0.8
FVC [#] L	3.28 ± 1.0	3.54 ± 1.0
FVC % reference [†]	80.2 ± 11.5	86.5 ± 14.3
PostBD FVC L	3.38 ± 1.0	3.80 ± 1.3
FEV ₁ /FVC %	71.7 ± 9.0	68.4 ± 11.4
PostBD FEF _{25–75%} L·s ⁻¹	2.53 ± 1.04	1.97 ± 0.76
Asthma control ACQ	1.69 ± 0.89	1.83 ± 0.89
AM PEF L·min ⁻¹	347 ± 77	354 ± 120
PM PEF L·min ⁻¹	349 ± 75	369 ± 121
AM BD use puffs	0.30 ± 0.78	0.38 ± 0.78
PM BD use puffs	0.37 ± 0.98	0.75 ± 1.19

Data are presented as mean ± sd. At visit 1 (baseline), spirometry was performed three times with 30-min intervals between sets of measurements. FEV₁: forced expiratory volume in 1 s; BD: bronchodilator; FVC: forced vital capacity; FEF_{25–75%}: forced expiratory flow at 25–75% of FVC; ACQ: Asthma Control Questionnaire; AM: morning; PEF: peak expiratory flow; PM: afternoon. [#]: means of the best values from each of the three sets; [†]: reference values are derived from National Health and Nutrition Examination Survey III [5]. Fenzian™ is manufactured by Eumedic Ltd (Hungerford, UK).

TABLE 2 Changes in physiological measures and symptom assessments after 6 weeks of Fenzian™ or sham treatment

	Sham	Fenzian™	p-value
FEV ₁ mL	-28 ± 7	74 ± 7	0.281
FVC mL	-21 ± 7	95 ± 7	0.261
FEF _{25–75%} L·s ⁻¹	-0.18 ± 0.14	0.25 ± 0.14	0.033
isoFEF _{25–75%} L·s ⁻¹	-0.10 ± 0.21	0.09 ± 0.20	0.507
TDI	-0.1 ± 0.8	1.8 ± 0.7	0.176
Asthma control ACQ	0.16 ± 0.22	-0.55 ± 0.22	0.032
Asthma symptoms ASUI	-0.04 ± 0.05	0.03 ± 0.05	0.279
Quality of life AQLQ	-0.04 ± 0.23	0.38 ± 0.21	0.183
Quality of life SF-12	0.95 ± 0.98	1.07 ± 0.93	0.258
AM PEF L·min ⁻¹	-2.8 ± 4.8	10.5 ± 4.8	0.029
AM BD use puffs	0.16 ± 0.07	-0.25 ± 0.07	<0.001
AM symptoms	0.21 ± 0.07	-0.06 ± 0.07	0.338
PM PEF L·min ⁻¹	1.95 ± 5.07	5.30 ± 4.88	0.278
PM BD use puffs	0.03 ± 0.10	-0.58 ± 0.10	<0.001
PM symptoms	0.00 ± 0.11	-0.17 ± 0.11	0.120
AM dyspnoea	0.76 ± 0.63	2.43 ± 0.53	<0.001
PM dyspnoea	0.66 ± 0.64	1.08 ± 0.55	0.052
Daily dyspnoea	1.51 ± 1.17	3.57 ± 0.98	<0.001

Data are presented as mean ± sd, unless otherwise stated. FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; FEF_{25–75%}: forced expiratory flow at 25–75% of FVC; isoFEF_{25–75%}: forced expiratory flow between isovolumes of 25 and 75% of FVC; TDI: transition dyspnoea index; ACQ: Asthma Control Questionnaire; ASUI: Asthma Symptom Utility Index; AQLQ: Asthma Quality of Life Questionnaire; SF-12: Short-Form 12; AM: morning; PEF: peak expiratory flow; BD: bronchodilator; PM: afternoon. Significance tested by mixed effects models except isoFEF_{25–75%} and TDI which were compared by t-test. Fenzian™ is manufactured by Eumedic Ltd (Hungerford, UK).

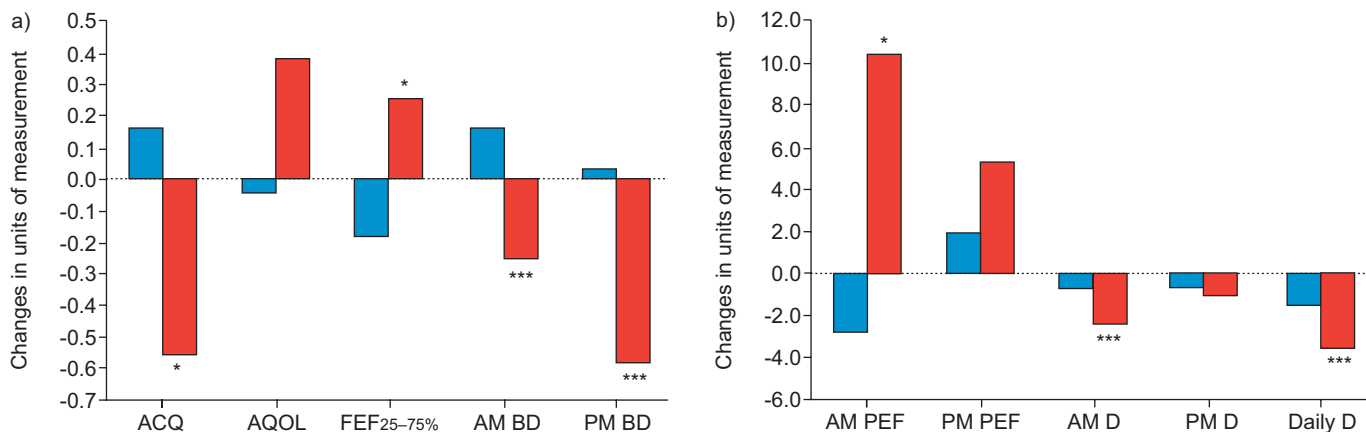


FIGURE 1. Changes in key outcome measures with sham (blue) and Fenzian™ (red) treatments. Fenzian™ is manufactured by Eumedic Ltd (Hungerford, UK). ACQ: Asthma Control Questionnaire (a reduced score indicates improvement); AQOL: Asthma Quality of Life; FEF: forced expiratory flow between 25 and 75% of forced vital capacity ($L \cdot s^{-1}$); AM BD: morning bronchodilator use (puffs); PM BD: afternoon bronchodilator use (puffs); AM PEF: morning peak expiratory flow ($L \cdot \text{min}^{-1}$); PM PEF: afternoon peak expiratory flow ($L \cdot \text{min}^{-1}$); AM D: morning dyspnoea score; PM D: afternoon dyspnoea score; Daily D: daily dyspnoea score. *: $p < 0.05$; ***: $p < 0.001$.

blinded as to whether the subject received active or sham treatment. The personnel administering the treatments obviously could not be blinded but care was taken to follow similar treatment routines in each group.

Asthma control, symptoms and quality of life were assessed using the Asthma Control Questionnaire (ACQ) [4], Asthma Symptom Utility Index [5], Asthma Quality of Life Questionnaire and Short Form-12 [6]. Subjects recorded the best of three peak flow measurements twice daily along with symptoms (breathlessness, chest tightness, cough, wheezing) and albuterol use on diary cards (AM-2 Asthma Monitor; Cardinal Health, Yorba Linda, CA, USA). Baseline characteristics were well matched between groups as seen in table 1. Significant differences in physiological measures and questionnaires were not detected between visits 1 and 2 verifying clinical stability.

Changes in key outcome measures with sham and Fenzian™ treatments are shown in table 2 and figure 1. With CES we found significant improvements in morning peak flow (from 349 to 360 $L \cdot \text{min}^{-1}$; $p = 0.029$), morning bronchodilator use (from 0.55 to 0.30 puffs; $p < 0.001$), afternoon bronchodilator use (from 1.06 to 0.48 puffs; $p < 0.001$), and a composite of daily symptoms including breathlessness, chest tightness, cough and wheezing by Likert scales ($p < 0.001$). Breathlessness was also assessed using the dyspnoea index of MAHLER *et al.* [7]. Transition dyspnoea index was +1.8 with CES but unchanged with sham treatment. These improvements were accompanied by a significant improvement in asthma control by the ACQ ($p = 0.023$). Evaluation of the ACQ against GINA and National Institutes of Health (NIH) guidelines determined a cut-off point of 1.50 as identifying patients whose asthma is not well controlled, with a positive predictive value of 0.88 [8]. Thus both groups of subjects were not well controlled on entry into the current study. Those treated with CES showed an improvement in ACQ score from 1.83 to 1.30, *i.e.* became well controlled, whereas those receiving sham treatments showed deterioration in ACQ score from 1.69 to 1.84.

Spirometry was performed three times at each visit. There were nonsignificant differences in the changes of FEV₁ (102 mL) and forced vital capacity (FVC; 116 mL) between the groups favouring CES. Forced expiratory flow at 25–75% of FVC increased by 0.25 $L \cdot s^{-1}$ with CES but decreased by 0.18 $L \cdot s^{-1}$ in controls ($p = 0.033$).

This sham-controlled study shows proof of concept that CES with Fenzian™ might offer a novel alternative to conventional pharmacotherapy in patients with mild persistent asthma and perhaps an adjunct therapy for patients with more severe disease. We found a consistent pattern of improved asthma symptoms, including dyspnoea, and reduced bronchodilator use with small changes in airway function. The mechanism of action remains unknown but biofeedback could induce relaxation of bronchial smooth muscle or changes in the perception of asthma symptoms through central nervous system mechanisms.

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Sarcoidosis-related pulmonary veno-occlusive disease presenting with recurrent haemoptysis

To the Editors:

A 52-yr-old female nonsmoker presented with haemoptysis consisting of streaks of bright red blood daily for 3 weeks. She gave a 3-yr history of dry cough, episodic wheeze and mild exertional dyspnoea. The symptoms had not improved with inhaled corticosteroids (fluticasone 250 µg *b.i.d.*). The patient denied fever, sweats or weight loss and had no significant past medical history. Physical examination was unremarkable. Chest radiograph showed no focal pulmonary abnormality or obvious lymphadenopathy, and electrocardiogram was normal. Pulmonary function tests recorded a forced expiratory volume in 1 s (FEV1) of 2.22 L (86% predicted), a forced vital capacity (FVC) of 2.93 L (96% pred) and a diffusing capacity of the lung for carbon monoxide (DL_{CO}) of 7.23 mmol·m⁻¹·kPa⁻¹ (88% pred).

Laboratory investigations showed a haemoglobin level of 12.9 g·dL⁻¹, and a normal coagulation screen, metabolic screen and erythrocyte sedimentation rate (21 mm·h⁻¹). Serum auto-antibodies were negative and the angiotensin converting enzyme (ACE) level was 53 IU·L⁻¹ (normal range 0–52 IU·L⁻¹). High-resolution computed tomography (HRCT) of the chest showed thickening of central bronchovascular bundles and scattered, nodular, ground-glass and airspace opacities (fig. 1a). Fibreoptic bronchoscopy was requested. At 1 h prior to the procedure, the patient had a large haemoptysis of 200 mL bright red blood. Bronchoscopy showed diffuse fresh blood and grossly hyperaemic bronchial mucosa with generalised oozing from major and lobar bronchi (fig. 1b).

The patient subsequently underwent rigid bronchoscopy, bronchial biopsies and surgical lung biopsies from the left lower lobe. Histological examination of the bronchial biopsies was unremarkable. Lung biopsies demonstrated a cluster of noncaseating granulomata on the pleural surface but normal lung parenchyma and pulmonary vessels. Based on clinical, radiological and histological appearances, the patient was

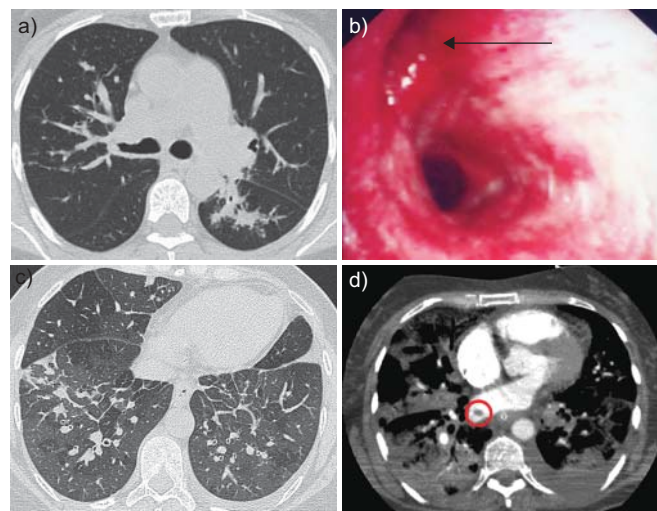


FIGURE 1. a) Axial high-resolution computed tomography (HRCT) image showing nodular thickening extending along central bronchovascular bundles in the apical segment of the left lower lobe. Elsewhere, there were scattered nodular, ground-glass and airspace opacities consistent with pulmonary sarcoidosis. b) Bronchoscopic view of the right main and right upper lobe bronchus (arrow) showing diffuse mucosal erythema. c) HRCT thorax image taken 15 months after initial presentation showing thickened interlobular septa and patchy ground-glass attenuation. The subsegmental pulmonary arteries were enlarged relative to accompanying bronchi, reflecting raised pulmonary artery pressure. There was a small left pleural effusion. d) Contrast-enhanced computed tomography pulmonary angiogram during the patient’s final illness, displaying a persistent left pleural effusion with superadded bilateral, patchy airspace consolidation. In addition, a filling defect, presumed thrombus, was seen in the right pulmonary venous confluence (circled in red).

diagnosed with sarcoidosis. No specific therapy was initiated partly due to patient choice, because her symptoms had resolved and lung function tests were within normal limits.