

Table 1 Bronchoalveolar lavage features of sarcoidosis patients and control subjects

	Cell recovery ($\times 10^3$)	Alveolar macrophages ($\times 10^3$ (%))	Lymphocytes ($\times 10^3$ (%))	Neutrophils ($\times 10^3$ (%))
Active sarcoidosis (n=25)	333 \pm 73	249 \pm 58 (74 \pm 6)	82 \pm 27 (25 \pm 6)	2.5 \pm 2.5 (0.8 \pm 0.9)
Inactive sarcoidosis (n=11)	109 \pm 31	102 \pm 27 (94 \pm 4)	5 \pm 4 (4 \pm 2)	0.6 \pm 0.9 (0.5 \pm 0.8)
Controls (n=10)	128 \pm 27	119 \pm 27 (93 \pm 3)	9 \pm 4 (7 \pm 4)	0.5 \pm 0.8 (0.4 \pm 0.7)

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

Table 1 integrates information given in our published paper,² clearly demonstrating that the number of BAL neutrophils was fair in our case series. This unfortunately prevented a definitive evaluation of whether polymorph nucleates represent a source of IL-17. 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 the role of the IL-17 and neutrophil interaction in fibrogenic diffuse parenchymal lung disease (DPLD), including sarcoidosis. In fact, neutrophils are known to play a crucial role in alveolar injury mechanisms in idiopathic pulmonary fibrosis and other types of DPLD. Furthermore, it has recently been shown that Th17 cells and IL-17A favour the development of fibrosis in a murine model of bleomycin-induced pulmonary fibrosis.³ Finally, patients with idiopathic pulmonary fibrosis show high BAL levels of IL-17.³

Concerning putative mechanism through which IL-17 could in theory regulate neutrophil activation and recruitment, we are evaluating whether pulmonary IL-17 favours granulopoiesis in DPLD (via granulocyte colony stimulating factor or granulocyte-macrophage colony stimulating factor)^{4,5} 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 neuro-

phil phagocytosis through macrophages.⁶ 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.

Monica Facco,^{1,2} Anna Cabrelle,^{1,2} Carlo Agostini^{1,2}

¹Department of Clinical and Experimental Medicine, Hematology-Immunology Section, Padua University School of Medicine, Padua, Italy; ²Venetian Institute of Molecular Medicine, Padua University School of Medicine, Padua, Italy

Correspondence to Prof Carlo Agostini, Padua University School of Medicine, Giustiniani 2, Padua, 35128, Italy; carlo.agostini@unipd.it

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artery 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 commonly seen in venocclusive disease¹); albumin macroaggregate lung perfusion scan showed normal perfusion without significant intrapulmonary shunt (IPS). He 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 PaO₂ 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 PAP of 100 mm Hg. Peripheral injection of 10 ml agitated saline evidenced delayed appearance of bubbles in the left atrium, suggestive of IPS (figure 1). After discontinuing sildenafil for 48 h, his PaO₂ improved to 64 mm Hg and the SC-TTE showed no evidence for IPS. Thirty minutes after a challenge dose of 50 mg sildenafil orally, the SC-TTE evidenced IPS recurrence with a PaO₂ 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 iloprost 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 IPS. 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 IPS (four to eight cycles).² 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.³ 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*⁴ demonstrated, in a porcine model, that a high dose of sildenafil results in a dose-dependent fall in vascular pulmonary resistance associated with a marked increase

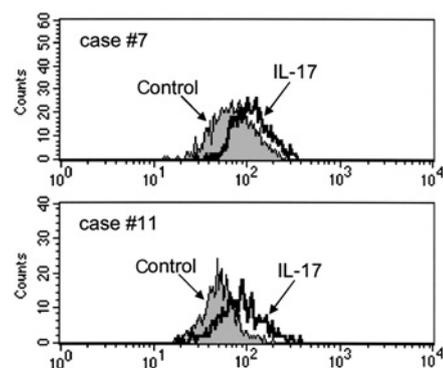
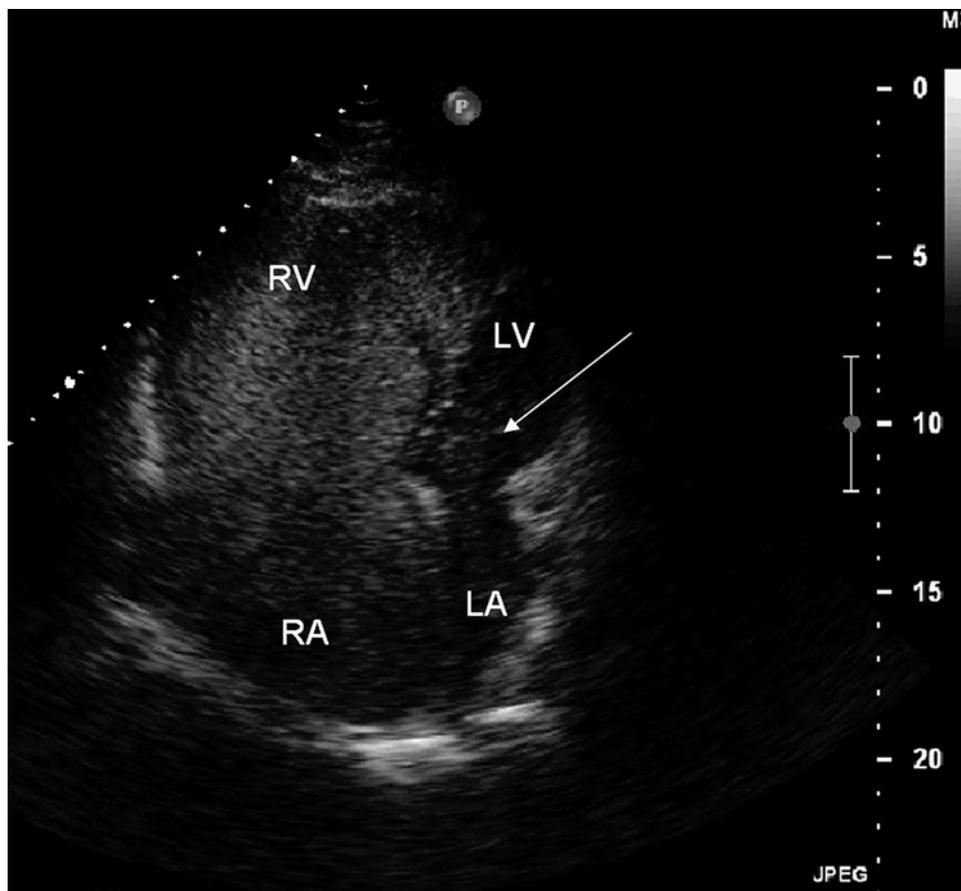


Figure 1 Analysis of IL-17 expression in neutrophils freshly obtained from the bronchoalveolar lavage (BAL) of two sarcoid patients (5% and 4% of BAL cells were neutrophils, respectively). Neutrophils were identified on the basis of CD16 positivity and morphological gating. As shown by the IL-17 staining profile, a faint positivity for the cytokine was detectable in both subjects.

Intrapulmonary shunting associated with sildenafil treatment in a patient with idiopathic pulmonary arterial hypertension

We reported a case of a 30-year-old Hispanic patient with a history of idiopathic pulmonary arterial hypertension (PAH). A baseline catheterisation showed a mean pulmonary

Figure 1 Saline-contrast transthoracic echocardiogram showing right-to-left shunt. LA, left auricle; LV, left ventricle; RA, right auricle; RV, right ventricle.



in ventilation–perfusion heterogeneity, as seen in patients treated with a high dose of intravenous epoprostenol in whom IPS and severe hypoxaemia occurred.⁵ 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.

Pablo F Castro,¹ Douglas Greig,¹ Hugo E Verdejo,¹ Iván Godoy,¹ Samuel Córdova,¹ Marcela P Ferrada,¹ Robert C Bourge²

¹Department of Cardiovascular Diseases, Coronary Care Unit, Pontificia Universidad Católica de Chile, Santiago de Chile, Chile; ²Division of Cardiovascular Disease, Department of Medicine, The University of Alabama at Birmingham, Birmingham, Alabama, USA

Correspondence to Pablo F Castro, Department of Cardiovascular Diseases, Coronary Care Unit, Pontificia Universidad Católica de Chile, Marcoleta 367, 7 floor, Santiago de Chile, Chile; pcastro@med.puc.cl

Institution at which the work was performed: Pontificia Universidad Católica de Chile, Santiago de Chile, Chile.

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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 al*¹ and the accompanying edito-

rial² 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 three-test approach is not statistically significant.