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STATE OF THE ART REVIEW

# Diffuse Alveolar Hemorrhage in Cardiac Diseases

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**Abstract**
Diffuse alveolar hemorrhage (DAH) is a rare condition with reported mortality ranging between 20 and 100%. There are many etiologies of DAH. Cardiac diseases are likely underreported causes of DAH. Heart failure and mitral valve diseases are the most common cardiac causes of DAH. The DAH results from pulmonary venous hypertension leading to stress failure of the pulmonary capillaries. There is also a contribution of the bronchial circulation. The Alveolar-capillary membrane or blood-gas barrier is an extremely thin structure that allows rapid and passive diffusion of oxygen from the inhaled air to the pulmonary capillaries while preventing pulmonary edema and DAH with chronic elevation of the transmural hydrostatic pressure. The purpose of this manuscript is to inform the clinician about this rare cause of DAH, which may be overlooked unless specifically sought after. We also discuss the pathophysiologic aspects of DAH and the safety mechanisms in place to prevent such occurrences.

**Keywords** Diffuse alveolar hemorrhage · Heart failure · Mitral stenosis · Mitral regurgitation

## Introduction

Diffuse alveolar hemorrhage (DAH) refers to the occurrence of intraalveolar bleeding due to disruption of the alveolar-capillary basement membrane. There are many causes of DAH, including infection, inflammation (immune and non-immune mediated vasculitis), diffuse alveolar damage (DAD), cardiac diseases, drugs and toxin exposure, use of anticoagulants and coagulation disorders, and idiopathic pulmonary hemosiderosis (IPH), among others [1]. Patients with DAH classically presents with hemoptysis, shortness of breath, anemia, and radiologic chest abnormalities [2]. However, hemoptysis may be absent in up to 30% of patients [3, 4]. Accurate identification of the etiology for DAH is important as the treatment varies based on the cause. For example, DAH due to antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is treated with corticosteroid and immunosuppressive medications, whereas a pulmonary infection precipitating DAH would respond to antimicrobial therapy [5, 6]. In addition, recognition of a specific etiology is important for prognostication. The reported mortality from DAH has ranged from 20 to 100% [7–9].

DAH secondary to cardiac diseases is often less appreciated and possibly underreported [10]. The clinical presentation and radiologic features of DAH are non-specific, and a definitive diagnosis of DAH can only be made after a bronchoscopic evaluation. Demonstration of progressively bloody fluid return on serial aliquots of bronchoalveolar lavage is diagnostic of DAH. Since a bronchoscopic evaluation is not routinely performed in all patients with hemoptysis, and both pulmonary edema and pneumonia can cause hemoptysis and radiologic chest infiltrate, differentiation of DAH from pulmonary edema or pneumonia can be challenging. The purpose of this review is to scrutinize the literature to inform the clinician regarding the pathophysiologic basis of alveolar hemorrhage in patients with cardiac diseases and a detailed discussion of specific well-known cardiac causes of DAH. Additionally, we also focus on the specific radiologic presentation, diagnostic workup, and histopathologic changes that are typically seen in DAH of cardiac causation. We believe that a comprehensive cardiac evaluation may identify a cardiac etiology of DAH in many patients with occult cardiac disease and potentially prevent invasive testing, such as surgical lung biopsies. In this manuscript, the

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term 'cardiac diseases' will refer to valvular heart diseases and heart failure unless otherwise specified.

## Mechanism of DAH in Cardiac Disease

The pathogenesis of pulmonary edema or DAH due to cardiac diseases is similar [11]. The evolution from pulmonary edema to alveolar hemorrhage represents an escalating structural alteration in the blood-gas barrier along a spectrum of changes. The primary mechanism responsible for alveolar hemorrhage in cardiac diseases is the acute stress failure of the pulmonary capillaries resulting from elevated transmural hydrostatic pressure [12]. Increased hydrostatic pressure in the pulmonary capillaries occurs due to pulmonary congestion. Pulmonary congestion refers to the accumulation of fluid in the pulmonary parenchyma leading to gas exchange abnormalities. Pulmonary congestion in cardiac diseases result from elevated left sided filling pressure (elevated left ventricular end diastolic pressure). The resultant pulmonary venous hypertension can be easily identified as an increased pulmonary capillary wedge pressure (PCWP) on right heart catheterization. The elevated hydrostatic pressure in the capillaries promotes ultrafiltration and interstitial fluid accumulation following the starling equation [13]. The alveolar-capillary membrane remains intact. The resulting ultrafiltrate initially has a low protein concentration [14]. However, as the transmural pressure continues to increase, changes occur in the alveolar-capillary membrane leading to exudation of larger molecules by 'pore stretching' [15, 16]. Pore stretching refers to the passage of high molecular weight serum components from the capillary lumen into the peri-capillary interstitium and alveolar space after passing through the junction between the endothelial cells due to high transmural pressure without disrupting the basement membrane [17]. When the hydrostatic pressure is high enough to cause ultrastructural damage to the blood-gas barrier, frank hemorrhage ensues [12]. There could also be a contribution from the engorged bronchial circulation [10, 18]. Moreover, mechanical and hypoxic injury to the pulmonary capillary endothelium may also precipitate alveolar hemorrhage [10].

### Stress Failure of the Pulmonary Capillaries

The pulmonary blood-gas barrier is a remarkably thin structure with a mean thickness of only 0.6 µm [19]. The blood-gas barrier has a surface area between 50 and 150 $m^2$, and in more than half of the areas (the thin side of the barrier), the thickness varies between 0.2 and 0.4 µm [20]. The blood-gas barrier is formed by the single layer of endothelial cells on one side and alveolar epithelial cells on the other. The epithelial and endothelial cells have a shared basement membrane. The extraordinarily thin nature of the barrier allows for rapid diffusion of oxygen from the alveolus to the pulmonary capillaries. However, some degree of diffusion limitation can be seen in elite athletes [21, 22]. Despite the minimal thickness, the blood-gas barrier needs to be immensely strong to sustain life.

The exact pulmonary capillary pressure in humans has not been measured directly. The value is estimated to be halfway between the mean pulmonary artery pressure and the pulmonary venous pressure (measured by PCWP) [23]. There is some indication that the capillary pressure may be closer to the arterial pressure than the venous pressure [24]. Experimental studies in humans have shown a significant elevation of the pulmonary capillary pressure during exercise [22, 25, 26]. In fact, a pulmonary capillary pressure of 36 mmHg was estimated at the base of the lungs in healthy exercising volunteers [23]. These individuals demonstrated no evidence of hydrostatic pulmonary edema or alveolar hemorrhage.

However, it is crucial to emphasize that the pulmonary capillaries function under high wall stress [27]. The wall stress in these capillaries can be calculated using the following formula:

Wall stress = transmural hydrostatic pressure X radius / thickness of the barrier (assumed to be 0.3 µm at the thin side of the barrier).

When the transmural capillary gradient (capillary hydrostatic pressure-alveolar pressure) is about 30 mmHg, human pulmonary capillaries bulge into the alveolar space and assume a circular shape. The capillary lumen measures approximately 10 µm in diameter [27, 28]. Therefore, with a transmural pressure of 30 mmHg, the calculated wall stress in pulmonary capillaries is 70 kPa, comparable to the wall stress in the human aorta [29]. Hence it is not surprising that increased capillary hydrostatic pressure may disrupt the capillary integrity causing alveolar hemorrhage. Although no data exists in humans, the rabbit pulmonary capillary preparation in experimental studies has shown consistent vascular damage with a transmural pressure of 40 mmHg [12]. Whether similar changes occur in humans is unknown. It is important to emphasize that once there is a disruption of the pulmonary capillary endothelium, there may be additional insults because of the release of pro-inflammatory mediators and oxidative damage, further perpetuating the alveolar hemorrhage [30–33].

The mechanical strength of the blood-gas barrier primarily depends on the shared basement membrane. The endothelial and epithelial cell layers contribute minimally [16, 34]. The basement membrane is composed of two distinct layers, lamina densa and lamina rara [35]. The lamina densa in the central electron-dense layer, composed of type IV collagen. The lamina rara layers are present on both sides of lamina densa and attach lamina densa to the epithelial

and endothelial layers. Besides the collagen, the basement membrane is composed primarily of three other extracellular matrix components, laminin, heparan sulfate, and entactin. The laminin connects the type IV collagen present in the lamina densa to the epithelial and endothelial layers. The heparan sulfate regulates selective permeability, and the entactin binds type IV collagen to laminin. The type IV collagen present in lamina densa forms a meshwork of fibers, the tensile strength of which approaches that of type I collagen [16, 27, 36]. The lamina densa of the basement membrane is approximately 50 nm in thickness. When exposed to a persistently high capillary hydrostatic pressure, the capillary basement membrane thickens as an adaptive response. These changes have been observed in patients with mitral stenosis as well as in renal capillary bed, where the hydrostatic pressure is higher compared to the pulmonary capillaries [37, 38]. The adaptive changes occur rapidly, within days to weeks [39].

### Role of Bronchial Circulation

The lungs receive dual blood supply, both from the bronchial and pulmonary circulation. The bronchial arteries arise from the thoracic aorta and its branches, and the bronchial veins drain to the intercostal and azygous veins. The bronchial arteries supply the airways, including terminal bronchioles and the visceral pleura [40]. There are no direct large anatomic anastomoses between the pulmonary and bronchial circulations, but anastomoses exist at the microvasculature level. As a result, changes in the pulmonary circulation also affects the bronchial circulation.

Pulmonary venous hypertension can cause dilation of the bronchial vasculature through transmitted back pressure. Moreover, the increased left atrial pressure may diminish blood flow, causing higher blood volume, congestion, and enlarged bronchial vessels [18]. These changes may translate into airway mucosal swelling, narrowing of the airways, causing respiratory impairment. In extreme cases, the elevated pressure may precipitate life-threatening bleeding from the airways [41]. The airway bleeding might cause airway occlusion and asphyxia.

### Mechanical and Hypoxic Injury to the Capillary Endothelium

Although not directly related to cardiac dysfunction, mechanical and hypoxic injury to the vascular endothelium can potentiate alveolar hemorrhage. Many patients with cardiac diseases require mechanical ventilation. Inappropriately large tidal volumes can cause a mechanical breakdown of the vascular endothelium causing alveolar hemorrhage at a capillary hydrostatic pressure that would be otherwise unexpected [42]. Similarly, hypoxia-induced pulmonary vasoconstriction is not uniform, and some capillary beds may experience higher pressures than others, precipitating pulmonary hemorrhage [16]. Vascular thrombosis is also commonly seen in patients with cardiac diseases, increasing the possibility of hemorrhage [10]. Table 1 summarizes the mechanisms of DAH in cardiac diseases. Figure 1 provides a schematic presentation of structures affected in DAH.

## Histopathologic Changes

As DAH is caused by a broad spectrum of etiologies, lung biopsies are often necessary to attain a definitive diagnosis. In addition to the intraalveolar hemorrhage, Immunologic causes of alveolar bleeding generally demonstrate necrotizing capillaritis, inflammatory infiltrate with or without immunocomplex deposition [43]. In contrast, DAH due to

**Table 1** Pathogenesis of diffuse alveolar hemorrhage in cardiac diseases

| Mechanisms | |
|---|---|
| Increased transmural capillary pressure | Transmural pressure = (capillary hydrostatic pressure-alveolar pressure)<br>Progressive increase in capillary hydrostatic pressure changes the ultrafiltrate from low protein to high protein containing exudate<br>Transmural capillary pressure of 40 mmHg consistently causes break in the alveolar-capillary membrane in experimental animal preparation |
| Increased blood volume and congestion of the bronchial circulation | Pulmonary venous hypertension increases pressure in the bronchial circulation due to anastomoses at the level of the microcirculation<br>Reduced forward flow into the systemic venous circulation due to increased left atrial pressure<br>Dilation of the bronchial submucosal small vessels cause airway narrowing and may precipitate severe bleeding |
| Mechanical and hypoxic endothelial injury of the pulmonary capillary | Pulmonary infarction, hypoxic endothelial damage is common<br>Inappropriately high tidal volume ventilation with respiratory failure cause further damage to the alveolar-capillary membrane |
| Inflammatory endothelial damage | Cellular damage of the alveolar-capillary basement membrane induces inflammatory changes, including transcription of pro-inflammatory cytokines and influx of inflammatory cells |

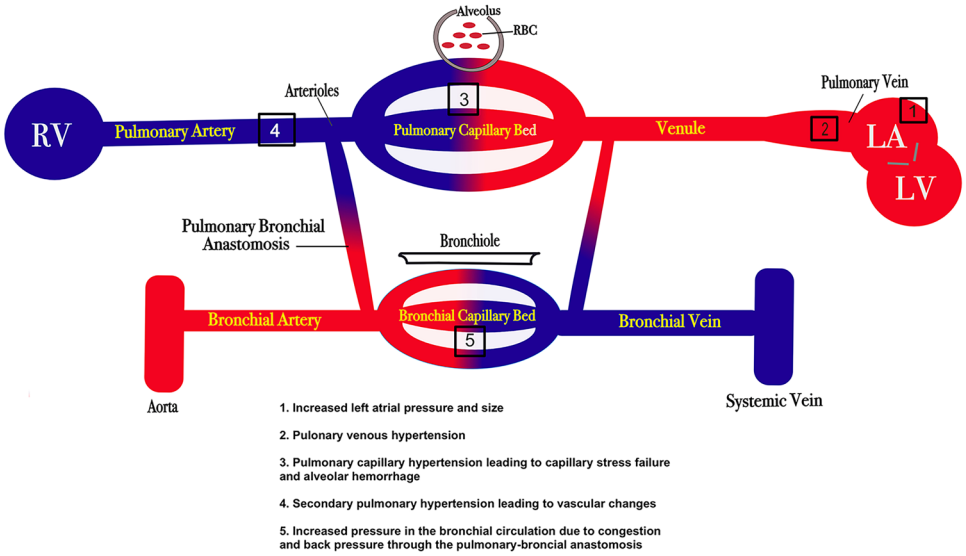


**Fig. 1** Schematic representation of the pulmonary and bronchial circulation and potential areas of involvement with volume overload due to cardiac diseases leading to diffuse alveolar hemorrhage

elevated cardiac pressures is typically described as 'bland pulmonary hemorrhage.' The term 'bland pulmonary hemorrhage' refers to the absence of any vasculitis, inflammatory infiltrate, and disruption of alveolar-capillary membrane on light microscopy [44]. Hemosiderin laden macrophages can be seen in the intraalveolar and interstitial space. Similar histopathologic changes can also be seen in patients with coagulation abnormalities or anticoagulant therapy, IPH, and in rare cases of systemic lupus erythematosus and anti basement membrane antibody syndrome [8, 45].

Although not routinely performed for clinical decision making, scanning electron microscopy of the blood-gas barrier provides intriguing details of the changes that occur with increasing transmural pulmonary capillary pressure. Capillary endothelial disruption with or without damage to the alveolar epithelial membrane is often seen. As the basement membrane is the strongest component of the alveolar-capillary membrane, damaged endothelial and epithelial cells with an intact basement membrane have also been reported. Thickening and separation between the epithelial and endothelial basement membranes can be seen in this particular situation due to increased fluid influx in the interstitium due to increased pressure. Finally, damage to all three layers of the blood-gas barriers with extravasation of red blood cells has been reported [12, 16].

Researchers have demonstrated consistent damage to the blood-gas barrier with increasing transmural pressure in the experimental preparation of rabbit pulmonary capillary. For example, at transmural capillary pressure of 10 cm of $H_2O$, no disruption of the blood-gas barrier was seen. However, when the pressure was increased to 50 cm of $H_2O$ (40 mmHg), there was consistent damage at different layers of the membrane [12]. It is crucial to remember that these values were obtained from animal studies, and humans may or may not demonstrate reciprocal changes with changing transmural capillary pressures. However, these numbers provide a solid foundation from a conceptual point of view.

## Clinical and Radiologic Presentation of DAH in Cardiac Diseases

The classic presentation of DAH includes hemoptysis, radiologic chest abnormalities, and anemia. However, the 'triad' is present only in a minority of patients [46]. The hemoptysis can vary significantly in volume. Although most patients complain of small volume hemoptysis, exsanguinating life-threatening pulmonary hemorrhage with florid respiratory failure can also occur [47, 48]. As elevated left sided filling pressures can be present for days to weeks before acute decompensation, some patients may present with cough, wheezing, and exertional shortness of breath [11]. The majority of patients have known cardiac disease. However, occult cardiac disease may be present in the minority [49]. The physical examination may be suggestive of heart failure and/or valvular heart diseases. Chest auscultation generally reveals diffuse crackles and occasionally wheezing, the so-called cardiac asthma. Laboratory workup demonstrates anemia, elevated pro-brain natriuretic peptide levels, among others.

The radiologic findings in DAH are non-specific. However, the presence of cardiomegaly may point toward a cardiac origin of DAH. Similarly, patients with mitral stenosis may also demonstrate straightening of the left heart border and double contour of the right heart border [41, 50]. Moreover, prior evidence of mitral valve manipulation, such as a prosthetic valve, may suggest a valvular etiology.

An initial chest X-ray is usually available for patients in whom DAH is suspected. The chest radiograph typically shows peri-hilar alveolar opacity predominantly in the mid and lower lung zones [51]. If the hemorrhage is extensive, the opacity may affect all lung zones. The alveolar infiltrate evolves into more interstitial changes over time. Subpleural sparing is frequently seen with DAH creating a 'window frame effect' on chest radiography (Fig. 2) [41, 50]. Non-resolving upper lobe consolidation is rarely seen in patients with DAH secondary to cardiac origin [52]. There are also reports of right sided DAH in patients with severe mitral regurgitation [44]. The appropriate diagnosis of DAH is often delayed with these unusual presentations and requires a low threshold of suspicion.

Computed tomography (CT) of the chest is more sensitive to chest radiography. Ground-glass opacity is typically seen in the same distribution described above. With recurrent episodes of bleeding, patients may also demonstrate centrilobular nodularity and interlobular septal thickening from intraalveolar and septal deposition of hemosiderin [41, 53]. When acute bleeding occurs on the background of chronic bleeding, a crazy paving pattern may be seen. Long-standing alveolar hemorrhage may cause pulmonary fibrotic changes [41]. Pulmonary ossifications, predominantly in the mid and lower lung zones with a confluence of lesions, can be seen in mitral stenosis [54]. Many radiologic abnormalities that are seen in DAH are also present with hydrostatic pulmonary edema, which makes the identification of DAH even more challenging in patients with cardiac diseases. The absence of radiologic improvement with adequate diuresis may point toward the diagnosis of DAH. The presence of air bronchograms may be more suggestive of DAH than pulmonary edema (Fig. 3) [41]. Table 2 summarizes commonly seen radiologic abnormalities in DAH.

## Specific Cardiac Causes of DAH

Among cardiac etiologies, valvular heart diseases and heart failure are the most common causes of DAH. Among hospitalized patients, cardiac causes account for approximately 30% of cases of DAH [46]. Patients with DAH due to cardiac diseases appear to be older compared to other causes of DAH and more likely to present with shock [46]. Similarly, this group of patients has the worst survival [46]. Cardiovascular disease is an independent predictor of poor outcomes in patients with DAH [55]. Although mitral stenosis has classically been taught to be the number one etiology of alveolar hemorrhage, there has been a recent shift. Heart failure, both systolic and diastolic, is more common than mitral stenosis as the cause of DAH [46]. This is likely due to increased awareness and optimal treatment of rheumatic fever as well as an increased prevalence of cardiovascular diseases overall [56].

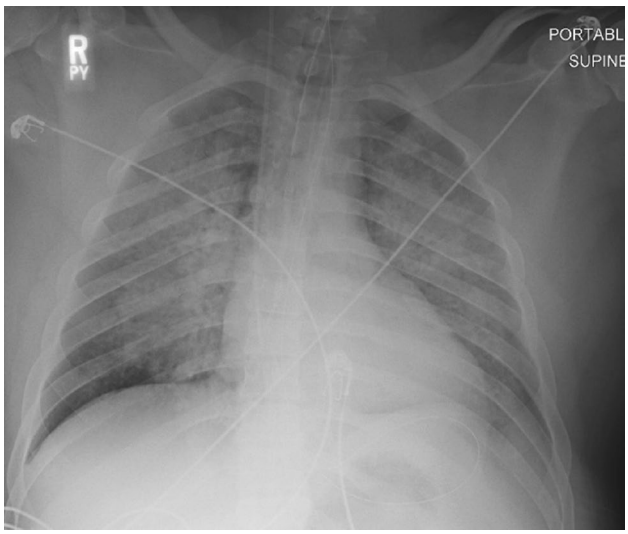


**Fig. 2** A 57-year old man with pulmonary hemorrhage resulting in respiratory failure due to acute mitral regurgitation in the setting of acute myocardial infarction. The chest radiography demonstrated bilateral peri-hilar diffuse alveolar infiltrate with sparing of the periphery, causing a window frame effect, suggestive of diffuse alveolar hemorrhage

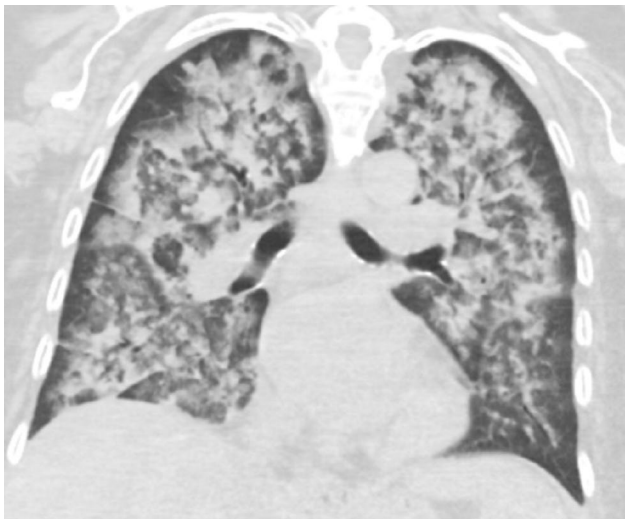

**Fig. 3** A 63-year old man with diffuse alveolar hemorrhage due to heart failure with preserved ejection fraction. The coronal computed tomographic image showed diffuse bilateral infiltrate affecting all lung lobes. The infiltrate(s) are characterized by both ground glass opacities and consolidation with air bronchograms. There are also areas on centrilobular nodularity and interlobular septal thickening. Additionally, subpleural sparing is a striking feature in this CT image

**Table 2** Radiologic abnormalities in diffuse alveolar hemorrhage in cardiac diseases

| Disease | Radiologic abnormalities |
|---|---|
| Diffuse alveolar hemorrhage | Chest radiology<br>Diffuse alveolar infiltrate(s) in the peri-hilar distribution<br>The mid and lower lung zones are predominantly involved but all lung zones can be affected<br>Peripheral sparing may cause 'window frame effect'<br>Computed tomography<br>Ground-glass opacity<br>Consolidation with air bronchograms are more suggestive of DAH than pulmonary edema<br>Hemosiderin deposition in the interlobular septa can cause 'crazy paving'<br>Centrilobular nodularity<br>Pulmonary fibrosis, honeycombing, and traction bronchiectasis<br>Pulmonary ossification<br>Findings suggestive of a cardiac etiology<br>Non-resolving right upper lobe infiltrate (rarely left upper lobe)<br>Cardiomegaly<br>Straightening of the left heart border<br>Double contour of the right heart border<br>Heavily calcified and Prosthetic valves |

## Valvular Heart Diseases

Mitral valve disease is the most common valvular abnormality to cause DAH. Both mitral stenosis and regurgitation can precipitate DAH. The pathogenesis involves elevated left atrial pressure, pulmonary venous hypertension resulting in capillary stress failure, and DAH. In addition, bleeding from the bronchial circulation can also occur [57, 58]. Recurrent hemoptysis is common in patients with mitral stenosis, but life-threatening massive hemoptysis is rare [47, 59, 60]. The paroxysmal episodes of hemoptysis typically occur with exertion and pregnancy. The occurrence of life-threatening massive pulmonary hemorrhage follows an unpredictable temporal course [61]. Rheumatic fever (RF) is the most common cause of mitral stenosis. RF is more prevalent in underdeveloped countries compared to the developed countries. Some patients may have congenital mitral stenosis.

Both acute and chronic mitral regurgitation can cause DAH [62–65]. Acute mitral regurgitation is commonly seen in the setting of infective endocarditis, papillary muscle, or chordae tendineae rupture from cardiac ischemia, trauma or acute rheumatic fever. Acute mitral regurgitation is associated with a sudden and severe increase in the left atrial pressure as the left atrium does not have enough time to accommodate and compensate for the regurgitant flow. This results in severe pulmonary venous hypertension and DAH. In contrast, hemodynamic changes in chronic mitral regurgitation are much less dramatic. Generally, the DAH from mitral regurgitation is diffuse. However, rarely, pulmonary edema or DAH due to mitral regurgitation can result in asymmetric radiologic chest infiltrate(s). Only the right upper lobe is involved in many patients, which can be confusing for clinicians. The pathogenesis of this unusual development stems from the selective directionality of the regurgitant flow toward the right upper lobe pulmonary vein during ventricular systole [64].

### Heart Failure

Both systolic and diastolic heart failure can cause DAH. The pathogenesis of DAH in heart failure (DAH-CHF) is similar to valvular heart diseases and involves both pulmonary and bronchial circulation. Based on the recent reports, the incidence varies between 1 and 3.3 cases per year in large academic centers [44, 52, 55]. It is possible that the true incidence of DAH from heart failure is higher, and with increased awareness, there will be an increase in the number of cases in the future.

Left atrial enlargement and at least some degree of mitral valve regurgitation are seen in almost all patients with DAH-CHF. The left atrium plays a crucial role in the prevention of DAH-CHF, at least initially. The LA is a thin and compliant chamber that can dilate in response to chronically elevated LVEDP and prevents a rapid increase in the pulmonary venous pressure. However, with progressive dilation, the compliance reduces, and the protective role is lost [66]. Chest radiography typically shows bilateral symmetric infiltrate(s). However, asymmetric infiltrate can also occur [44, 52]. Predominantly right sided infiltrate is more common than left sided infiltrate [44]. The speculative explanation for such findings includes mitral valve regurgitation, alteration of left ventricular structure impeding venous return from the left side, and inadequate lymphatic and venous return on the right side [65, 67–69]. To contradict

this hypothesis, right sided DAH in the absence of mitral regurgitation has been reported [70].

## Safety Factors Against the Development of Diffuse Alveolar Hemorrhage

Based on animal studies, a transmural pulmonary capillary pressure of 40 mmHg would cause predictable damage to the blood-gas barrier. During resting in supine position, the mean pulmonary artery and pulmonary capillary wedge pressures are estimated to be 15 and 5 mmHg at the hilar level, respectively. This would translate into a pulmonary capillary pressure of approximately 10 mmHg at the hilar level. When upright, due to the effect of gravity, the resting pulmonary capillary pressure at the lung base reaches 17 mmHg. Research in exercising individuals in an upright position has demonstrated an increase in the pulmonary capillary pressure up to 36 mmHg in the lung base due to both increased pulmonary artery and left atrial pressures [22]. Thus the safety factor operating at the base of the lungs against the occurrence of pulmonary edema or DAH appears to be minimal, especially during maximal exercise. The safety factor can be calculated by the following formula:

Safety factor = Transmural capillary pressure that causes stress failure/physiologic pressure.

If the findings of the animal studies are applied to humans, a transmural pulmonary capillary pressure of 40 mm Hg would be considered the pressure required to cause stress failure [12]. Since the measured pulmonary capillary pressure during exercise can be as high as 36 mm Hg, the safety factor during maximal exercise is only 1.1 (40/36 mmHg). The pulmonary capillary pressures observed in patients with severe mitral stenosis and heart failure can be significantly high, often exceeding the safety factor [71, 72]. This raises the question of why life-threatening DAH is so rare in patients with cardiac diseases.

The explanation for this can be found by histopathologic analysis of lung biopsy specimens from patients with chronically elevated pulmonary capillary pressure. Pulmonary vasculature shows remarkable remodeling in patients with mitral stenosis [37]. Such changes can also be expected in patients with heart failure [38]. The changes in the vasculature occur at all levels, including pulmonary arteries, arteriole, capillaries, venules, and veins. The changes are most prominent in the capillaries and peri-capillary vessels. Larger pulmonary arteries undergo intimal hyperplasia, medial hypertrophy, and thickening of the adventitia. Adventitial thickening can also be appreciated in the pulmonary veins. Light microscopy of the alveolar-capillary membrane shows thickening of the pulmonary capillary walls and dense connective tissue in the alveolar walls. Scanning electron microscopy demonstrates thickening of the basement membrane. The basement membrane thickening can be appreciated in both the thick and thin side of the alveolar-capillary membrane [71]. As the basement membrane is responsible for the tensile strength of the blood-gas barrier, it is not unexpected that these remodeled capillaries can withstand higher stress without suffering failure. The protective vascular changes happen rapidly within days to weeks [39].

The left atrium also plays a crucial role in the prevention of DAH in patients with chronically elevated left atrial pressure. Although the protective effects are insignificant during an acute episode of catastrophic mitral regurgitation, chronic volume overload leads to a series of adaptive changes that help the left atrium to act as a buffer and minimize the elevation of pressure in the pulmonary venous circulation. These adaptive changes include an initial increase in contractility, myocyte hypertrophy and work performance, increased compliance, and enlargement of the left atrial diameter [73–75]. Unfortunately, progressive worsening of heart failure may lead to adverse cardiac remodeling and apoptosis, resulting in increased atrial stiffness and reduced contractility [76]. Table 3 summarizes the safety mechanism in patients with chronically elevated cardiac filling pressures.

## Conclusions

The extremely thin alveolar-capillary membrane is necessary to allow rapid passive diffusion of oxygen from the alveolus to the pulmonary capillaries in order to sustain life. The blood-gas barrier is formed by a single layer of capillary endothelium, alveolar epithelium, and shared basement membrane. The basement membrane is the primary contributor to the tensile strength of the barrier that operates under high stress, comparable to the wall stress in the aorta. A transmural pressure of 40 mmHg has been shown to cause capillary stress failure in animal studies. In exercising humans, the pulmonary capillary pressure often reaches 36 mmHg in the base of the lung. Thus, the safety factor that prevents DAH is minimal. Similarly, cardiac diseases causing chronically elevated pulmonary venous hypertension may cause damage to the blood-gas barrier and promote pulmonary edema and DAH. Mitral stenosis, mitral regurgitation, and heart failure are common causes of post-capillary pulmonary hypertension in clinical practice. Thickening of the capillary basement membrane and collagen deposition around the alveolar epithelial layer are primary adaptive mechanisms to prevent or minimize the occurrence of DAH in such conditions. A thorough workup is necessary to exclude a cardiac etiology in patients with DAH.

**Table 3** Safety mechanisms to prevent diffuse alveolar hemorrhage in chronically elevated pulmonary venous hypertension

| Mechanisms | Changes associated with adaptation |
|---|---|
| Adaptive changes in the pulmonary arteries | Intimal hyperplasia and hypertrophy of the smooth muscle in the tunica media |
| Adaptive changes in the pulmonary capillaries | Thickening of the basement membrane by increasing the type IV collagen content, which increases tensile strength<br>Deposition of type 1 collagen around the alveolar epithelial cells<br>Thickening of the tunica adventitia by connective tissue deposition<br>The changes occur rapidly within days to weeks |
| Pulmonary vasoconstriction | Pulmonary vasoconstriction reduces the stress on the pulmonary capillaries and thereby preventing stress failure |
| Anastomoses between pulmonary and systemic circulation | Increased hydrostatic pressure in the pulmonary capillaries enhances anastomotic communication between the pulmonary and systemic microcirculation. This resulting redistribution of the blood volume reduces pressure in the pulmonary venous system |
| Left atrial adaptations | Remodeling of the left atrium acts as a buffer to reduce pulmonary venous pressure<br>Increased contractility and enhanced work performance<br>Increased compliance and chamber diameter |

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**Author Contribution** BKS and WHC were involved in the planning, collection of data and the preparation of initial and final manuscript.

## Declarations

**Conflict of interest** The authors have no conflict of interest.

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