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High-altitude pulmonary hypertension now: A mechanism-informed, region-ready care framework

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High-altitude pulmonary hypertension (HAPH) is an underrecognized pulmonary vascular disease driven by sustained or recurrent hypobaric hypoxia, typically above 2,500 m. More than 140 million people live at high altitude, while tourism, migration, and occupational exposure expand the population at risk. Prevalence estimates range from 5% to 35% according to altitude, exposure, and population background. Susceptibility varies across populations. Tibetan highlanders show population-level adaptations involving EPAS1 and EGLN1 that may attenuate hypoxic responses.[1,2] Chronic hypoxia can convert adaptive vasoconstriction into vascular remodeling, elevated pulmonary artery pressure (PAP), and right ventricular (RV) dysfunction. Current care remains largely symptomatic and extrapolated from pulmonary arterial hypertension (PAH). We propose a mechanism-informed, region-ready framework linking molecular discovery, altitude-adapted trials, risk stratification, and tele-enabled care.

MOLECULAR AND CELLULAR MECHANISMS OF HYPOXIA-INDUCED PULMONARY VASCULAR REMODELING

The central axis in the altered cellular microenvironment: HIF-2α–NO/ET-1 imbalance

Hypoxia stabilizes HIF-1α and HIF-2α by limiting prolyl hydroxylase domain (PHD)-dependent hydroxylation and von Hippel-Lindau (VHL)-mediated degradation. Acute responses often involve HIF-1α, which promotes glycolytic metabolism and ion-channel remodeling in pulmonary artery smooth muscle cells (PASMCs). Sustained hypoxia increasingly engages endothelial HIF-2α, reducing nitric oxide (NO) and prostacyclin signaling while increasing endothelin-1 and vascular endothelial growth factor. This imbalance creates a vasoconstrictive and proliferative environment that promotes pulmonary vascular remodeling.

Amplifying cascades and subcellular stress

Downstream pathways amplify this response. Dysregulated BMP/TGF-β and Rho/ROCK signaling promote PASMCs migration and proliferation. Mitochondrial dysfunction, unfolded protein response activation, reactive oxygen species, and endoplasmic reticulum–mitochondria coupling reinforce redox stress, inflammation, and apoptosis resistance. These mechanisms support investigation of reverse-remodeling strategies, including sotatercept, in high-altitude cohorts rather than reliance on vasodilation alone.

Genetic and epigenetic susceptibility

Susceptibility is shaped by genetic and epigenetic factors. Population-level EPAS1 and EGLN1 variants associated with Tibetan high-altitude adaptation may attenuate excessive HIF-2α activation, erythrocytosis, and endothelin signaling, whereas some migrant populations may develop greater endothelial dysfunction. Hypoxia-induced methylation, histone modification, and noncoding RNA networks may create a durable "hypoxic memory," potentially explaining incomplete treatment responses and supporting stratification by exposure, population background, and hypoxia-pathway variants.

THERAPEUTIC ADVANCES: CURRENT EVIDENCE AND KNOWLEDGE GAPS

Treatment for HAPH is largely extrapolated from idiopathic PAH because dedicated, adequately powered trials are scarce. Phosphodiesterase-5 inhibitors, endothelin receptor antagonists (ERAs), prostacyclin-pathway drugs, acetazolamide, and Rho-associated protein kinase (ROCK) inhibition have mechanistic or limited clinical support, but responses vary across high-altitude populations. Distinct features of HAPH, including intermittent hypoxia, erythrocytosis, right ventricular–pulmonary arterial coupling, and heterogeneous adaptation, should inform trial design and outcome interpretation.[3]

Future studies should prioritize altitude-stratified, pragmatic randomized trials with standardized endpoints, wearable physiologic monitoring, and region-appropriate delivery models. Disease-modifying approaches targeting BMP/TGF-β imbalance, mitochondrial metabolism, inflammation, or hypoxic signaling deserve testing in high-altitude cohorts. Adjuncts derived from traditional Chinese medicine, such as *Rhodiola*-derived salidroside and *Salvia miltiorrhiza* compounds, have experimental rationale and preliminary clinical signals. However, multicenter validation is needed with standardized formulations, quality control, mechanistic endpoints, and pharmacovigilance.[4]

INTEGRATED MANAGEMENT: TOWARD ALTITUDE-ADAPTED CARE PATHWAYS

Early identification should focus on long-term residents and workers, lowland migrants, patients with chronic mountain sickness, and individuals with genetic or clinical susceptibility factors. Transthoracic echocardiography and natriuretic peptides can support screening, while right heart catheterization remains necessary for confirmation and exclusion of left heart or thromboembolic disease.[5] A pragmatic phenotype-guided approach can then be considered.

Mild cases with vasoconstrictive-predominant phenotype

Lifestyle optimization and supplemental oxygen remain foundational. Relocation to a lower altitude is recommended when practical to restore oxygen availability.

Moderate-to-severe cases with remodeling-predominant or advanced phenotype

For moderate-to-severe HAPH, early combination vasodilator therapy may be considered alongside aggressive management of comorbidities (e.g., chronic mountain sickness). ERAs or prostacyclin analogs may be selected in specialist care, with escalation guided by clinical response.

Refractory cases with advanced interventions and comorbidity-focused care

Referral to an expert center for transplantation evaluation or other advanced interventions should be considered. Comprehensive management of polycythemia, sleep-disordered breathing, and physical deconditioning at high altitude is essential.

Bridging distance through technology

Rapid referral networks, tele-echocardiography, wearable oximetry, and standardized home oxygen protocols can support longitudinal monitoring and timely escalation in resource-limited settings.

WHAT SHOULD MOVE FORWARD?

Progress requires international registries across the Qinghai–Tibet Plateau, Pamir Plateau, Yunnan–Guizhou Plateau, Andean highlands, and other high-altitude regions, with harmonized definitions of altitude exposure, eligibility,

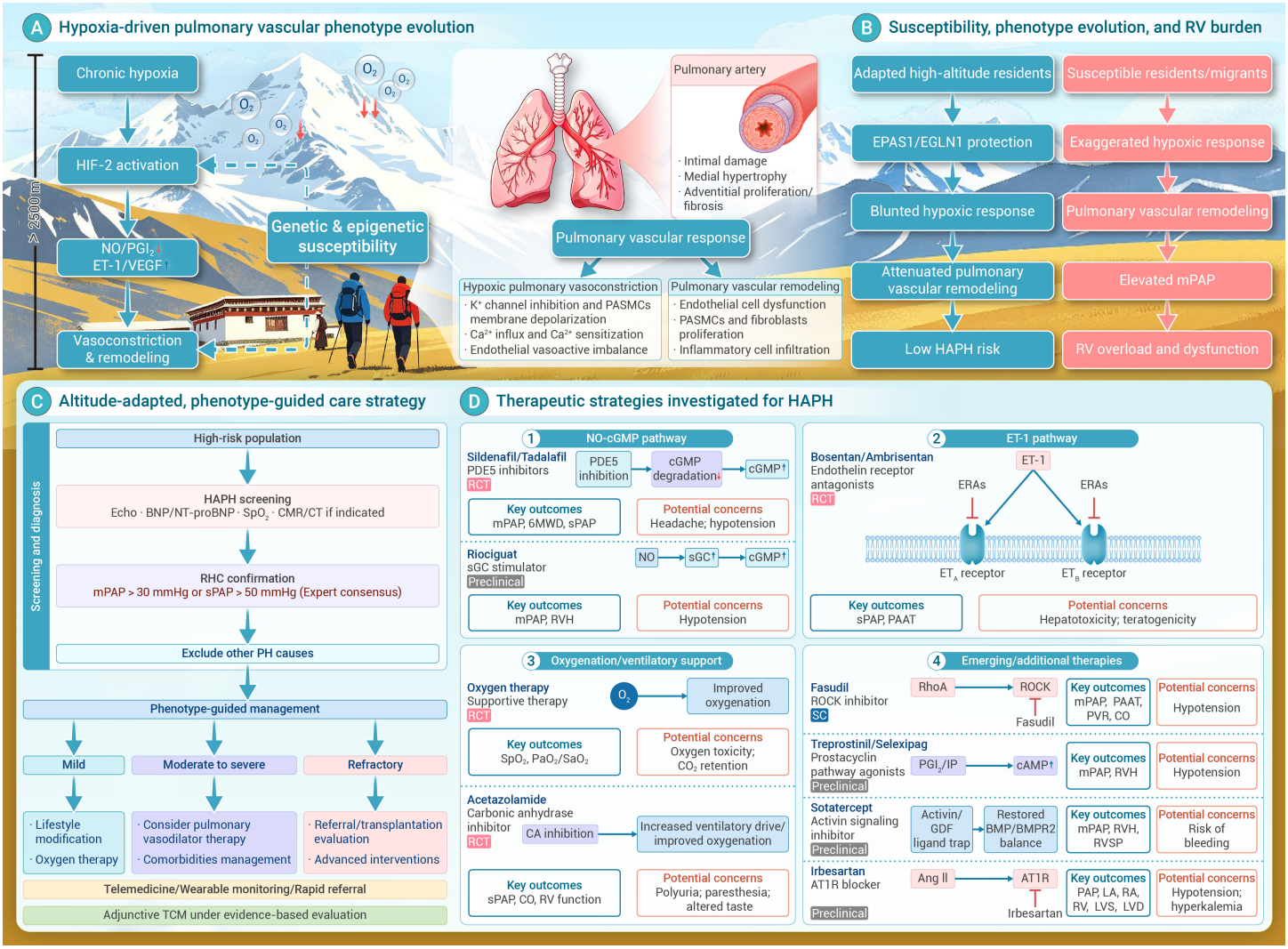

Figure 1. Mechanism-informed and altitude-adapted framework for high-altitude pulmonary hypertension (HAPH) (A) Chronic hypoxia activates HIF-2, disrupts NO/PGI2 and ET-1/VEGF signaling, and, together with genetic and epigenetic susceptibility, drives pulmonary vasoconstriction and remodeling. (B) EPAS1/EGLN1-associated adaptation blunts this response, whereas susceptible residents or migrants develop increased mPAP and RV dysfunction. (C) High-risk screening is followed by RHC confirmation, exclusion of other PH causes, and phenotype-guided management, including oxygen and lifestyle measures, vasodilator therapy, comorbidity management, advanced referral, and telemonitoring. (D) Investigated therapies target NO-cGMP and ET-1 pathways, oxygenation and ventilation, Rho-ROCK, prostacyclin, BMP/BMPR2, and angiotensin signaling; evidence levels, key outcomes, and safety concerns are summarized.

and core outcomes. Multi-omics profiling, advanced cardiopulmonary imaging, wearable biosensors, and AI-assisted analytics could improve early detection and dynamic risk prediction. Policy frameworks should support regional surveillance, oxygen access, portable concentrators, and equitable care delivery so that mechanism-informed advances can reach high-altitude communities.

CONCLUSION

HAPH is a hypoxia-programmed vasculopathy shaped by environmental exposure, molecular susceptibility, and health-system constraints. A pragmatic framework integrating early risk identification, phenotype-specific therapy, technology-enabled follow-up, and altitude-responsive policy may advance personalized, potentially disease-modifying care.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.