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LETTER TO THE EDITOR OPEN ACCESS

High-Dose Calcium Channel Blockade in PH: Old Lessons, New Tools

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ABSTRACT

This letter to the editor revisits the origins of high-dose calcium channel blocker use in pulmonary arterial hypertension (PAH) in light of bedside vasoreactivity testing, reaffirming its present-day relevance for a selected subgroup.

Integrating historical insights with modern tools, the authors highlight: the "responder" phenotype as an expression of precision medicine; ion channels as pathobiological targets; the value of real-world registries and benchmarks for high-quality care pathways; attention to special contexts (interstitial lung disease in connective-tissue diseases, and sex differences in diastolic dysfunction/HFpEF). In sum, we propose a personalized approach that pairs careful high-dose titration in appropriate candidates with molecular phenotyping and standardized follow-up.

Dear Editor,

We read with great interest the article titled "My Quest for Calcium Channel Blockers as the First Medical Treatment for Patients With Pulmonary Hypertension" by Rich et al., a historical vignette showing how meticulous bedside vasoreactivity testing and bold nifedipine titration reshaped the management of a selected subgroup of patients with pulmonary arterial hypertension [1].

Several points deserve emphasis for their present-day relevance. First, the pathophysiological intuition and clinical courage that led to invasive titration of nifedipine until achieving a marked reduction in pulmonary pressures and discharge on 80 mg three times daily, a regimen that today would be considered only in expert settings and with strict selection criteria. Second, the recognition that responders to calcium channel blockers represent a specific phenotype, anticipating a precision-medicine approach later corroborated by genetic signatures associated with vasoreactivity.

This bedside lesson dovetails with the contemporary pathophysiological framework of ion channels: A recent review highlights how these channels, critical determinants of cellular electrophysiology in PASMCs/PAECs, contribute meaningfully to PH progression and constitute innovative therapeutic targets [2].

Clinical progress has also been enabled by shared knowledge bases: the NHLBI national registry for "primary" PH was implemented across 32 centers with rigorous hemodynamic criteria (mPAP > 25 mmHg at rest or > 30 mmHg with exercise; PAWP ≤ 12 mmHg), enrolling 187 patients between 1981 and 1985, with centralized collection of baseline and 6-month data. Its results became comparators for therapy development and cemented collaborations that continue to this day [3].

Currently, real-world data propose useful benchmarks for PAH quality of care: near-universal completion of echocardiography (99%) and PFTs (91%); increased use of V/Q scanning up to 90% 2015–2019; right heart catheterization performed in all patients with greater hemodynamic completeness at the expert center versus referring centers (55.4% vs. 30.4%); and survival estimates of 94% at 1 year, 75% at 5 years, and 60% at 10 years [4].

In parallel, within connective tissue diseases, the presence of ILD in Sjögren's syndrome is associated with early echocardiographic signs of PH: in a recent single-center cohort the catheter-confirmed prevalence was low, but within the pSS-ILD subgroup there was a higher frequency of sPAP > 35 mmHg and a reduced TAPSE/sPAP ratio, supporting targeted follow-up [5].

Finally, a truly personalized approach cannot overlook sex-specific differences in diastolic dysfunction and HFpEF, more frequent and phenotypically distinct in women, with implications for diagnosis (Doppler echocardiography, atrial/ventricular strain, E/e′, LAVI) and therapy (documented benefits of SGLT2 inhibitors and, in selected populations, GLP-1 receptor agonists) [6]. Relatedly, in systemic sclerosis, vitamin D insufficiency has been associated with higher systolic pulmonary arterial pressure and a lower TAPSE/PAPs ratio, reinforcing integrated risk stratification with RV-pulmonary coupling indices [7].

In summary, the historical roots of clinical PH and collaborative registries have paved the way to an era of precision medicine: high-dose, carefully monitored, for the right patient remains a valid principle, to be integrated with molecular phenotyping, rigorous diagnostic pathways, and shared quality metrics.

Author Contributions

Gianluca Pagnoni and **Francesca Coppi:** conceptualization. **Aurora Vicenzi** and **Francesca Coppi:** methodology. **Gianluca Pagnoni** and **Aurora Vicenzi:** investigation (literature review). **Gianluca Pagnoni:** writing original draft. **Aurora Vicenzi** and **Francesca Coppi:** writing review and editing. **Francesca Coppi:** supervision. **Gianluca Pagnoni:** project administration.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

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