Management of Pulmonary Hypertension in Left Heart Disease

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ABSTRACT: Pulmonary hypertension due to left heart diseases (PH-LHD) is the most prevalent form of pulmonary hypertension. It frequently complicates heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF) and negatively impacts prognosis, particularly when a precapillary component is present.

PH-LHD is distinctive from pulmonary arterial hypertension (PAH) even though both conditions may share some common characteristics. In addition, the mechanisms involved in the development of a precapillary component are yet to be fully clarified, in particular in PH due to HFpEF.

Several studies have been exploring PAH pathways as potential therapies for PH-LHD, but no PAH-approved drug has demonstrated efficacy in PH-LHD. Rather, some classes of drugs, such as endothelin-receptor antagonists or prostacycline-analogues, have been found to be harmful in patients with HF. Therefore, at present, the only established treatments for PH-LHD are those that target the heart as recommended in the international guidelines for HF. Based on current knowledge, off-label prescription of PAH-approved drugs in PH-LHD patients must be strongly discouraged.

INTRODUCTION

Pulmonary hypertension (PH) is a common complication of heart failure (HF) with reduced or preserved ejection fraction (HFrEF or HFpEF), with an estimated prevalence from 36% to 80% depending on the population and the tool used for diagnosis.1 It may also complicate all forms of left heart disease (LHD), which is the most common cause of PH.2,3 This manuscript describes how PH may develop in LHD, sets the scene for different management approaches, and reviews the evidence for treating PH-LHD.

THE PROBLEM

Pathophysiology of PH-LHD

Heart failure (HF) is known to affect the pulmonary circulation. Early in its natural history, HF leads to the increase in left atrial filling pressure (LAP), which is then transmitted to the pulmonary veins and capillaries, leading to a “passive” rise in pulmonary artery pressure (PAP).2,3 The increase in LAP, commonly measured by the pulmonary artery wedge pressure (PAWP), fully accounts for the development of PH. However, a further increase in mean PAP (mPAP), disconnected from the rise in LAP/PAWP, may occur in the presence of several additional factors and in longstanding disease. This results in the development of a precapillary component (reflected by an increase in pulmonary vascular resistance, PVR) and is associated with an even more severe clinical condition.2,3

International guidelines have defined the two hemodynamic phenotypes of postcapillary PH (mPAP ≥ 25 mm Hg and a PAWP > 15 mm Hg) as follows: (1) isolated postcapillary PH when the diastolic pressure gradient (DPG) is < 7 mm Hg and/or PVR is ≤ 3 Wood units (WU), and (2) combined post- and precapillary PH (CpcPH) when DPG is ≥ 7 mm Hg and/or PVR is > 3 WU. This hemodynamic classification of PH was recently revised during the 6th World Symposium on Pulmonary Hypertension, lowering the normal value for mPAP from 25 to 20 mm Hg and introducing PVR in the general definition.3 However, this definition has not yet been implemented in international guidelines.

It is unclear why some patients evolve towards CpcPH while others do not, although several mechanisms have been shown to participate in the process:4

• **Vasoconstriction:** Due to endothelial function impairment, there is an imbalance between nitric oxide (NO) production (vasodilation) and endothelin-1 pathway (vasoconstriction), with the result of arteriolar vasoconstriction.

• **Vascular remodeling:** Inflammatory stimuli, and perhaps genetic predisposition,5 lead to changes in vascular wall structure. This is characterized by thickening of extracellular matrix, collagen deposition, leucocytes infiltration, and arteriolar intima-medial hypertrophy, which together determine the reduction in pulmonary vascular bed and the rise in small vessels pulmonary resistance.
Even though these abnormalities may be seen as a maladaptive response, it is speculated that they serve as "protection strategies" against the acute pulmonary edema resulting from the increase in LAP.4 Some of the structural changes described in CpcPH may be similar to pulmonary arterial hypertension (PAH), such as intima-medial hypertrophy and the so called "muscularization" of distal arterioles. Both conditions may even share some genetic predisposing factors.5 However, the structural changes on the arterial side do not include the typical plexiform lesions seen in PAH, and the venular involvement may be similar to pulmonary veno-occlusive disease.6

**PH-LHD or PAH?**

Some common mechanisms make it tempting to believe that there is an overlap between idiopathic PAH (iPAH) and PH-LHD, especially in patients with HfP EF. In addition, the clinical distinction between iPAH and PH due to HfP EF may be difficult, especially in the elderly population where the burden of cardiovascular comorbidities may represent significant confounding factors.4,7 However, the belief that there is overlap between iPAH and HfP EF is incorrect, as these are two very distinct conditions summarized in Table 1.4

**PH-LHD and Prognosis**

Treating PH in LHD may make sense because it is associated with a poorer prognosis. A high systolic pulmonary pressure estimated by echocardiography predicts all-cause and cardiovascular hospitalization and mortality in HF patients.8 Other analyses, focusing on invasive hemodynamic parameters, showed that the presence of a precapillary component of PH, defined as PVR > 3 WU, is associated with worse prognosis, with a parallel between outcome and the progressive increase in PVR.9 Moreover, recent data suggest that the normal value for PVR may be even lower than 3 WU. According to a recent multicenter retrospective analysis of > 40,000 cases, a PVR of 2.2 WU was found to be the cutoff value to predict outcome.10

Left-sided valvular heart diseases (VHD) are frequently associated with PH of variable extent. Traditionally, the "model disease" for this pathological condition is mitral stenosis: Severe preintervention PH has been demonstrated to be associated with a worse outcome after mitral valve replacement. Similarly, patients with either primary or functional mitral regurgitation are at high risk of developing postcapillary PH, which is an additional risk factor for surgery.11
A variable degree of PH may persist after mitral valve replacement, affecting long-term prognosis. Preoperative PH, female sex, and older age were clinical factors associated with higher risk of PH persistence, suggesting that more advanced disease could be associated with deeper pulmonary vascular remodeling that does not abate after surgery. Overall, the development of PH in VHD is associated with worse outcomes after both medical and surgical treatment. Therefore, an elevated PAP at rest is an additional factor to be considered when anticipating optimal timing of surgery.

Finally, among selected young patients with advanced HFrEF who could be candidates for heart transplantation and/or left ventricular assist device (LVAD) implantation, the development of severe CpcPH (resulting from persistently elevated PVR) is an additional risk factor for a worse surgical outcome.

Left ventricle mechanical support can reduce and normalize pulmonary pressure in advanced HFrEF and is usually considered as a bridge to heart transplantation. However, CpcPH itself may be a risk factor for worse outcome post-LVAD implantation because high PVR and DPG were found to be associated with increased risk of right ventricular (RV) failure and death.

Severe CpcPH is a contraindication to heart transplantation. Moreover, retrospective analysis of a United States-based registry showed that even less severe pretransplant PH has a negative impact on early post-transplant survival, although it does not affect mid- or long-term outcomes. Surprisingly, some studies reported that a history of PH was associated with worse early post-transplant outcomes even when pulmonary pressure was normalized by an LVAD implanted as a bridge-to-transplant. This may suggest that either some degree of pulmonary vascular remodeling may persist beyond the improvement of hemodynamic parameters, or RV dysfunction may not be reversed due to myocardial injury. Therefore, PH—and particularly CpcPH—clearly represents an additional risk factor in several left-heart conditions and may be one of the targets for intervention.

### The Options: Targeting the Heart or the Pulmonary Circulation?

Target the Heart First!

The primary treatment of PH-LHD is management of the underlying condition.

### Table 1

Clinical and pathobiological characteristics of pulmonary arterial hypertension (PAH) and pulmonary hypertension (PH) due to left heart diseases. ACE: angiotensin converting enzyme; ARB: angiotensin receptor antagonist; ARNI: angiotensin receptor neprilysin inhibitor; ERA: endothelin receptor antagonist; F: female; HF: heart failure; HfPEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LA: left atrium; LBBB: left bundle branch block; LHF: left heart failure; LV: left ventricle; M: male; MRA: mineral-corticoid receptor antagonist; PAP: pulmonary artery wedge pressure; PDE5: phosphodiesterase-5; PVOD: pulmonary veno-occlusive disease; RA: right atrium; RBBB: right bundle branch block; RHF: right heart failure; RV: right ventricle; sGC: soluble guanylate cyclase; SGLT2: sodium–glucose cotransporter 2; TR: tricuspid regurgitation; VCO₂: CO₂ output; VE: ventilation; VO₂: oxygen uptake.
In HFrEF, the activation of adrenergic and renin-angiotensin-aldosterone systems promotes sodium retention, renal vasoconstriction, LV dilatation, and fibrosis. These maladaptive responses contribute to fluid retention and increased left-heart filling pressures, triggering the development of PH.4,18 Interrupting this vicious circle by neurohormonal antagonism has been demonstrated to be effective in improving symptoms, cardiovascular biomarkers, hemodynamics, LV function, and eventually survival whether or not PH is present.19 Targeting the mechanisms leading to HFrEF is much more challenging because of the multifactorial nature of this syndrome, incomplete understanding of its pathophysiology, and scarcity of recommended treatments. HFrEF has been associated with a peculiar neurohormonal setting, particularly in the setting of obesity: Aldosterone is overproduced by adipocytes, the renin-angiotensin system is directly activated, and natriuretic activity is increased. All these mechanisms could lead to decreased sensitivity to natriuretic peptides, inflammation, and eventually to sodium retention and congestion.20

Despite this solid pathophysiologic rationale, no treatment has yet been shown to clearly reduce morbidity or mortality in HFrEF. In addition, several PAH-specific targets—including endothelin-receptor antagonists and drugs targeting the NO/cyclic guanosine monophosphate pathway—failed to demonstrate a benefit in this disease.3 Therefore, the management of HFrEF focuses on managing comorbidities and decongestion with diuretics. However, the CHAMPION trial (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients), which evaluated the efficacy of an implantable device for continuously monitoring pulmonary pressure in HF, suggested that hemodynamic-guided management yielded a better outcome in terms of HF hospitalization, irrespective of LV ejection fraction or HF etiology.21 This highlights the importance of hemodynamic balance as a therapeutic target in HF.

**Target the Pulmonary Circulation**

In recent decades, the potential to treat PH-LHD has grown significantly due to its common biological characteristics with PAH.5 In particular, it was suggested that patients with CpcPH are not only younger than those with isolated postcapillary PH (even in the presence of the same degree of “disease chronicity”) but also share with PAH patients a significant number of gene polymorphisms related to cytoskeletal structure and immune system. These results, together with the similar changes in vascular wall structure,4 feed the hypothesis that PAH-specific drugs might be helpful in tackling pulmonary vascular remodeling. Nitric oxide acts as a modulator of pulmonary vascular tone via the activation of soluble guanylate cyclase (sGC); experimental models showed that an HF-induced proinflammatory state promotes oxidative stress and reduces the bioavailability of NO, resulting in decreased sGC activation and, eventually, derangement of endothelial function with coronary/pulmonary vasoconstriction and myocardial stiffness.22 Endothelin-1, a vasoactive peptide with potent vasoconstriction properties, is overproduced in patients with HF, and its circulating levels were found to be directly associated with the severity of PH.23 This suggests that this pathway could play a major role in development and worsening of pulmonary vascular remodeling. These observations were considered a good rationale for attempting to treat PH-LHD by targeting the same pathways proven effective in PAH. Unfortunately, the crude reality of randomized controlled trials (RCTs) didn’t confirm these promises.

**THE SOLUTIONS: TREATMENTS FOR PH-LHD**

**Target the Heart**

The cornerstone for treatment of HFrEF is represented by beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor/nephrilysin inhibitor (ARNI), and aldosterone antagonists, since these drugs have been shown to significantly improve outcomes.19 Unfortunately, similar studies that investigated these same treatments in HFrEF did not demonstrate similar improvement in outcome, and management still relies on strict control of coexisting diseases and risk factors.19 Despite the above-mentioned physiopathological rationale, trials that investigated the role of angiotensin receptor blockers—irbesartan in the I-PRESERVE trial (Irbesartan in Heart Failure With Preserved Systolic Function),24 aldosterone-antagonists (spironolactone in TOPCAT [Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function]),25 or ARNI (sacubitril/valsartan in PARAGON-HF [Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction])—failed to show a significant benefit in HFrEF outcome.26 Since HFrEF is a heterogeneous syndrome, and subgroup analysis suggested that selected groups of patients could benefit more than others (ie, obese patients would benefit more from aldosterone antagonists or angiotensin blockers than nonobese ones; patients with mildly reduced LVEF could benefit more than others from sacubitril/valsartan), some drugs have been considered as treatment options for selected patients in the latest updates of HF guidelines.27 Given these considerations, accurate patient selection based on underlying pathophysiologic mechanisms might be the key for future RCTs.

Recently, the antidiabetic drugs sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown an additional benefit in improving HF-related outcomes in patients with type 2 diabetes, regardless of the LV ejection fraction.
fraction or previous history of HF. This effect seems to occur beyond the strict control of glycemia and may be related to several mechanisms—for example, promoting sodium excretion and osmotic diuresis, improving LV diastolic function, or preventing vascular remodeling.28 These favorable effects have been investigated in the EMPEROR-Preserved trial (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction), comparing the outcome of 5,988 patients with HF and LVEF > 40% who were treated with empagliflozin or placebo.29 At the time this manuscript was written, the results were not yet available. If positive, this compound will become the first treatment showing a significant benefit on hard end points for patients with HFP EF.

Finally, some recent encouraging evidence came from the VICTORIA study (Vericiguat in Participants With Heart Failure With Reduced Ejection Fraction), where patients with worsening chronic HFREF treated with sGC stimulator vericiguat showed a lower risk of cardiovascular death or hospitalization for HF than those in the placebo group.30

Once again, a similar trial conducted in symptomatic HFP EF patients did not demonstrate any beneficial effect from vericiguat, even in less ambitious end points such as quality of life and 6-minute walking distance 6MWD.31 This is further confirmation that HFREF constitutes a different, multifaceted, and heterogeneous syndrome with complex pathological mechanisms that are not fully understood.

Target the Pulmonary Circulation

Drugs approved for PAH are not recommended for the treatment of patients with PH-LHD. Nevertheless, off-label, compassionate use of these drugs, particularly sildenafil, has been reported in small, monocentric studies exploring their effects on functional capacity in patients with severe PH-LHD complicated by RV dysfunction.32 This may indicate that a subgroup of patients may indeed benefit from such intervention.

There is, however, no proper RCT supporting this strategy. Several RCTs explored the role of PAH-approved drugs in PH-LHD, addressing the metabolic pathways known to be involved in iPAH; those studies and their results are summarized in Table 2.33-42

In the FIRST study (Flolan International Randomized Survival Trial), patients with advanced HFREF were randomized to receive epoprostenol infusion or placebo; however, the trial was aborted prematurely due to excessive mortality in the treatment group, but subsequent analysis showed that the magnitude of hemodynamic response, in terms of decrease in PAWP, was not able to predict the outcome.33

As oral therapies became available for PAH, a genuine interest grew to test other pathways in PH-LHD. The first small studies with sildenafil in PH due to HF revealed an improvement in exercise tolerance and hemodynamic variables in the treatment group compared with placebo.34-36 However, these encouraging results were not confirmed by multicenter RCTs, which did not show any benefit from treatment in terms of exercise capacity, RV function, or hemodynamic parameters.37,38

Further confirmation on the role of sildenafil in PH-LHD comes from the SIOVAC trial (Sildenafil for Improving Outcomes after Valvular Correction), which analyzed the response to sildenafil or placebo in 200 patients with persistent PH 1 year after correction of valvular disease. Results showed that treatment with sildenafil did not improve survival or exercise tolerance but was associated with even worse clinical outcomes than the placebo.39

Among endothelin receptor antagonists, a small RCT tested bosentan in patients with PH secondary to HFP EF and did not show any benefit on 6MWD, hemodynamic parameters, and N-terminal pro-brain natriuretic peptide. Of note, the study was interrupted due to excessive fluid retention in the active group.40

The same disappointing results came from the MELODY-1 trial (Macitentan in Subjects With Combined Pre- and Post-capillary Pulmonary Hypertension [CpcPH] Due to Left Ventricular Dysfunction),42 which specifically addressed patients with CpcPH due to HF, mainly with HFP EF; this trial aimed to explore the safety and tolerability of macitentan in this patient population since previous studies in HF patients had raised concerns about fluid retention and edema as serious secondary effects of endothelin receptor antagonists.43 Results from MELODY-1 were consistent with the previous ones, with a higher rate of fluid retention and/or worsening functional class in the treatment group.42

Finally, a recent meta-analysis on the effects of pulmonary vasodilator therapy in PH-LHD included 10 RCTs for a total of 777 patients. Even if none of the differences reached statistical significance, PAH-approved treatment was associated with a trend toward higher risk of all-cause and cardiovascular death and worsening HF compared to controls, with no hemodynamic benefit.44

Taken together, these results confirm that the PAH-specific drugs are not currently suitable for the treatment of PH-LHD.

CONCLUSION

Pulmonary hypertension is a common complication of HF and is associated with a high burden of morbidity and poor prognosis, even more so when a precapillary component is present. Although iPAH and PH-LHD share some common mechanisms, these are two distinct conditions with no evidence of overlap. In addition, many uncertainties remain regarding the
| STUDY | TARGET PATIENTS | DRUG (N) | END POINTS | RESULTS |
|-------|----------------|----------|------------|---------|
| FIRST*30 | Severe HFrEF (LVEF < 25%) NYHA III/IV Congestive HF (PAWP > 15, CI < 2.2) | Epoprostenol (237) vs conventional medical therapy (234) | Primary: death, major event (death, need for mechanical ventilation, inotropic drugs, mechanical circulatory support) Secondary: 6MWD, QoL, clinical status at 3 months | Early termination due to increased mortality for HF in treatment group |
| Lewis GD et al.*34 | HFpEF (LVEF < 40%) NYHA II-IV PH (mPAP > 25 mm Hg at RHC) | Sildenafil (17) vs placebo (17) for 12 weeks | Primary: VO2 peak Secondary: 6MWD, PVR | Increase peak VO2, improved 6MWD, decrease PVR in treatment group |
| Guazzi M, et al.*35 | HFrEF (LVEF > 50%) NYHA II-IV PH (sPAP > 40 mm Hg at echo) | Sildenafil (22) vs placebo (22) for 1 year | Primary: pulmonary hemodynamics, RV function (TAPSE) Secondary: QoL | Significant reduction in RAP, mPAP, PAWP and PVR, improvement in RV function, CI and QoL |
| Guazzi M, et al.*36 | HFrEF (LVEF < 45%) PH (mPAP 25-35 mm Hg at RHC) EOB at CPET | Sildenafil (16) vs placebo (16) for 1 year | Respiratory pattern during CPET Pulmonary hemodynamics | Significant EOB reversal in treatment group Significant reduction in pulmonary pressure and PVR, and increase in CO in treatment group |
| Hoendermis ES, et al.*37 | HFpEF (LVEF ≥ 45%) NYHA II-IV PH (mPAP > 25, PAWP > 15 mm Hg) | Sildenafil (26) vs placebo (26) for 12 weeks | Change in mPAP, PAWP, CO and peak VO2 | No significant differences |
| Liu LC, et al.*38 | HFpEF (LVEF ≥ 45%) NYHA II-IV PH (mPAP > 25, PAWP > 15 mm Hg) | Sildenafil (26) vs placebo (26) for 12 weeks | Echocardiographic parameters (RV/LV dimensions and function) CPET, QoL | No significant differences |
| SIOVAC*39 | PH (mPAP > 30 mm Hg at RHC) Left-side valvular replacement or repair 1 year before | Sildenafil (104) vs placebo (96) for 12 weeks | Primary: composite clinical score (death or HF + NYHA class + QoL) Secondary: clinical score components, 6MWD, BNP, echocardiography | Significant worsening in clinical status of patients in sildenafil group (driven by higher risk of readmission for HF). No differences in sPAP, 6MWD, NYHA class |
| BADDHY*40 | HFpEF (LVEF ≥ 50%) PH (mPAP > 25 mm Hg, PAWP > 15 mm Hg at RHC) RV dysfunction (echo) | Bosentan (5) vs placebo (11) for 12 weeks | 6MWD sPAP and RAP estimated by echocardiography | Insignificant trend in increase of 6MWD in placebo group Acute HF event in 3 patients in bosentan group vs 1 patient in placebo group |
| LEPHT*41 | HFrEF (LVEF ≤ 40%) NYHA II-IV PH (mPAP ≥ 25 mm Hg at RHC) | Iloigcuit (132) vs placebo (69) for 16 weeks | Primary: mPAP changes Secondary: hemodynamic parameters Exploratory: clinical worsening, death, HF hospitalization, 6MWD, NYHA class, QoL | No significant changes in mPAP Significant increase in CI and decrease in PVR in iloprost group. |
| MELODY-1*42 | HFpEF and HFrEF (LVEF > 35%) NYHA II-IV CpcPH (mPAP ≥ 25, PAWP ≥ 15, DPG ≥ 7, PVR > 3.0 WU) | Macitentan (31) vs placebo (32) for 12 weeks | Primary: safety and tolerability (fluid retention, worsening NYHA class) Exploratory: changes in hemodynamics, NT-proBNP, 6MWD | More patients in macitentan group than in placebo group experienced fluid retention No significant differences in any of the exploratory endpoints |

Table 2.

Design and main results of randomized clinical trials exploring pulmonary arterial hypertension (PAH)-specific drugs in pulmonary hypertension (PH) due to left heart diseases.*33-42 6MWD: 6-minute walk distance; BNP: B-type natriuretic peptide; CI: cardiac index; CO: cardiac output; CPET: cardiopulmonary exercise test; DPG: diastolic pulmonary gradient; EOB: exercise oscillatory breathing; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LV: left ventricle; mPAP: mean pulmonary artery pressure; NYHA: New York Heart Association (functional class); PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; QoL: quality of life; RAP: right atrial pressure; RHC: right heart catheterization; RV: right ventricle; sPAP: systolic pulmonary artery pressure; VO2: oxygen uptake; WU: Wood units
pathobiology of HFpEF and PH due to HF. This explains, at least in part, why no trial testing PAH pathways in HF has met its primary end point and why the very few studies using PAH therapies for PH-LHD were associated with, at best, a neutral effect.

As knowledge stands today, the only established treatments for PH-LHD are those that target heart function and are recommended in the current guidelines for HF. Off-label prescription of PAH-approved drugs in this setting has been proven useless or even harmful and must be strongly discouraged.

**KEY POINTS**

- Pulmonary hypertension (PH) often complicates left heart diseases (LHDs) as a result of increased left-heart filling pressures and is a marker of disease severity and a negative prognostic factor.
- The presence of a precapillary component (such as combined post- and precapillary PH) has an additional impact on outcome.
- Although the mechanisms leading to the development of a precapillary component are not yet known, a sustained increase in left atrial pressure and inflammatory and genetic factors may play a role in promoting pulmonary vascular remodeling.
- The management of PH due to LHD must focus on the underlying condition and optimization before assessment of PH is considered. Therapies for heart failure with reduced ejection fraction must be implemented and structural left heart disease corrected according to guidelines.
- Despite several attempts, no specific therapy of PH due to LHD has been identified. This is especially true in PH caused by heart failure with preserved ejection fraction, which may be difficult to distinguish from rare forms of PH. Therefore, drugs approved for pulmonary arterial hypertension are not recommended in PH due to LHD.

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**Conflict of Interest Disclosure:**
Dr. Vachiéry (through his institution) receives honoraria from Acceleron, Bayer, MSD, Novartis, and Actelion-Janssen and holds the Actelion-Janssen research chair for PH at his institution.

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- heart failure
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- hemodynamics

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