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Refractory hypoxemia due to pulmonary microfistulas: Therapeutic response to terlipressin

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Abstract

Pulmonary microfistulas are rare vascular anomalies characterized by right-to-left intrapulmonary shunt, often undetectable by conventional imaging. They may lead to severe, refractory hypoxemia and orthodeoxia, especially when not amenable to embolization or surgery. Here, we report the case of a previously healthy 26-year-old woman with progressive hypoxemia and severe functional limitation. Extensive investigation confirmed intrapulmonary shunt and histopathologic evidence of pulmonary microfistulas. Standard treatments were not applicable. A 48-hour continuous infusion of terlipressin led to rapid and sustained improvement in oxygenation and clinical status. This case highlights the potential role of terlipressin as a therapeutic option in selected patients with untreatable pulmonary microfistulas.

Keywords: Pulmonary arteriovenous malformations; Intrapulmonary shunt; Terlipressin; Refractory hypoxemia.

Abbreviations: PAVMS: Pulmonary Arteriovenous Malformations; HHT: Hereditary Hemorrhagic Telangiectasia; 99mTc-MAA: Technetium-99m-Labeled Macroaggregated Albumin; VEGF: Vascular Endothelial Growth Factor; HRS: Hepatorenal Syndrome; PFO: Patent Foramen Ovale; HPS: Hepatopulmonary Syndrome; 6MWT: Six-Minute Walk Test; NO-cGMP: Nitric Oxide–Cyclic Guanosine Monophosphate; AGA: American Gastroenterological Association.

Introduction

Pulmonary Arteriovenous Malformations (PAVMS) are abnormal communications between branches of the pulmonary arterial and venous circulation that bypass the capillary network, resulting in right-to-left shunt and arterial hypoxemia. Although classically associated with Hereditary Hemorrhagic Telangiectasia (HHT), they may also occur sporadically or secondary to hepatopulmonary syndromes, cirrhosis, or acquired vascular malformations [1]. Beyond macroscopic lesions visible on imaging, there is growing recognition of microscopic fistulas, whose diagnosis is more challenging. These may go undetected on conventional structural imaging modalities such as pulmonary CT angiography or arteriography but manifest clinically through resting or exertional desaturation, refractory hypoxemia, and an increased alveolar–arterial oxygen gradient. Functional tests, including technetium-99m-labeled Macroaggregated Albumin (99mTc-MAA) scintigraphy or contrast-enhanced echocardiography, are essential for detecting such shunts [2]. The treatment of PAVMs depends on the morphology and extent of the lesions. Transcatheter embolization is considered the gold standard for accessible malformations, while surgical resection is reserved for refractory or inaccessible cases [3,4]. Lung trans-

plantation may be considered in extreme cases of severe and diffuse hypoxemia, although survival data suggest that many patients experience prolonged clinical stability without the need for transplant [5]. In early stages of arteriovenous malformation development, particularly in HHT, the use of bevacizumab has been proposed as an experimental therapeutic strategy, inhibiting Vascular Endothelial Growth Factor (VEGF) mediated neo angiogenesis. While it may represent a potential alternative to embolization, its clinical application remains limited and lacks large-scale validation [6]. In cases of pulmonary microfistulas not amenable to invasive intervention, therapeutic options remain limited. Terlipressin, a vasopressin analogue with predominant vasoconstrictive action via V1a receptors, is well established in the management of Hepatorenal Syndrome (HRS), as it induces mesenteric arterial vasoconstriction, restores effective arterial volume, and improves renal perfusion [7,8]. Experimental studies suggest that its effects extend beyond the splanchnic circulation, potentially modulating pulmonary hemodynamics via vasopressin receptors expressed in the pulmonary vascular bed [9,10]. This raises the possibility that terlipressin may exert complex effects on pulmonary vasculature, potentially involving distinct receptor interactions or mechanisms within the lung tissue, an idea with clinical implications in the setting of intrapulmonary shunt. This report describes the case of a young patient with severe hypoxemia secondary to pulmonary microfistulas who exhibited marked clinical improvement following continuous terlipressin infusion, illustrating a possible novel therapeutic application for this agent in cases of pulmonary shunt not amenable to conventional treatment.

Case study

We describe the case of a 26-year-old previously healthy female patient who developed exertional dyspnea in December 2022, progressing to severe oxygen desaturation, peripheral cyanosis, and episodes of syncope upon assuming an upright position. Initial evaluation revealed a Patent Foramen Ovale (PFO), initially considered the cause of her clinical presentation. She underwent successful percutaneous PFO closure in June 2023; however, her symptoms persisted and gradually worsened, with increasing functional impairment. A renewed investigation was initiated. Whole-body scintigraphy performed in November 2023 was positive for a right-to-left shunt. A new transthoracic contrast echocardiogram revealed microbubbles in the left atrium after six cardiac cycles, raising the suspicion of an intrapulmonary shunt and guiding further diagnostic steps. Pulmonary CT angiography showed no evidence of macroscopic fistulas or vascular malformations. Right heart catheterization excluded pulmonary hypertension, and selective pulmonary arteriography confirmed the absence of macroscopic arteriovenous communications. There were no clinical signs of cutaneous or mucosal telangiectasias, no personal history of bleeding, and no family history suggestive of hereditary disease. Hepatic assessment, including laboratory tests and imaging, was normal, ruling out Hepatopulmonary Syndrome (HPS). In November 2024, the patient underwent a transesophageal contrast echocardiogram following selective catheterization of the left pulmonary artery, which revealed the presence of bubbles in the left pulmonary vein, further supporting the diagnosis of an intrapulmonary arteriovenous fistula. Throughout the diagnostic process, the patient remained symptomatic, with complete intolerance to exertion and orthostatic posture. A young woman without comorbidities, she had become entirely dependent for activities of daily living over a short period. An attempt was made to perform a Six-Minute Walk Test (6MWT) to objectively assess the degree of limitation; however, she was unable to even stand upright, with oxygen saturation dropping to approximately 70%. After extensive investigation, the patient finally underwent a transthoracic lung biopsy at the end of December 2024, with samples collected from the lingula and lower lobe of the left lung. Histopathological analysis revealed tortuous and dilated veins with microaneurysmal formations filled with erythrocytes, arterioles with medial layer hypertrophy, lymphatic ectasia, dilation of arteriolar lumens, and focal areas suggestive of arteriovenous communication. These morphological findings, in association with the clinical picture, supported the diagnosis of intrapulmonary shunt due to pulmonary microfistulas. The underlying etiology, considering the age of onset and disease course, remained unclear. Given the diagnosis, the next challenge was to identify a treatment capable of restoring the patient's functionality. In light of the limited therapeutic options and based on the theoretical rationale of the pulmonary vasoconstrictive effect of terlipressin, a therapeutic trial was undertaken using terlipressin at a dose of 2 mg/day, administered as a continuous intravenous infusion over 48 hours. The infusion was well tolerated, without adverse events. At the end of this period, a new clinical evaluation was performed. The patient was initially seated at the bedside without symptoms or changes in oxygen saturation, then stood and walked with assistance, remaining asymptomatic and maintaining stable oxygen saturation. The infusion was concluded at that time. A 6MWT was successfully performed, with a total distance of 350 meters and oxygen saturation of 99% at baseline and 98% at the end, on room air. The patient was discharged approximately 10 days after the terlipressin infusion, showing sustained clinical improvement and remaining asymptomatic. The mechanism underlying this response remains uncertain but is hypothesized to involve vasoconstriction and redistribution of pulmonary blood flow, possibly leading to functional closure of arteriovenous communications. The duration of this effect, or whether the treatment may have had a definitive impact, remains unknown. At outpatient follow-up 30 days after discharge, without further terlipressin administration, the patient remained asymptomatic.

Discussion

This report describes the case of a previously healthy young woman who presented with subacute-onset severe hypoxemia, orthostatic desaturation, and marked functional limitation. A comprehensive diagnostic investigation, integrating both structural and functional assessments, led to the diagnosis of an intrapulmonary shunt due to pulmonary arteriovenous microfistulas, a rare entity that is difficult to detect and presents significant management challenges. The absence of macroscopic vascular malformations, as well as any associated hereditary or hepatopulmonary conditions, contributed to the complexity of the case.

The diagnostic workup of pulmonary arteriovenous microfistulas requires a careful integration of structural and functional imaging, as such lesions frequently escape detection by conventional methods [2]. In this case, histopathologic confirmation proved critical, revealing vascular abnormalities consistent

with intrapulmonary shunt, thereby underscoring the value of lung biopsy in complex clinical scenarios. From a therapeutic standpoint, the absence of fistulas amenable to embolization and the diffuse nature of the vascular changes precluded local interventions, highlighting the limitations of traditional approaches. Although lung transplantation may be considered in extreme cases, its indication remains controversial, especially in the absence of progressive structural disease or associated organ failure. In this context, pharmacologic strategies aimed at modulating pulmonary blood flow emerge as a promising, albeit understudied, alternative. Given the lack of viable therapeutic options, terlipressin was employed based on the rationale that its mechanism of action could favorably influence pulmonary blood flow distribution. Experimental and observational data suggest that terlipressin may reduce pulmonary artery pressure in selected clinical settings, whether or not associated with liver disease [11-13]. This effect may be attributed not only to splanchnic vasoconstriction and reversal of the hyperdynamic circulatory state typical of portal hypertension [14], but also to direct action on vasopressin receptors expressed in the pulmonary vasculature [9,10]. In animal models, the pulmonary vascular response to vasopressin has been shown to be biphasic: at low concentrations and with preserved endothelial function, nitric oxide–mediated vasodilation predominates, whereas at higher concentrations or in the setting of endothelial dysfunction, direct vasoconstriction of smooth muscle is observed [15]. Based on this pathophysiologic framework, it is plausible to hypothesize that terlipressin may impact not only pulmonary hemodynamics but also the magnitude of functional intrapulmonary shunting. Clinical studies have demonstrated that terlipressin administration is associated with reduced shunt fraction measured by 99mTc-MAA scintigraphy in normoxemic cirrhotic patients, suggesting modulation of blood flow in small-caliber pulmonary vessels [16]. In another study including patients with cirrhosis and aortopulmonary hypertension, two out of five patients with positive contrast echocardiography findings showed normalization of the exam following terlipressin infusion, indicating a potential reversible component of the right-to-left shunt [11]. The efficacy of pharmacologic Vasomodulation in intrapulmonary shunts is further supported by studies demonstrating significant improvement in oxygenation and reduction of shunting in patients with HPS treated with methylene blue, which inhibits the nitric oxide–cyclic guanosine monophosphate (NO-cGMP) pathway [17]. Conversely, other studies involving patients with chronic HPS have shown opposing results, with worsening arterial oxygenation following administration of curcumin, terlipressin, or methylene blue, suggesting that the hemodynamic response may vary according to the specific pathophysiologic context and stage of pulmonary vascular compromise [18]. These findings support the hypothesis that the clinical improvement observed in this patient, marked by resolution of orthostatic desaturation and improved exercise tolerance, may be related to pulmonary perfusion redistribution and functional shunt reduction, even in the absence of anatomical closure of the fistulas. The decision to administer terlipressin as a continuous infusion was based on its favorable safety profile demonstrated in the treatment of HRS, along with evidence suggesting improved tolerability compared to intermittent dosing [19,20]. Furthermore, current guidelines from the American Gastroenterological Association (AGA) on the use of vasoactive agents in cirrhotic patients indicate that terlipressin can be safely administered via peripheral venous access and outside the intensive care unit, provided that close clinical monitoring is ensured [21]. Despite this favorable profile, safety concerns have emerged in recent studies. The CONFIRM trial, a randomized, controlled phase 3 study, evaluated the efficacy and safety of terlipressin plus albumin in patients with type 1 hepatorenal syndrome. Although it demonstrated superiority over placebo in reversing renal dysfunction, it also revealed a significantly higher incidence of respiratory failure, particularly in patients with baseline hypoxemia and advanced multiorgan dysfunction. These adverse events were attributed to mechanisms including increased cardiac afterload, albumin-related volume overload, and the potential development of hydrostatic pulmonary edema [8,22,23]. Therefore, we recommend cautious use of terlipressin in this context, with continuous clinical monitoring during treatment.

Conclusion

In summary, this case highlights the potential role of terlipressin as a therapeutic strategy in patients with pulmonary microfistulas and refractory hypoxemia who are not candidates for invasive therapies. The absence of effective alternatives, together with the observed clinical improvement, underscores the need for prospective studies to systematically evaluate the role of terlipressin in such scenarios, contributing to the development of individualized approaches in rare pulmonary vascular diseases.

Declarations

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Conflict of interest: The authors declare that there is no conflict of interests regarding the publication of this paper.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from patient in the study, as part of the standard of care.

Authors contribution: All authors make substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data according to ICMJE recommendations. All those who have made substantive contributions to the article have been named as authors.

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