Mauro Contini[1], Edoardo Conte[1], Piergiuseppe Agostoni[1,2]

piergiuseppe.agostoni@unimi.it

Lung function corner

Lung function evaluation in heart failure: possible pitfalls

Case history

A 59-year-old male former smoker, with a history of hypertension, diabetes and chronic ischaemic heart disease (prior non-ST-elevation myocardial infarction and percutaneous coronary intervention+stent on circumflex and descending anterior coronary arteries) was referred to our lab for progressive dyspnoea of unknown origin. Even if a temporary moderate left ventricular systolic dysfunction had been observed during the acute phase of non-ST-elevation myocardial infarction, a cardiac ultrasound performed a few months after revascularisation showed a normal systolic function. At the time of the visit, the patient complained of a progressive functional capacity decline in the last 3 months, with shortness of breath after more than usual efforts (New York Heart Association class II). Pharmacological treatment included amlodipine, ivabradine, low dose diuretics, acetylsalicylic acid and metformin. At physical examination rhythmic pulse (70 bpm) and normal arterial pressure (120/70 mmHg) were detected, together with minimal dependent oedema, absence of jugular distention, bibasilar reduced breath sounds with rare fine crackles and soft cardiac tones with grade 2 holosystolic murmur. Resting ECG was normal, except for signs of a previous inferior myocardial infarction. Resting pulmonary function test (PFT) showed a severe restrictive deficit with moderate reduction in lung diffusion for carbon monoxide (D_{LCO}) entirely due to a reduction in the alveolar volume (V_A). A maximal cardiopulmonary exercise test (CPET) showed a severe reduction in exercise capacity with ventilatory limitation to exercise and a restrictive ventilatory pattern. However, further investigations led to diagnosis of heart failure. Indeed, a chest radiograph (figure 1) showed vascular congestion and pleural effusion, cardiac ultrasound showed a severe reduction in left ventricular systolic function (23.5%) with left ventricular dilation, increased left ventricular filling pressure and pulmonary hypertension and brain natriuretic peptide (BNP) was significantly altered (579 pg·mL^{-1}). A primary lung disease was excluded by computed tomography lung scan.

Question

What is the best timing to perform PFTs in the context of heart failure?

Answer

Although symptoms and clinical signs were not specific, heart failure diagnosis became clear after further diagnostic analysis. In this context, however, PFT showed a restrictive ventilatory deficit suggesting lung disease comorbidity. Moreover, CPET identified a ventilatory and not a cardiac limitation to exercise.

In table 1, the results of PFT and CPET are reported. Forced vital capacity (FVC) was

Cite as: Contini M, Conte E, Agostoni P. Lung function evaluation in heart failure: possible pitfalls. *Breathe* 2020; 16: 190316.

@ERSpublications
Close to acute heart failure, a restrictive and/or obstructive lung impairment can be detected in the absence of any primitive lung disease. To avoid diagnostic pitfalls, lung function evaluation should be delayed until after full patient recovery. http://bit.ly/3aEy8ed

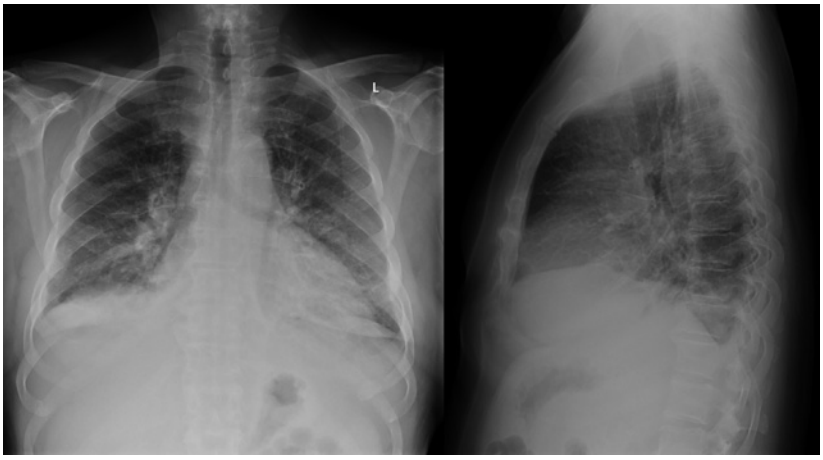

Figure 1 *Chest radiograph clearly showing the presence of lung vascular congestion and pleural effusion.*

Table 1 *Main CPET and PFT results from tests performed*

Variables	Pre-heart failure treatment	Post-heart failure treatment
CPET		
Peak V'_{O_2} mL·Kg^{-1}·min^{-1}	11.4	19.4
Peak V'_{O_2} % predicted	48	76
$\Delta V'_{O_2}/\Delta$Work mL·min^{-1}·W^{-1}	10.3	10.4
Peak O_2 pulse mL·beats^{-1}	9.4	13.4
Max workload W	54	121
V'_E/V'_{CO_2} slope	33	28
V'_E/V'_{CO_2} at AT	45	33
V'_E/V'_{CO_2} nadir	41	31
Peak V'_E L·min^{-1}	50	78
Peak respiratory rate breaths·min^{-1}	54	42
Breathing reserve %	3	14
Peak S_{PO_2} %	89	95
Peak RER	0.91	1.24
PFT		
FVC L	1.72	3.23
FVC % predicted	42	77
FEV_1 L	1.50	2.59
FEV_1 % predicted	47	81
FEV_1/FVC	0.87	0.80
D_{LCO} mL·mmHg^{-1}·min^{-1}	13.4	22.4
D_{LCO} % predicted	49	82
$D_{LCO_{adj}}$ mL·mmHg^{-1}·min^{-1}	12.6	21.0
$D_{LCO_{adj}}$ % predicted	46	77
$D_{LCO_{adj}}/V_A$ mL·mmHg^{-1}·min^{-1}·L^{-1}	5.22	5.04
$D_{LCO_{adj}}/V_A$ % predicted	119	117
V_A L	2.56	4.44
V_A % predicted	38	67

S_{PO_2}: arterial oxygen saturation measured by pulse oximetry; RER: respiratory exchange ratio; $D_{LCO_{adj}}$: D_{LCO} adjusted after correction for haemoglobin level.

significantly reduced (1.72 L, corresponding to 42% of the predicted value in a 172 cm tall male with a body mass index of 32.8 kg·m^{-2}), as well as forced expiratory volume in 1 s (FEV_1), but with a FEV_1/FVC ratio of 0.87 which is not consistent with an obstructive disease. Even in the absence of plethysmographic data, a prevalent restrictive disease was highly likely if the severe reduction in the V_A and the shape of the flow–volume loop are taken into account. D_{LCO}, measured by single breath technique, appeared to be severely reduced (13.4 mL·mmHg^{-1}·min^{-1}, 49% of the predicted value), especially after correction for haemoglobin level (17.1 g·dL^{-1}), and was entirely accounted for by the reduction in V_A (38% of the predicted value). Accordingly, D_{LCO}/V_A was higher than expected. This is consistent with a diagnosis of restrictive lung disease as well. A severe reduction in exercise capacity was also observed, with a maximal workload of only 54 W and a test duration <5 min in a ramp test set at 12 Watts per minute. Even if the patients subjectively performed a maximal exercise test, the test was submaximal from a "metabolic" point of view, as shown by a peak respiratory exchange ratio (RER) (carbon dioxide production (V'_{CO_2})/oxygen uptake (V'_{O_2})) <1.1. Accordingly, peak V'_{O_2} was severely reduced (11.4 mL·Kg^{-1}·min^{-1}, corresponding to a Weber class C and 48% of the predicted value). Anaerobic threshold (AT), calculated by the inflection point in the V'_{CO_2}/V'_{O_2} relationship was anticipated (9.3 mL·Kg^{-1}·min^{-1}, 32% of the maximal predicted V'_{O_2}) (figure 2a). Nevertheless, the rate of increase in V'_{O_2} with workload ($\Delta V'_{O_2}/\Delta$Work slope) was normal and not consistent with a cardiogenic limitation. Peak O_2 pulse was reduced as well (9.4 mL·beat^{-1}, 63% of the predicted); however, this finding cannot be considered as a marker of inadequate increase of systolic volume with exercise as a plateau is absent and the test is largely submaximal. In figure 3, O_2 pulse behaviour during exercise is shown both in pre- and post-treatment CPETs. However, the most obvious CPET anomaly observed is the ventilation response to exercise. Some degree of ventilation inefficiency was outlined by a V'_E/V'_{CO_2} slope slightly above the normal limit, which usually indicates an increase in dead space (V_D) ventilation. Of interest, V'_E/V'_{CO_2} ratio at the AT and nadir V'_E/V'_{CO_2} were both elevated and higher before (45 and 41, respectively) than after treatment (41 and 31 respectively), as detailed in table 1. Accordingly, measurement of V_D/tidal volume (V_T) course during CPET would have been of great help in the test interpretation, but it would have required serial arterial sample collection for blood gas analysis during exercise, which is not routinely performed. Presence of a lung disease could be even inferred by the increase in the y-intercept of the V'_E/V'_{CO_2} relationship, that was as high as 7.6 L (figure 4a). This value, which is usually <3 L in normal subjects, represents the amount of ventilation at a hypothetic null V'_{CO_2}, roughly representing V_D

ventilation. More importantly, a near complete erosion of breathing reserve (3%, 1.8 L) at the peak exercise was recorded. A ventilatory limitation to exercise is usually stated when breathing reserve is <10% or 11 L as an absolute value. Breathing reserve is calculated as the difference between the maximal voluntary ventilation and actual maximal ventilation. In this case maximal voluntary ventilation was not directly measured, but it was calculated by FEV_1 (maximal voluntary ventilation=FEV_1×35=1.50×35=52.5 L·min^{-1}; breathing reserve=52.5–50.7)/52.5×100=3.4%). Patient inability to adequately increase V_T during exercise also translated into an elevated peak respiratory rate (RR) (54 acts·min^{-1}). The pathological ventilatory pattern during exercise, consistent with restrictive lung impairment, is well depicted by the relationship between the increase in V_T and V'_E (figure 5b). Even in the very first part of exercise, ventilation increases almost exclusively thanks to an increase in RR, with only trivial increase in V_T. Moreover, conversely to what usually happens in obstructive lung disease, end-tidal carbon dioxide tension was below the upper limit throughout the whole exercise (maximal end-tidal carbon dioxide tension 32.1 mmHg). Finally, a significant O_2 desaturation was detected (arterial oxygen saturation measured by pulse oximetry from 95% to 89% at the peak), which is typically observed in lung diseases, but only rarely in heart failure.

Follow-up

The patient was treated with *i.v.* diuretic and inotropic therapy obtaining almost complete resolution of heart failure signs and symptoms, BNP reduction (245 pg·mL^{-1}) and pleural effusion disappearance. Before hospital discharge, PFT and CPET were repeated. As shown in table 1, PFT displayed an almost normalised FVC (77% of predicted) (figure 5a) and D_{LCO} and a dramatic improvement in maximal exercise capacity at CPET (peak V'_{O_2} 19.4 mL·Kg^{-1}·min^{-1}, 76% of predicted value, AT 46% of maximal V'_{O_2} predicted) (figure 2b). Exercise was now maximal even from a metabolic point of view (peak RER 1.24). V'_E/V'_{CO_2} slope was normalised and the y-intercept was significantly reduced (figure 4b). Breathing reserve was now 14%, with an increased peak ventilation (78 L·min^{-1}) and a reduced peak RR (42 breaths·min^{-1}). Ventilatory pattern during exercise, even if still abnormal, greatly improved, with a steeper increase in V_T with exercise (figure 5b). Oxygen desaturation was no more detectable. Of interest, O_2 pulse increased when compared to pre-therapy CPET (from 9.4 to 13.4 mL·beat^{-1}).

Only lung function investigations performed once heart failure was completely resolved were able to correctly describe the clinical picture of the patient.

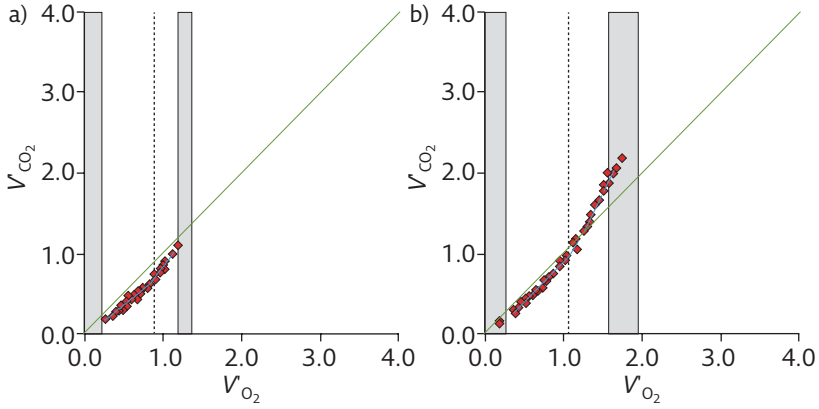

Figure 2 *AT identification by a V-slope ($V'CO_2$ versus $V'O_2$) graph. The change in the slope (dotted line) identifies the appearance of $V'CO_2$ surplus by anaerobic metabolism. The threshold is clearly anticipated in a) the test performed close to acute cardiac decompensation versus b) the pre-discharge test. Dotted lines show a) AT=9.3 mL·Kg^{-1}·min^{-1} (32% $V'O_{2max}$ predicted) and b) AT=11.8 mL·Kg^{-1}·min^{-1} (46% $V'O_{2max}$ predicted).*

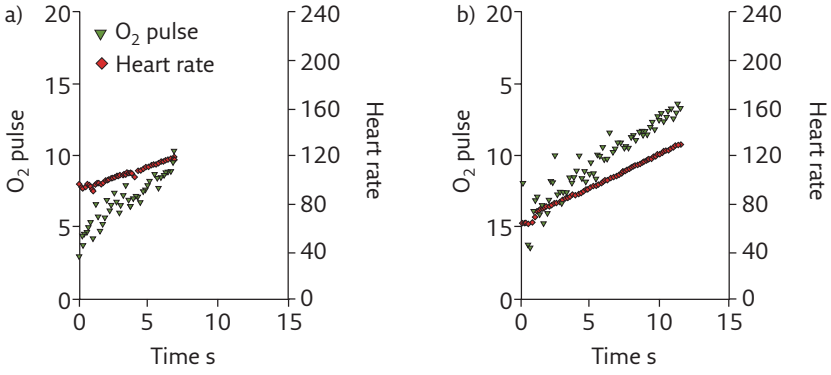

Figure 3 *a) Pre- and b) post-heart failure treatment O_2 pulse curves showing no change in slope morphology. Of note in (a), pre-treatment CPET showed a shorter exercise due to ventilatory limitation.*

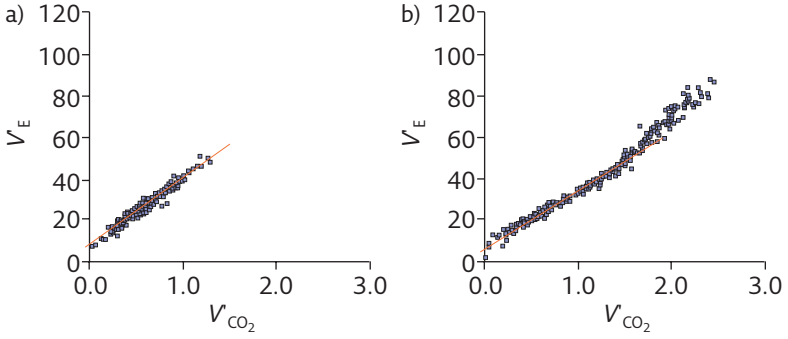

Figure 4 *$V'_E/V'CO_2$ slope a) pre- and b) post-heart failure treatment tests. In the first test, both a higher slope and y-intercept value are detectable. a) Slope=33, y=7.6 L. b) Slope=28, y=5.6 L.*

Discussion

The present case shows that, in a patient with severe heart failure, PFT and CPET may mimic severe lung disease, if tests are performed closely to the acute phase. Indeed, we observed a severe restrictive pulmonary pattern, low D_{LCO} and low V_A at rest coupled with low breathing reserve and

Self-evaluation questions

1. In a patient with lung restrictive disease which of the following CPET results is more likely?
   a. A steep increase in $V_E/V'CO_2$ slope throughout the whole exercise
   b. A poor increase in V_T and an inappropriate increase in RR already in the early phase of exercise
   c. A very high breathing reserve at the end of exercise
2. HF can cause a restrictive lung pattern by which of the following mechanisms?
   a. Cardiac enlargement, increased pulmonary stiffness, reduction in working alveolar–capillary units and respiratory muscle fatigue
   b. Cardiac enlargement, anaemia and increased lung stiffness
   c. Respiratory muscle fatigue, increased lung stiffness and reduced venous pulmonary pressure
3. In the context of HF, CPET usually shows:
   a. Normal $\Delta V'O_2/\Delta$Work slope, reduced peak oxygen pulse, delayed AT and preserved V_D/V_T reduction during exercise
   b. Reduced $\Delta V'O_2/\Delta$Work slope, reduced peak oxygen pulse, early AT and preserved V_D/V_T reduction during exercise
   c. Normal $\Delta V'O_2/\Delta$Work slope, reduced peak oxygen pulse, early AT and inadequate V_D/V_T reduction during exercise

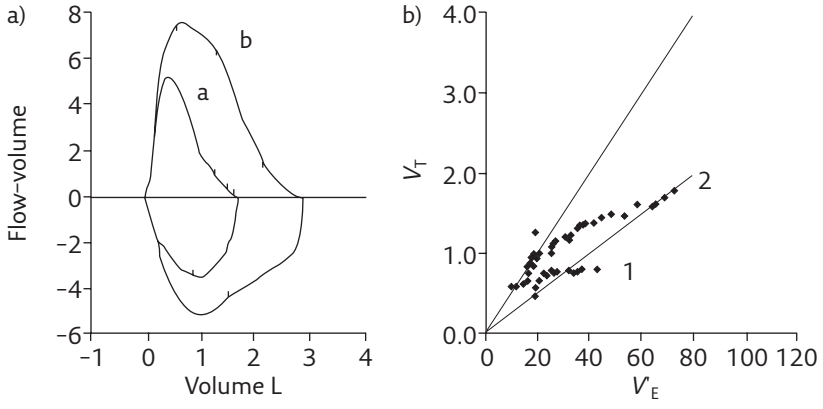

Figure 5 *a) The resting maximal expiratory flow–volume loops in acute conditions (line a) and at the pre-discharge evaluation (line b) are shown. At the first evaluation, an obvious reduction in FVC was recorded. b) The relationship between increase in V_T and V'_E during exercise is reported. Solid lines indicate points with the same RR. In the first CPET (1) there is an almost complete lack of increase in V_T, and V'_E increase is entirely due to increase in RR. This pattern greatly improved in the pre-discharge test (2).*

haemoglobin desaturation during exercise. All are considered signs of pulmonary disease and exercise-induced ventilatory limitation. Otherwise treatment was guided by cardiac ultrasound, BNP, chest radiography and clinical findings. After heart failure treatment, the respiratory abnormalities almost disappeared. However, it should be underlined that some clues could have been identified at CPET, possibly suggesting a cardiogenic origin to the functional limitation. In particular, $V'_E/V'CO_2$ at and nadir $V'_E/V'CO_2$ were elevated and improved after heart failure therapy. These findings could suggest a pulmonary vascular involvement as a contributor to pulmonary inefficiency, possibly due to heart failure underlining the importance of a comprehensive evaluation of CPET parameters in order to avoid misdiagnosis.

Dyspnoea and fatigue are cardinal symptoms of both cardiac and lung diseases. Frequently, these pathologies co-exist worsening clinical condition [1–4] and making it difficult for physicians to correctly identify the cause of dyspnoea and reduced exercise capacity [5]. A wide amount of evidence suggests that CPET, in conjunction with PFT, is a useful clinical tool to identify cardiac and/or pulmonary causes of dyspnoea of unclear or multifactorial origin [6]. As a rule, cardiovascular disorders are characterised by low $V'O_2$ and O_2 pulse at peak exercise, an abnormal $\Delta V'O_2/\Delta$Work relationship and normal breathing reserve. Low peak $V'O_2$ together with low breathing reserve, lack of V_D/V_T reduction during exercise and normal $\Delta V'O_2/\Delta$Work relationship are observed in the case of ventilatory limitation to exercise [7]. The y-intercept of the $V'_E/V'CO_2$ relationship is also of help, being normal in the absence of lung disease and elevated when the presence of lung disease induces an increase in V_D during exercise [8]. However, it is important to be aware of possible diagnostic pitfalls. Advanced heart failure may be associated with some amount of lung restriction [9], frequently neglected in clinical practice, mainly because in most cases it doesn't compromise accuracy in identifying exercise limitation. The close relationship between cardiac and pulmonary pathophysiology was first described in 1785 by Withering and in 1883 by Hope, who coined the term "cardiac asthma" [10]. Moreover, several studies showed a reduction in FEV_1, FVC and D_{LCO} in heart failure [11]. Several factors may be responsible for restrictive lung pattern in heart failure such as increased lung stiffness due to alveolar effusion, reduction of working alveolar–capillary units [12], respiratory muscle fatigue [13], cardiac enlargement [14] and constriction of under perfused alveoli leading to reduced lung compliance in a low cardiac output state [15]. However, evidence in this field is not extensive and pathophysiology regulating heart-lung interactions is complex and not completely cleared. This is particularly true in the set of acute or sub-acute HF, when pulmonary congestion and pleural effusion could cause both restrictive and obstructive lung deficiency [16]. A good rule is to refrain from performing pulmonary function evaluation (both PFT and CPET) during or soon after the acute phase of heart failure. This evaluation becomes very useful in pre-discharge conditions, when the correct identification of heart failure comorbidities is pivotal for the choice of the most suitable pharmacological treatment [17].

Key points

- Lung function evaluation is pivotal in the diagnostic assessment of heart failure, as lung disease comorbidities influence both prognosis and therapy
- A restrictive or obstructive lung impairment can be identified that is solely due to cardiac decompensation in the absence of any primitive lung disease, especially in the acute or subacute phases of heart failure
- Accordingly, lung function tests should not be performed prior to complete restoration of acute heart failure; however, a pre-discharge complete lung function evaluation is highly advisable in most patients

Suggested answer

1. b
2. a
3. b

Affiliations

Mauro Contini[1], Edoardo Conte[1], Piergiuseppe Agostoni[1,2]

[1]Centro Cardiologico Monzino, IRCCS, Milan, Italy. [2]Dept of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, Milan, Italy.

Conflict of interest

M. Contini has nothing to disclose. E. Conte has nothing to disclose. P. Agostoni reports nonfinancial support from Menarini, Novartis and Boehringer, grants from Daiichi Sankyo and Bayer, and grants and nonfinancial support from Actelion, outside the submitted work.

References

1. Dahlstrom U. Frequent non-cardiac comorbidities in patients with chronic heart failure. *Eur J Heart Fail* 2005; 7: 309–316.
2. Arnaudis B, Lairez O, Escamilla R, *et al.* Impact of chronic obstructive pulmonary disease severity on symptoms and prognosis in patients with systolic heart failure. *Clin Res Cardiol* 2012; 101: 717–726.
3. Braunstein JB, Anderson GF, Gerstenblith G, *et al.* Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol* 2003; 42: 1226–1233.
4. Mentz RJ, Felker GM. Noncardiac comorbidities and acute heart failure patients. *Heart Fail Clin* 2013; 9: 359–367.
5. Le Jemtel TH, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 2007; 49: 171–180.
6. Guazzi M, Adams V, Conraads V, *et al.* EACPR/AHA Joint Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Eur Heart J* 2012; 33: 2917–2927.
7. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; 167: 211–277.
8. Apostolo A, Laveneziana P, Palange P, *et al.* Impact of chronic obstructive pulmonary disease on exercise ventilatory efficiency in heart failure. *Int J Cardiol* 2015; 189: 134–140.
9. Apostolo A, Giusti G, Gargiulo P, *et al.* Lungs in heart failure. *Pulm Med* 2012; 2012: 952741.
10. Mancini DM. Pulmonary factors limiting exercise capacity in patients with heart failure. *Prog Cardiovasc Dis* 1995; 37: 347–370.
11. Kee K, Naughton MT. Heart failure and the lung. *Circ J* 2010; 74: 2507–2516.
12. Agostoni P, Bussotti M, Cattadori G, *et al.* Gas diffusion and alveolar-capillary unit in chronic heart failure. *Eur Heart J* 2006; 27: 2538–2543.
13. Witt C, Borges AC, Haake H, *et al.* Respiratory muscle weakness and normal ventilatory drive in dilative cardiomyopathy. *Eur Heart J* 1997; 18: 1322–1328.
14. Agostoni P, Cattadori G, Guazzi M, *et al.* Cardiomegaly as a possible cause of lung dysfunction in patients with heart failure. *Am Heart J* 2000; 140: e24.
15. Swenson EW, Finley TN, Guzman SV. Unilateral hypoventilation in man during temporary occlusion of one pulmonary artery. *J Clin Invest* 1961; 40: 828–835.
16. Hawkins NM, Virani S, Ceconi C. Heart failure and chronic obstructive pulmonary disease: the challenges facing physicians and health services. *Eur Heart J* 2013; 34: 2795–2803.
17. Agostoni P, Palermo P, Contini M. Respiratory effects of beta-blocker therapy in heart failure. *Cardiovasc Drugs Ther* 2009; 23: 377–384.