and eosinophils (table 1) coupled with a flow cytometry analysis of BAL cells.

Table 1 integrates information given in our published paper, clearly demonstrating that the number of BAL neutrophils was fair in our case series. This unfortunately prevented a definitive evaluation of whether polymorphonuclear cells represent a source of IL-17. Nonetheless, as shown in table 1, in selected cases with a significant number of BAL neutrophils (two subjects) a certain degree of IL-17 expression was shown. Experiments are in progress in our lab aimed at evaluating whether lung IL-17 upmodulates or downmodulates neutrophils during the different phases of DPLD, including sarcoidosis. Nonetheless, as shown in figure 1, in selected cases with a significant number of BAL neutrophils (two subjects) a certain degree of IL-17 expression was shown. Experiments are in progress in our lab aimed at evaluating whether lung IL-17 upmodulates or downmodulates neutrophils during the different phases of DPLD, including sarcoidosis.

Concerning putative mechanism through which IL-17 could in theory regulate neutrophil activation and recruitment, we are evaluating whether pulmonary IL-17 favours granulopoesis in DPLD (via granulocyte colony stimulating factor or granulocyte-macrophage colony stimulating factor) and induces neutrophil chemotaxis through stimulation of endothelial and epithelial cells. Nonetheless, it is important to note that IL-17 also has the capability of mediating neutrophil apoptosis and neutrophil phagocytosis through macrophages. Thus, since IL-17 regulates both recruitment and turnover of neutrophils, we are assessing whether lung IL-17 upmodulates or downmodulates neutrophils during the different phases of DPLD, including sarcoidosis. This study was conducted with the approval of the Padua Ethics Committee.

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No decompensating factor was identified. A saline-contrast transthoracic echocardiography (SC-TTE) showed a dilated right ventricle (70 mm) with mild ventricular dysfunction and an estimated systolic pulmonary arterial hypertension (PAP) of 50 mm Hg. Peripheral injection of 10 ml agitated saline evidenced delayed appearance of bubbles in the left atrium, suggestive of shunting (figure 1). After discontinuing sildenafil for 48 h, his PAP improved to 64 mm Hg and the SC-TTE showed no evidence for shunting. Thirty minutes after a challenge dose of 50 mg sildenafil orally, the SC-TTE evidenced IFS recurrence with a PAP drop to 55 mm Hg despite oxygen administration. After permanent discontinuation of sildenafil, the patient had a significant clinical improvement and was discharged with nebulised alprostadil 5 μg four times a day. At 6 months follow-up, he remains in FC II without further hospitalisations.

Hypoxaemia in PAH patients might be due to ventilation-perfusion mismatch, depression of cardiac output or right-to-left shunting. SC-TTE offers a fast, non-invasive approach to diagnose right-to-left shunting. Under normal circumstances, saline microbubbles only appear in the right heart chambers. Presence of microbubbles in the left chambers suggests an arteriovenous connection, either due to an atrial septal defect, ventricular septal defect with Eisenmenger’s syndrome or IFS. The time frame for contrast appearance in the left chambers allow to differentiate between intracardiac shunting (one or two cardiac cycles after its appearance in right chambers) and IFS (four to eight cycles). Sildenafil administration in PAH patients is associated with a significant reduction of pulmonary-to-systemic vascular resistance ratio, with improvement in arterial oxygenation and 6 min walk distance. However, any vasodilator may theoretically exacerbate hypoxaemia by increasing perfusion to poorly ventilated areas in patients with lung disease, resulting in further ventilation-perfusion mismatch.

Kleinsasser et al demonstrated, in a porcine model, that a high dose of sildenafil results in a dose-dependent fall in pulmonary vascular resistance associated with a marked increase in pulmonary arterial pressure (PAP) of 58 mm Hg, capillary wedge pressure of 14 mm Hg, cardiac index of 2.7 l/min/m² and pulmonary vascular resistance of 7.5 WU, with no response to adenosine. A pulmonary CT scan ruled out thromboembolism or significant abnormalities (such as glass opacities, septal lines or mediastinal node enlargement). A PET (18F-flourine deoxyglucose; 18F-FDG) scan revealed increased uptake in the left upper lobes, compatible with a chronic venoocclusive disease; albumin macroaggregate lung perfusion scan showed normal perfusion without significant intrapulmonary shunt (IFS).

Sildenafil was started on diuretics, oxygen and sildenafil 25 mg three times a day. Despite treatment, dyspnoea worsened and 2 months later the patient was referred to our centre. At admission, the patient was in WHO functional class (FC) IV; his resting PAP had dropped to 56 mm Hg. No decompensating factor was identifiable. A saline-contrast transthoracic echocardiography (SC-TTE) showed a dilated right ventricle (70 mm) with mild ventricular dysfunction and an estimated systolic pulmonary arterial hypertension (PAP) of 100 mm Hg. Peripheral injection of 10 ml agitated saline evidenced delayed appearance of bubbles in the left atrium, suggestive of shunting (figure 1). After discontinuing sildenafil for 48 h, his PaO₂ improved to 64 mm Hg and the SC-TTE showed no evidence for shunting. Thirty minutes after a challenge dose of 50 mg sildenafil orally, the SC-TTE evidenced IFS recurrence with a PAP drop to 55 mm Hg despite oxygen administration. After permanent discontinuation of sildenafil, the patient had a significant clinical improvement and was discharged with nebulised alprostadil 5 μg four times a day. At 6 months follow-up, he remains in FC II without further hospitalisations.

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in ventilation—perfusion heterogeneity, as seen in patients treated with a high dose of intravenous epoprostenol in whom IPS and severe hypoxaemia occurred. In these cases, an accurate diagnosis and drug down-titration or discontinuation allowed a rapid recovery of the symptoms. In conclusion, sildenafil may be associated with development of IPS and hypoxaemia in PAH patients. In these cases, an SC-TTE should be performed in order to disclose previously undiagnosed IPS.

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Risk stratification in pulmonary embolism: an algorithmic tool approach

It is with much interest we read the article by Jiménez et al4 and the accompanying editorial2 Focusing investigation on patients with symptomatic pulmonary thromboembolism (PTE) but who are normotensive at presentation, it reminds us that work still needs to be undertaken for the 95% of patients (including the 15% with submassive disease) who remain haemodynamically stable and excluded from thrombolysis, if current guidelines are followed.3 Anecdotally, with the increased use of CT pulmonary angiography, clinicians more readily visualise thrombus burden and, despite the lack of scientific evidence, consider thrombolytic therapy ahead of heparin even with submassive PTE. Although the mortality benefits from thrombolysis in this group are debatable, it does help improve the right ventricular function more rapidly than anti-coagulation alone, reducing complications of chronic thromboembolic pulmonary hypertension4 The paper by Jiménez1 recognises and evaluates the prognostic tools currently being used in risk analysis, reminding us that the use of a two-test strategy has a higher specificity and positive predictive value of pulmonary embolism-related death than any single test itself, whether using cardiac biomarkers such as troponin (cTnI/T), cardiac ECHO or lower extremity complete compression ultrasound. Importantly, it also clarifies that although there is a trend to better evaluation with all three tests used together, the difference comparing a two-test approach with a threetest approach is not statistically significant.

Figure 1 Saline-contrast transthoracic echocardiogram showing right-to-left shunt. LA, left auricle; LV, left ventricle; RA, right auricle; RV, right ventricle.
Intrapulmonary shunting associated with sildenafil treatment in a patient with idiopathic pulmonary arterial hypertension

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