Pulmonary hypertension with heart failure with preserved ejection fraction (PH-HFpEF) is a type of pulmonary hypertension recognized by the World Health Organization (WHO Group 2) and endorsed by worldwide regulatory authorities.

Confusion regarding different types of pulmonary hypertension (PH) began decades ago when pulmonary hypertension was considered either primary or secondary. However, numerous pathologies, pathobiology and genetic studies have clarified that the "secondary" or associated conditions are risk factors that, when exposed to patients with a permissive genotype, trigger a pathologic pulmonary vascular response. In 1998 the WHO sponsored an international symposium where a classification of the various types of pulmonary hypertension was adopted. This classification has since served as an important guide for studies of the pathology, genetics, pathophysiology and treatments of pulmonary hypertension. [1]

As one example, Group 1 pulmonary arterial hypertension (PAH) includes idiopathic PAH and congenital heart disease (primarily left-to-right cardiac shunts). Fifty years ago, PH was thought to occur only with post-tricuspid valve shunts (VSD or patent ductus arteriosus), but studies have since confirmed that pre-tricuspid shunts (ASD and anomalous pulmonary venous drainage) are also risk factors, but to a lesser degree. The common trigger appears to be a chronic, sustained increase in shear stress in the pulmonary arteries from the elevated pulmonary blood flow from the shunt. The pulmonary vascular pathology of PAH and PH-congenital heart disease are similar. [2]

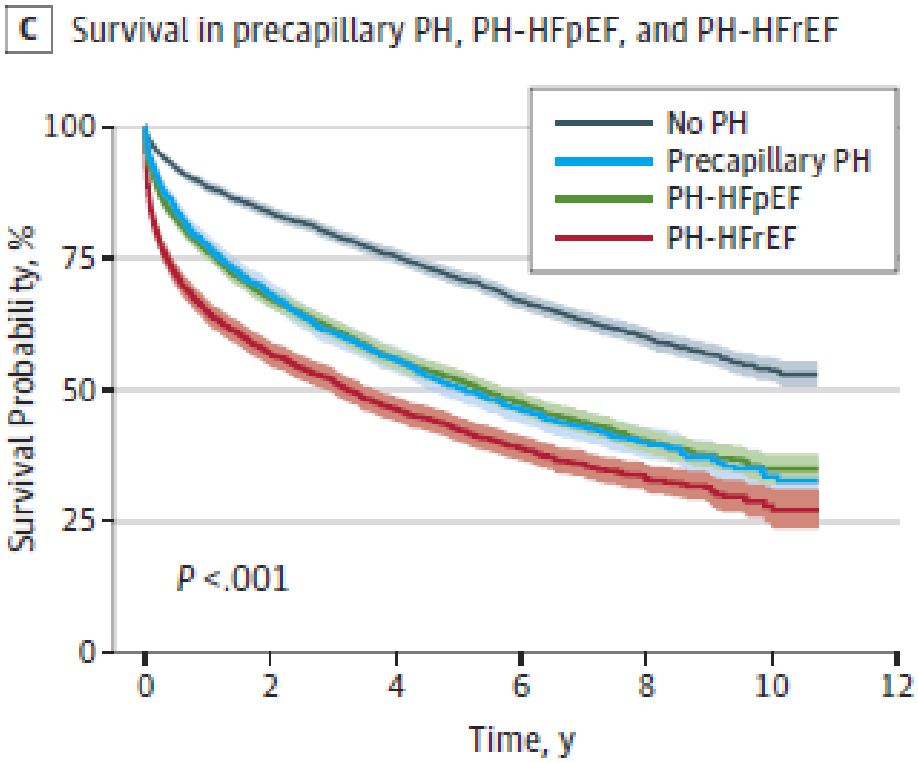
Group 2 PH is defined as pulmonary venous hypertension (PVH) from left heart disease (LHD). The current sub-classification of Group 2 PH includes valvular heart disease, heart failure with reduced ejection fraction (HFrEF), and heart failure with preserved ejection fraction (HFpEF). In these patients the elevation in pulmonary artery pressure (PAP) was once believed to be "passive" and related to a retrograde transmission of increased left ventricular end-diastolic pressure (LVEDP). However, studies have now shown that elevations in PV pressure (synonymous with pulmonary capillary wedge pressure or PCWP) may result in overfilling of the LV, thereby causing the LVEDP to rise. Studies also show that a chronic, sustained elevation of the PCWP can trigger a pulmonary arterial vasculopathy in patients with a permissive genotype. Pulmonary vasodilators have never been shown to be effective in this patient group. [3]

Distinctive Features of Pulmonary Hypertension with Heart Failure with Preserved Ejection Fraction

Epidemiology

HFpEF, a complex cardiac disease, is a risk factor for the development of PH-HFpEF. Consequently, the epidemiology of PH-HFpEF parallels that of HFpEF. Over the past decades the prevalence and hospital admissions of HFpEF have gone up markedly compared to HFrEF where the numbers of patients hospitalized appears to be stable, although there are few large prevalence studies.[4] The mortality of PH-HFpEF is similar to PAH (aka precapillary PH) as shown below in a cohort study from a data repository at The University of Pittsburgh (Figure 1). [5]

Figure 1.



Hemodynamics

The hemodynamic features of PH-HFpEF differ from PAH and from isolated PVH. The proposed hemodynamic definitions of Group 1 and Group 2 PH have undergone several revisions over the past decade, but the principle behind the hemodynamic definitions remain. PAH is defined and an increase in mean PAP with a normal PCWP and is also referred to as pre-capillary PH. PVH is defined in an increase in PA pressure along with an increase in PCWP, with little to no gradient between the PA diastolic pressure and the PCWP. This is also referred to as post-capillary PH. Patients with PH-HFpEF have a more marked increase in PA pressure along with an increase in

PCWP with a sizeable gradient between the PA diastolic pressure and the PCWP. This is commonly referred to as combined pre/post-capillary pulmonary hypertension. Recently it has been proposed to characterize the hemodynamics of PH-HFpEF as a pulmonary vascular resistance (PVR) >3.0 WU and PCWP >15 mmHg. [6]

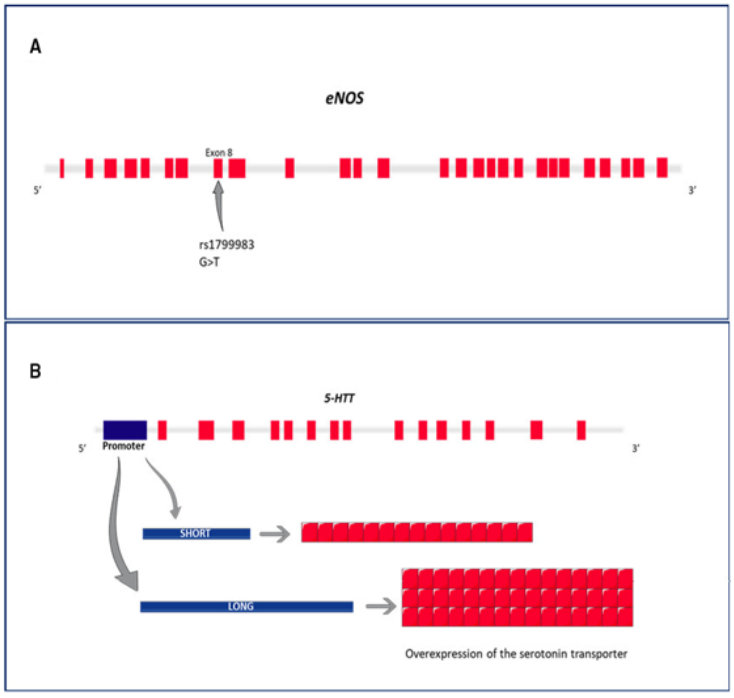
Permissive genotypes linked to PH-HFpEF

A single nucleotide polymorphism (SNP) within the gene encoding for the endothelial nitric oxide synthase enzyme has been associated with the transpulmonary gradient, diastolic pressure gradient, PVR, and mean PAP in patients with PH-LHD. The association was not present in a separate cohort of patients with PAH nor in patients with PH attributable to lung disease, suggesting a specific linkage with PH-LHD. This specific polymorphism has been associated with lower nitric oxide levels in humans which plays a major role in vascular tone regulation. [7]

Another association was demonstrated between the repeat length polymorphism in the promoter region of the serotonin transporter gene in patients with PH-LHD. This polymorphism was associated with overexpression of the serotonin transporter and serotonin uptake by pulmonary arterial smooth muscle cells contributing to their proliferation. [8]

A Single nucleotide polymorphism within the gene encoding for the endothelial nitric oxide synthase enzyme has been shown to be associated with pulmonary hypertension in left heart disease.
eNOS* = *endothelial nitric oxide synthase gene

B Repeat length polymorphism in the promoter region of the serotonin receptor gene was associated with overexpression of the serotonin transporter and elevated PA pressure in patients with heart failure.
5-HTT indicates serotonin receptor gene



A study from the DNA biorepository at Vanderbilt University looked at shared genetic variants between PAH and PH-HFpEF compared with PVH by using pre-existing SNP data. 75 shared exonic SNPs were identified between PH-HFpEF and PAH in pathways involving cell structure, extracellular matrix, and immune function. An exploratory genetic analysis of the PH-HFpEF genes and biological pathways in the lung known to contribute to PAH pathophysiology suggests that PH-HFpEF may be a distinct and highly morbid PH subphenotype. [9]

In summary, studies indicate that PH-HFpEF is a recognized subtype of Group 2 PH with distinct clinical features and genetic abnormalities. Some of the features of PH-HFpEF overlap with PAH and are associated with a similar poor outcome.

References:

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