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Reversal of periodic breathing after aerobic training in heart failure

To the Editors:

A 58-yr-old male was referred for participation in a cardiac rehabilitation programme. He had a long-term history of hypertensive cardiomyopathy and systolic dysfunction and was clinically stable, being treated with β-blocker carvedilol, losartan, digitalis, diuretics and spironolactone, with no changes in medication in the previous 16 weeks. An echocardiogram showed a 17% left ventricular ejection fraction and the patient was in New York Heart Association Functional Class III.

Before starting the exercise training programme, the patient was submitted to a maximal progressive cardiopulmonary exercise test, on an electromagnetically braked cycle ergometer (Medifit 400L; Medical Fitness Equipment, Maarn, The Netherlands), with work rate increments of 5 W every 1 min at 60 rpm until exhaustion. Oxygen uptake ($V'O_2$) and carbon dioxide production were determined by means of gas exchange on a breath-by-breath basis in a computerised system (Vmax 229 model; SensorMedics, BuenaVista, CA, USA). Peak $V'O_2$ was defined as the maximum attained $V'O_2$ at the end of the exercise period in which the patient could no longer maintain the cycle rate. During this test, the patient showed a very low exercise capacity, with a peak $V'O_2$ of 9.3 mL·kg^{-1}·min^{-1} and 35 W of peak power load. Evaluation of ventilation during exercise revealed the presence of periodic breathing (fig. 1), as identified by the criteria proposed by LEITE *et al.* [1] and others [2].

The patient underwent 4 months of exercise training, which consisted of 60-min exercise sessions 3 times·week^{-1} under medical supervision at the Heart Institute (affiliation) [3]. Each

exercise session consisted of 5 min stretching exercises, 25 min cycling on an cycle ergometer in the first month and up to 40 min in the next 3 months, 10 min local strengthening exercises (sit-ups, push-ups and pull-ups) and 5 min of cool down with stretching exercises. The exercise intensity was established by heart-rate levels that corresponded to anaerobic threshold up to 10% below the respiratory compensation point obtained in the cardiopulmonary exercise test. When a training
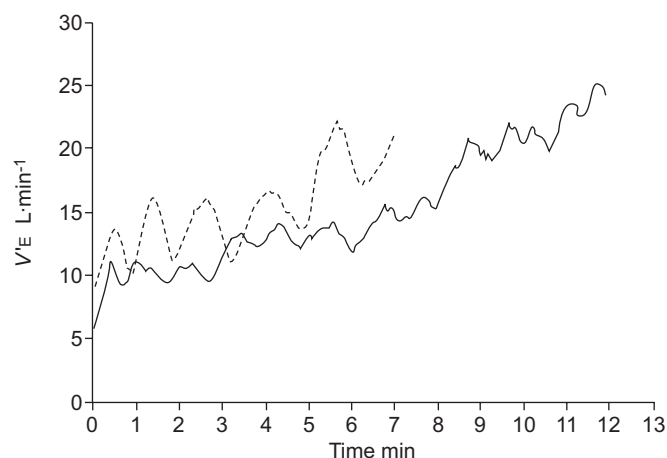

FIGURE 1. Ventilatory responses to graded cycle exercise of a patient with heart failure before (-----) and after (——) four months of exercise training. $V'E$: minute ventilation.

effect was observed, as indicated by the patient using a Borg perceived exertion scale, the cycle workload was slightly increased. Heart-rate reduction was rarely used to adjust the bicycle workload, since the patient was under β-blocker treatment. Aerobic exercise training duration increased progressively so that the patient could perform 40 min of bicycle exercise at the established intensity. Throughout the training period, medication was kept the same and no major clinical event occurred.

After 4 months of exercise training, left ventricular ejection fraction remained the same (17%), New York Heart Association Functional Class improved to II, and the patient was submitted to another cardiopulmonary exercise test, following the same exercise increment protocol and the same equipment used in the first evaluation. Peak results of both tests are presented in table 1. As noted in figure 1, maximal exercise time increased. Although the ventilation pattern in the second test still presented some oscillation, it was much closer to the expected physiological linear increase and thus, did not comply with the criteria for exercise periodic breathing [2].

RIBEIRO et al. [4] have shown reversal of periodic breathing with pharmacological intervention, more specifically, with milrinone or cardiac transplantation. To our knowledge, this is the first report of reversal of periodic breathing related to exercise training in a patient with chronic heart failure.

Periodic breathing seems to be related to mechanisms within central nervous system, more specifically with nuclei involved in respiratory control [5]. In addition, YAJIMA et al. [6] found that periodic breathing was consequent to fluctuations in pulmonary blood flow during exercise in heart failure patients. Although periodic breathing independently predicts cardiac mortality in heart failure patients [1], it is not a phenomenon directly correlated to low left-ventricular ejection fraction, as it could be suspected. For example, the occurrence of periodic breathing could predict cardiac mortality in patients who were waiting for cardiac transplantation, independent of ejection fraction. Indeed, in the present case report, left-ventricular ejection fraction and peak oxygen pulse (which is directly correlated to maximum cardiac output) remained the same, despite the improvements in peak V'_{O_2} and New York Heart

Association Functional Class. Although the mechanisms involved in the development of periodic breathing are not completely understood, its role as a marker of worse prognosis in heart failure is well established. Thus, the reversal of periodic breathing after exercise training may have practical implications.

One could hypothesise that the non-occurrence of periodic breathing after exercise training could have happened by chance. Although a single case is not a strong enough evidence to exclude this possibility, it is important to notice that medication and clinical status were stable throughout exercise training period. In addition, CORRA et al. [7] have shown that occurrence of exercise periodic breathing is a reproducible phenomenon; thus, it is very unlikely that the reversal of periodic breathing was not consequent to exercise training. Whether the reversal of periodic breathing after exercise training will occur in larger series of heart failure patients and if this reversal is related to prognosis improvement desires further investigation.

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TABLE 1	Peak exercise data of a patient with heart failure before and after 4-month exercise training	
Variable	**Before**	**After**
Time to exhaustion	7 min 00 s	11 min 46 s
V'_{O_2} mL·kg^{-1}·min^{-1}	9.3	11.0
V'_{CO_2} mL·kg^{-1}·min^{-1}	10.0	11.8
V'_E L·min^{-1}	24.3	27.2
Oxygen pulse	6.3	6.6
Power load W	35	60
Heart rate beats·min^{-1}	101	115
Systolic blood pressure mmHg	160	180
Diastolic blood pressure mmHg	90	110

V'_{O_2}: oxygen uptake; V'_{CO_2}: carbon dioxide production; V'_E: minute ventilation.

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Smoking resumption after lung transplantation: a sobering truth

To the Editors:

About 40% of lung transplants (LTx) are performed for end-stage emphysema in former smokers [1]. Patients are principally only enrolled on the waiting list after having quit smoking for at least 6 months [1]. Some LTx recipients may resume smoking, which could complicate post-transplant outcome [2]. Surprisingly, most LTx centres do not monitor smoking habits. We assessed all 267 LTx recipients currently in follow-up at our centre for smoking, after informed consent and approval by the local Ethical Review Board.

Smoking behaviour was investigated by a standardised questionnaire, measurement of urinary cotinine (COT) and exhaled carbon monoxide (eCO) levels. The questionnaire addressed past and current smoking habits (regular or occasional active smoking and second-hand smoking, *i.e.* passive exposure *via* relatives or environmental exposure *via* social/work-related contacts) as well as the use of nicotine-replacement therapy (NRT). COT was assessed by gas chromatography and mass spectrometry (Thermo Scientific, Geel, Belgium) and eCO by using an electrochemical sensor (Bedfont Scientific, Kent, UK; detection limit 1 ppm), as previously described [3, 4]. Statistical analyses were performed with Graphpad Prism 4.0 (San Diego, CA, USA). An unpaired t-test, Mann–Whitney U-test or Fisher's exact test were used where appropriate and receiver–operating characteristic curve analysis was used for calculation of predictive values.

LTx recipients (bilateral/single/heart–lung transplantation n=190/59/18) were assessed at a median (interquartile range) of 3.4 (1.5–6.0) yrs after LTx. Prior to LTx, 166 (62%) out of 267 patients were former smokers and 101 (38%) out of 267 never-smokers. Former smokers reported smoking cessation at a median of 4.0 (1.5–10.0) yrs before LTx. The majority of former smokers were transplanted for COPD (n=109 out of 166, 41% of the studied cohort), the remaining for pulmonary fibrosis (10%), α_1-antitrypsin deficiency-related emphysema (5.2%) or various other indications (5.8%).

Based on the questionnaire, 30 (11%) out of 267 patients reported ever smoking after LTx, of which, the majority had been transplanted for emphysema due to COPD (n=25) or α_1-antitrypsin deficiency (n=2). Of these 30 patients, 27 were current active smokers at the time of evaluation (''smokers''). Three reported smoking only some cigarettes during a few weeks after LTx, but not at the time of evaluation, whereas the remaining 237 patients denied ever smoking after LTx (''nonsmokers''; n=240) (fig. 1). Second-hand smoking was reported in 105 (39%) out of 267 patients, of whom 86 had smoking relatives (of which 40 smoked indoors), 31 regularly attended smokey bars and/or three worked in smokey conditions. The abstinence period between pre-LTx smoking cessation and subsequent LTx was shorter in smokers compared with nonsmokers: 1.0 (0.5–2.0) *versus* 5.0 (2.0–11.0) yrs, respectively (p<0.0001). Smokers resumed smoking at a median of 1.0 (0.5–3.0) yr post-LTx and smoked 3 (2–5) cigarettes·day^{-1}. Smokers were more likely to be transplanted for emphysema (OR 17.5 (95% CI 4.1–75.6); p<0.0001), more
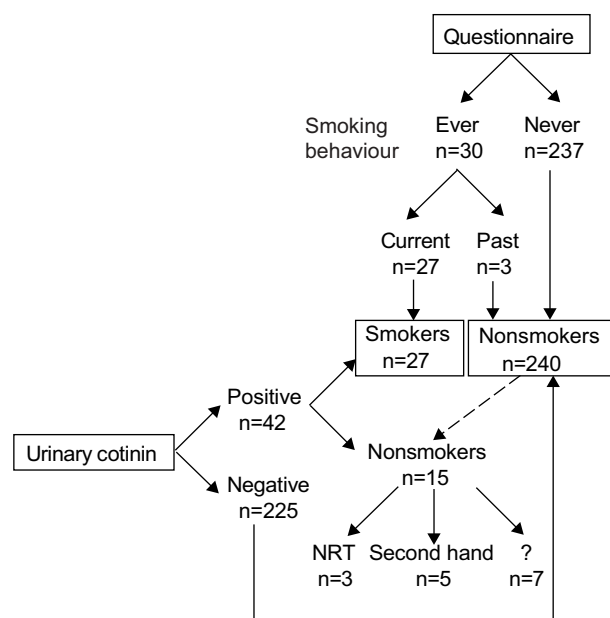

FIGURE 1. Flow-diagram of lung transplant recipients categorised according to reported smoking behaviour and urinary cotinin levels. NRT: nicotine-replacement therapy.