Pulmonary hypertension due to left heart disease: Updated Recommendations of the Cologne Consensus Conference 2011[☆]

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ABSTRACT

The 2009 European Guidelines on Diagnosis and Treatment of Pulmonary Hypertension (PH) have been adopted for Germany. While the guidelines contain detailed recommendations regarding pulmonary arterial hypertension (PAH), they contain only a relatively short paragraph on other, much more frequent forms of PH including PH owing to left heart disease. The guidelines point out that the drugs currently used to treat patients with PAH (prostanoids, endothelin receptor antagonists and phosphodiesterase type 5 inhibitors) have not been sufficiently investigated in other forms of PH. However, despite the lack of respective efficacy data an uncritical use of targeted PAH drugs in patients with PH associated with left heart disease is currently observed at an increasing rate. This development is a matter of concern. On the other hand, PH is a frequent problem that is highly relevant for morbidity and mortality in patients with left heart disease. It that sense, the practical implementation of the European Guidelines in Germany requires the consideration of several specific issues and already existing novel data. This requires a detailed commentary to the guidelines, and in some aspects an update already appears necessary. In June 2010, a Consensus Conference organized by the PH working groups of the German Society of Cardiology (DGK), the German Society of Respiratory Medicine (DGP) and the German Society of Pediatric Cardiology (DGPK) was held in Cologne, Germany. This conference aimed to solve practical and controversial issues surrounding the implementation of the European Guidelines in Germany. To this end, a number of working groups was initiated, one of which was specifically dedicated to PH due to left heart disease. This commentary describes in detail the results and recommendations of the working group which were last updated in October 2011.

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Preliminary remarks

This article is part of a supplement of the *International Journal of Cardiology* in which the results of a Consensus Conference on pulmonary hypertension are described that took place in June 2010 in Cologne, Germany, and was organized by the PH working groups of the German Society of Cardiology (Deutsche Gesellschaft für Kardiologie, DGK), the German Society of Respiratory Medicine (Deutsche Gesellschaft für Pneumologie, DGP) and the German Society of Pediatric Cardiology (Deutsche Gesellschaft für pädiatrische Kardiologie, DGPK). This conference addressed practical issues surrounding the implementation of the European Guidelines for diagnosis and treatment of pulmonary hypertension in Germany. To this end, a number of working groups was initiated, one of which was specifically dedicated to the diagnosis and treatment of PH due to left heart disease. The authors were members of this working group. The corresponding articles were initially published in the *Deutsche Medizinische Wochenschrift*, and the information was now updated in October 2011. Below, the corresponding sections of the European Guidelines are summarized [1–3] whereby comments and additions appear in italics. The information on class of recommendation and level of evidence correspond to the tables listed in the preamble of this supplement.

1. Introduction

While the enormous progress that has recently been achieved in the field of pulmonary hypertension (PH) is mostly related to pulmonary arterial hypertension (PAH), virtually no progress has been made for other, much more common forms of PH, particularly those associated with chronic left heart disease or lung disease [1–3]. Even though no corresponding efficacy data is available, targeted PAH drugs are used with increasing frequency in other forms of PH ("Non-PAH PH"). Such a treatment attempt may be clinically justified in carefully selected individual cases, but may not be effective or even harmful in many other cases. This development is a matter of concern, and the uncritical use of targeted PAH treatments for other forms of PH – especially in the context of left heart disease – is strongly discouraged at this time. Nevertheless, PH in patients with left ventricular dysfunction constitutes a common problem which has impact on the morbidity and mortality of patients with congestive heart failure [4–6].

Comment:

Diagnosis and treatment of PH due to left heart disease according to group 2 of the Dana Point classification [7], are discussed rather briefly in the European guidelines. This article addresses these issues in detail and in some sections falls back on the recommendations of the 4th World Symposium on Pulmonary Hypertension that took place in 2008 in Dana Point, California [8] as well as on contemporary literature. The focus is on borderline areas of hemodynamic definition, uncertainties regarding the diagnostic work-up, and on the differentiation between pre- and post-capillary PH. Potential treatment indications in special cases, as well as unresolved issues and the necessity of prospective controlled clinical trials are discussed in greater detail.

2. Hemodynamic definitions

PH is defined by an increase of the invasively measured mean pulmonary arterial pressure (PAP) to ≥25 mmHg at rest with normal or decreased cardiac output [1,2,9]. (**Comment:** *An increase in PAP due to a hyperkinetic cardiovascular state associated with pulmonary-to-systemic shunts, anemia or hyperthyroidism are thus excluded from the definition of PH.*) The hemodynamic definitions for different forms of PH are based on various combinations of values of pulmonary capillary wedge pressure (PCWP), pulmonary vascular

Table 1
Hemodynamic definitions of pulmonary hypertension (HP) [1,2].

Definition	Characteristics	Clinical group(s)
PH	mean PAP ≥25 mmHg	All groups
Pre-capillary PH	mean PAP ≥25 mmHg PCWP ≤15 mmHg CO normal or reduced	Group 1: PAH Group 3: PH associated with chronic lung diseases Group 4: CTEPH Group 5: PH due to unclear and/or multifactorial mechanisms
Post-capillary PH	mean PAP ≥25 mmHg PCWP >15 mmHg CO normal or reduced	Group 2: PH associated with left heart diseases
Passive	TPG ≤12 mmHg	
Reactive ("out of proportion")	TPG >12 mmHg	

PAH, pulmonary arterial hypertension; CO, cardiac output; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; TPG, transpulmonary gradient (mean PAP − PCWP).

resistance (PVR) and cardiac output (CO) (Table 1). In *pre-capillary PH* the PCWP is ≤15 mmHg and the PVR is usually increased to >3 Wood units [1,2,9,10]. In *post-capillary PH* the PCWP is increased to values >15 mmHg. Pre-capillary PH includes the clinical groups 1, 3, 4, and 5, while post-capillary PH is represented by the clinical group 2 (Table 1) [1,2,11].

Comment:

It is indicated in the guidelines that the normal value for the mean PAP at rest is 14 ± 3 mmHg, and therefore the upper limit of normal (defined as mean value + 2 SD) was specified as 20 mmHg [12]. This results in a discrepancy to the hemodynamic definition of PH as outlined in the guidelines (mean PAP ≥25 mmHg), which is essentially based on the fact that all treatment studies for PAH were conducted in patients with a mean PAP >25 mmHg. The "grey zone" between 20 and 25 mmHg (referred to as "borderline PH") has yet to be sufficiently defined. In patients with PH owing to left heart disease, data indicate that mean PAP values below 25 mmHg may already be of prognostic relevance [13]. However, lower cut-off values would lead to an increase in the number of patients who would be incorrectly diagnosed with PH, and the clinical benefit of treating patients with borderline PH has not been documented, especially with regard to left heart diseases. In view of these uncertainties, the current hemodynamic definition of PH seems justified.

The cut-off value of 15 mmHg for the PCWP (also termed pulmonary arterial occlusion pressure; PAOP) which is used for the differentiation between pre- and post-capillary PH is not based on scientific data. According to the principle of communicating vessels, the PCWP generally corresponds to the left atrial pressure (LAP) and the left ventricular end-diastolic pressure (LVEDP). However, according to standard definitions in cardiology, the normal value for the LVEDP is 5–12 mmHg [14]. Thus, the definitions result in a certain grey area in the range between 12 and 15 mmHg (Fig. 1). With regard to the proper classification of PH and potential therapeutic consequences, this uncertainty must be characterized in more detail in the future. Furthermore, one should be aware of the fact that the measurement of PCWP may be highly variable and depend on the volume status of the patient, particularly in patients with (diastolic) heart failure. Some authors have suggested a volume challenge test that may lead to an increase in PCWP/LVEDP in patients with underlying left heart disease and may therefore unmask diastolic heart failure in patients pretreated with diuretics [15]. However, such tests have not yet been standardized.

In addition, the accurate measurement of the PCWP often proves difficult. Clinical studies indicate frequent problems regarding the proper measurement of PCWP and the correct interpretation of the
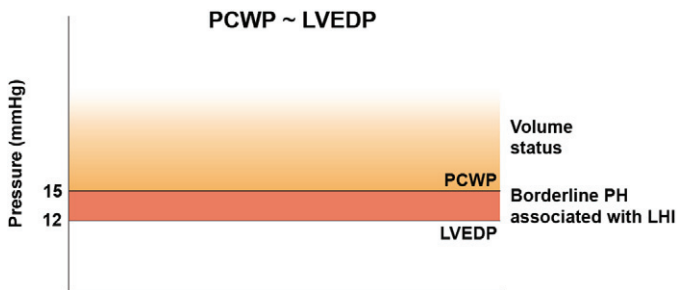
Fig. 1. Borderline zone of the PCWP and LVEDP for the classification of pre- versus post-capillary PH, and dependency of the filling pressure on the volume status (according to S. Rosenkranz)*.
PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; LHD, left heart disease.
*In certain situations (e.g. valvular disease, pronounced LV hypertrophy, myocardial infarction) the PCWP does not correspond to the LVEDP.

pressure curves. Such studies have shown that in 31% of cases PCWP measurements were not performed technically correctly, and that in approximately 50% the registered pressure curves were misinterpreted [16–18]. A retrospective analysis found that in a significant number of measurements, deviations in PCWP of >5 mmHg were observed as compared to direct LVEDP measurement in clinical practice [19]. This may results in an incorrect classification between pre- and post-capillary PH. If the PCWP cannot be measured reliably, the LVEDP must be measured directly. It should be emphasized that measurements obtained by right heart catheterization must always be interpreted in accordance with echocardiographic findings, and in some cases left heart catheterization may be required to clarify possible discrepancies.

3. Epidemiology and prognostic significance of PH in left heart disease

Even if constitutional factors may play a role in the development of PH in patients with left heart disease, no specific genetic linkages have been identified so far [11]. The prevalence of PH in patients with chronic heart failure increases with the extent of clinical severity (NYHA classification). Up to 60% of patients with severe systolic heart failure and up to 70% of patients with isolated left ventricular diastolic dysfunction may present with PH [4]. In patients with chronic heart failure, PH is associated with an adverse outcome [5]. In one study, the mortality rate during a 28-month observation period was 57% in patients with moderate PH as compared to 17% in patients without PH. Furthermore, patients with a PVR >6–8 Wood units (480–640 dyn s cm^{-5}) have an increased risk of post-operative right ventricular failure after heart transplantation [1,2]. (**Comment:** Even though the ESC/ERS guidelines cite 6–8 Wood units at this point, data indicate that a PVR >2.5 Wood units is already of prognostic relevance after heart transplantation.)

Comment:

PH owing to left heart disease is a common phenomenon that appears to be highly relevant for the patients' outcome. However, the development and severity of PH in left heart disease are characterized by a high level of variability. With regard to the pathophysiology of elevated pulmonary artery pressures as well as to therapeutic concepts, a detailed etiological classification of PH owing to left heart disease seems necessary (Table 2). It is of particular interest to provide a detailed differentiation between heart failure with reduced left ventricular ejection fraction (HFrEF; "systolic heart failure"), heart failure with preserved ejection fraction (HFpEF; "diastolic heart failure"), left-sided valvular heart disease, and other causes.
Heart failure with reduced ejection fraction (HFrEF; systolic heart failure) – Overt heart failure with reduced systolic left ventricular function usually develops as a consequence of ischemic (ICM)

Table 2
Classification of PH owing to left heart diseases (modified from [20]).

Heart failure with reduced ejection fraction (HFrEF; EF ≤50%)*
- Ischemic cardiomyopathy (ICM)
- Dilated cardiomyopathy (DCM)

Heart failure with preserved ejection fraction (HFpEF; EF >50%)*
- Hypertensive heart disease
- Coronary heart disease (CHD)
- Diabetic cardiomyopathy
- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy
- Constrictive pericarditis

Valvular diseases
- Aortic valve stenosis
- Aortic valve insufficiency
- Mitral valve stenosis
- Mitral valve insufficiency
- Persistent/residual PH after corrected valvular defect

Other causes
- Atrial fibrillation
- Other arrhythmias
- Triatrial heart
- Myxoma or left atrial thrombus

*Instead of differentiating between systolic and diastolic heart failure, the differentiation between heart failure with reduced versus preserved LV function (ejection fraction) is made in accordance with current recommendations and guidelines; in most cases, heart failure with reduced LV function is associated with signs of left ventricular diastolic dysfunction.

or dilated (DCM) cardiomyopathy. The prevalence of ICM is approximately 3,000–4,500 cases per million, while DCM occurs at a prevalence of approximately 360 cases per million. Observational studies have shown that 60–70% of patients with systolic heart failure develop PH [4,5]. In contrast to PAH which is an orphan disease, PH associated with left heart failure thus represents a common disease. In patients with chronic heart failure, there is an inverse correlation between the extent of the increase in both PCWP and PAP and survival [5,6,13]. As is the case in PAH, chronic elevation of PAP and/or PVR results in permanent right ventriclular strain, which ultimately leads to progressive right heart failure and premature death. A number of studies have shown that in patients with left heart failure, the presence and extent of PH, the degree of right ventricular dysfunction, and especially the combination of RV dysfunction and PH is associated with a particularly poor prognosis [4,5,13,21,22]. In fact, survival of patients with chronic left heart failure is frequently limited by progressive right ventricular dysfunction.
Heart failure with preserved ejection fraction (HFpEF; diastolic heart failure) – No reliable data is available on the frequency of left ventricular diastolic dysfunction, and the information depends on the definition chosen, the population studied, and the applied diagnostic tool. However, recent studies have consistently shown that – according to echocardiographic criteria – the prevalence of diastolic heart failure is up to 25% of the (elderly) population [23,24]. Comparative studies revealed that the prevalence of heart failure with preserved LV function is greater than that of heart failure with reduced LV function, while the prognostic impact is comparable. The reported 5-year survival rate was 43% in patients with heart failure and preserved LV function as compared to 46% in patients with reduced LV function, indicating that the ejection fraction has no significant influence on survival in patients with clinical signs of heart failure [25]. The most common causes for diastolic dysfunction of the left ventricle are hypertensive heart disease and CHD. A recent population study revealed that PH (defined as PASP >35 mmHg as assessed by echocardiography) was detected in 83% of patients with diastolic heart failure [26]. Furthermore, PH was severe in many cases as indicated by a median PASP of 48 mmHg. Although the increase in PAP primarily resulted from elevated left-sided filling pressures, it could frequently not be fully explained by pulmonary venous congestion, so that a pre-capillary component

contributed to the extent of PH in many patients. In this study, the correlation between the presence and severity of PH and survival was highly significant (HR 1.3 per 10 mmHg PASP).

Left-sided valvular diseases – In left-sided valvular disease, the prevalence of PH correlates with the severity of the valve disease and clinical symptoms. PH is present in almost all patients with severe, symptomatic mitral valve disease and in up to 65% of patients with symptomatic aortic valve stenosis [9,11,27,28]. Even though PH constitutes a risk factor for valvular surgery, the surgical correction of significant mitral valve disease generally results in a considerable reduction of PH within weeks or months [28,29]. It should be pointed out, however, that in some cases PH may persist even after successful valve surgery.

4. Pathobiology

The mechanisms that are responsible for the increase in pulmonary artery pressure in patients with left heart disease are multiple and include the passive backward transmission of the left-sided pressure elevation [1,2]. Any increase of the LVEDP or PCWP will raise the level of pulmonary vascular pressure in order to maintain a sufficient pressure gradient that enables the filling of the left ventricle against the elevated LVEDP (protective pulmonary vasoconstriction). If the pulmonary pressure elevation is merely a result of passive backward transmission into the pulmonary circulation, the transpulmonary gradient (TPG), calculated as the difference between mean PAP and PCWP, remains normal at ≤12 mmHg (post-capillary passive PH, see Table 1). In other circumstances, pulmonary venous congestion may be associated with reactive changes of the pulmonary vessels so that the elevation of PAP is greater than that of PCWP (Fig. 2). This leads to an increase of the TPG to values >12 mmHg and also to an increase in PVR (post-capillary reactive PH, see Table 1). The ESC/ERS guidelines therefore differentiate between passive and reactive post-capillary PH [1,2].

In reactive post-capillary PH, the elevation of PVR is due to an increase in the vasomotor tone of the pulmonary arteries and/or to fixed, structural, obstructive remodeling of the pulmonary arterial resistance vessels [30,31] (Fig. 3). The morphological and pathological changes of the pulmonary vessels in this type of PH are characterized by enlarged and thickened pulmonary veins, dilation of the pulmonary capillaries, interstitial edema, alveolar hemorrhage, and enlarged lymphatic vessels and lymph nodes. The distal pulmonary arteries may be affected by medial hypertrophy and intimal fibrosis [1,2]. The functional component of reactive PH is reversible under acute pharmacological testing with pulmonary vasodilators, while the structural obstructive changes, characterized mainly by medial hypertrophy and intimal proliferation of the pulmonary arterioles, do not respond to acute vasodilators [11]. Which factors lead to reactive ("out of proportion") PH and why some patients develop the acutely reversible or the fixed obstructive

components or both remains largely unknown. Pathophysiological mechanisms may include vasoconstrictive reflexes arising from so-called stretch receptors which are localized in the left atrium and the pulmonary veins. Furthermore, endothelial dysfunction of pulmonary arteries which favors pulmonary vasoconstriction and proliferation of vessel wall cells is of importance [1,2].

5. Diagnosis

The diagnostic approach to PH due to left heart disease basically corresponds to that of PAH. Doppler echocardiography remains the best non-invasive tool in the diagnostic work-up of left-sided myocardial damage or valvular disease, and plays a key role in the initial diagnosis of PH. The reliable differentiation between PH owing to left heart disease and PAH, the measurement of pulmonary hemodynamics prior to valvular surgery, and the preoperative hemodynamic evaluation prior to heart transplantation require right heart catheterization [1,2]. The characteristics of individual diagnostic procedures that are useful in the diagnostic work-up of PH due to left heart disease are described below.

5.1. Echocardiography

Echocardiography plays a key role in the initial diagnosis of PH as well as the detection of possible cardiac causes of PH. In addition to the assessment of chamber sizes and contractile function, it enables the estimation of left-sided filling pressures and the pulmonary artery systolic pressure (PASP). Estimation of the PASP is based on the Doppler-assisted measurement of the tricuspid regurgitation peak velocity (V_{max}). The simplified Bernoulli equation ($\Delta P = 4 \times V_{max^2}$) uses the peak velocity to determine the systolic pressure gradient between the right ventricle and right atrium, and the PASP is then estimated by adding the right atrial pressure (see section on "non-invasive diagnosis" in this Supplement). However, this method only serves to estimate the PASP and cannot be used to secure the diagnosis of PH. In a current study, the invasively measured PASP values deviated from the values determined with echocardiography by more than 10 mmHg in 50% of cases [32]. Sources of error include an overestimation of right atrial pressure and the reliance on inadequate Doppler signals. With regard to the significance of echocardiography in the diagnosis of PH due to left heart disease and the differentiation between pre- and post-capillary PH, several particularities are of importance: In overt heart failure with reduced systolic LV function, it is usually not difficult to establish a diagnosis. However, in case of predominant or pure diastolic dysfunction of the left ventricle, the differentiation between PAH and PH due to diastolic heart failure is often difficult, and in many cases a reliable differentiation is not possible. Left ventricular diastolic dysfunction may be suspected in case of a dilated left atrium, atrial fibrillation, characteristic changes in mitral and pulmonary venous flow profile, typical mitral annulus tissue
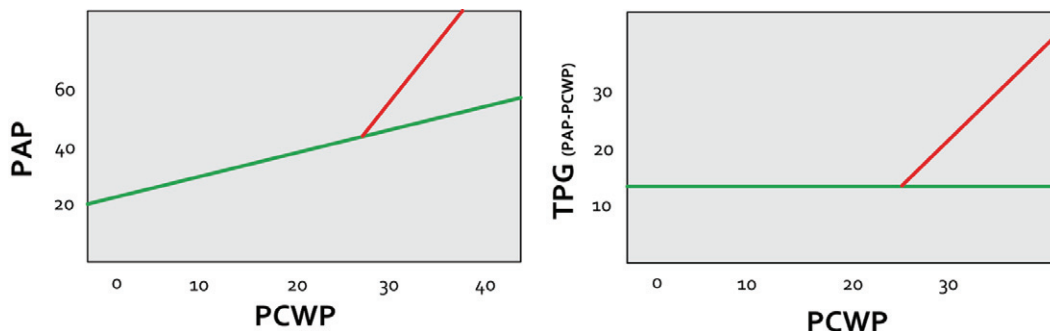

Fig. 2. Passive (green) versus reactive (red) elevation of pulmonary arterial pressure in patients with left heart disease (according to C. Opitz). PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; TPG, transpulmonary gradient.
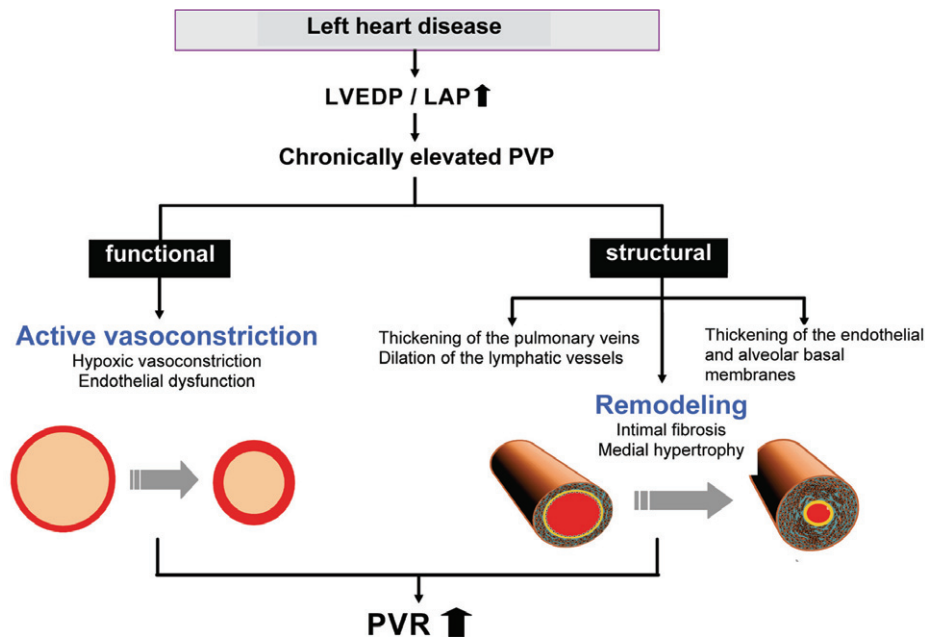
Fig. 3. Pathophysiology of elevated pulmonary arterial pressure in heart failure: Functional (reversible) versus structural (irreversible) changes of the pulmonary circulation ("congestive arteriopathy"). LVEDP, left ventricular end-diastolic pressure; LAP, left atrial pressure; PVP, pulmonary venous pressure; PVR, pulmonary vascular resistance.

Doppler signals, and left ventricular hypertrophy [33,34]. Data on tissue Doppler assessment show that the ratio (E/E') of early mitral valve flow velocity (E) and the early diastolic lengthening velocities (E') correlates closely with left ventricular filling pressures independent from left ventricular systolic function: If the E/E' ratio exceeds 15, the left ventricular filling pressure is elevated. If the ratio is lower than 8, the left ventricular filling pressure is low. If 15 > E/E' > 8, additional non-invasive or invasive investigations are required [33]. Characteristic clinical and echocardiographic features of PH associated with diastolic dysfunction are summarized in Table 3 [8].

Comment:

Despite its limitations, echocardiography is the most important initial diagnostic tool in patients with left heart disease, especially when PH is suspected. Vice versa, in patients with PH it is of major importance to detect diseases of the left heart as a potential underlying cause of PH. However, in both cases echocardiography features certain limitations. The limited diagnostic accuracy of echocardiographic PASP measurements was already pointed out above. Even though tissue Doppler measurements increasingly contribute to a differentiated analysis of left ventricular diastolic dysfunction, this is often associated with considerable uncertainties in clinical practice. In addition, important parameters such as the TPG cannot reliably be measured with echocardiography. In clinical practice, a better standardization of the echocardiographic assessment of the right heart is highly warranted. To this end, current recommendations of the American Society of Echocardiography and the European Association of Echocardiography on the echocardiographic assessment of the right heart may be helpful [35]. It is of great importance that the examiner is aware of the limitations of this procedure and interprets the findings with the necessary prudence. As in other types of PH, the diagnosis should, in principle, not be established on echocardiography alone, especially if therapeutic consequences are being considered.

5.2. Right heart catheterization

PH is defined as an increase of the invasively measured mean PAP to $\geq$25 mmHg at rest [1,2,11]. The reliable determination of the filling pressures in the left heart is decisive for the classification of pre- versus post-capillary PH. Although increased left-sided filling pressures can be estimated by Doppler echocardiography [33,36], invasive measurements of PCWP (or LVEDP) by right heart catheterization is generally necessary to confirm the diagnosis of PH due to left heart disease and to distinguish PH from PAH (see also the section on "invasive diagnosis" in this Supplement) [33]. An increased PCWP or LVEDP (>15 mmHg) confirms the presence of left ventricular dysfunction, which is however not ruled out by a normal PCWP. PCWP and LVEDP can be (pseudo)normal at the time of testing, especially when patients have been treated with diuretics. In unclear situations, a volume challenge (e.g., 500–1,000 ml NaCl 0.9% over 5–10 min) or exercise hemodynamics have been proposed to identify or exclude LV dysfunction [11,15]. However, such diagnostic tests require further standardization. An elevated transpulmonary gradient (mean PAP minus PCWP) >12 mmHg is suggestive of intrinsic changes in the pulmonary circulation, over-riding the passive increase in PAP caused by the elevated PCWP [1,2]. In some patients, it may be difficult to distinguish PAH from PH associated with left ventricular dysfunction. This especially

Table 3
Factors indicating left ventricular diastolic dysfunction in PH as assessed by Doppler echocardiography (according to [8]).

Clinical features
- Age >65 years
- Arterial hypertension
- Obesity, metabolic syndrome
- Coronary heart disease (CHD)
- Diabetes mellitus
- Atrial fibrillation

Echocardiography
- Left atrial (LA) enlargement
- Concentric remodeling of the left ventricle (LV) (relative wall thickness >0.45)
- Left ventricular hypertrophy
- Echocardiographic indicators of elevated left ventricular filling pressure [33,34]

Follow-up evaluation (after echocardiography)
- Symptomatic improvement to diuretics
- Exaggerated increase in systolic blood pressure with exercise
- Chest radiograph: signs of congestive heart failure [34]

applies to patients with borderline increased PCWP values (15–18 mmHg) [1,2].

Comment:

The ESC/ERS guidelines do not provide a clear recommendation regarding the indication for right heart catheterization in patients with left heart disease and suspected PH. This seems, however, an important and clinically relevant issue. The guidelines do not recommend that all patients with left heart disease and signs of PH should undergo right heart catheterization. Instead, the indication must be determined critically in each case. Invasive measurement of pulmonary hemodynamics is only deemed necessary if therapeutic consequences are expected, or if important prognostic information is required for continued patient management (e.g. in valvular disease or for transplant listing). Since the European guidelines generally do not recommend targeted PH treatment in patients with underlying left heart disease, right heart catheterization will only be necessary in exceptional cases at present (see below). However, invasive measurements are indicated if a reliable differentiation between PAH and PH associated with left heart disease is aspired, since this has direct therapeutic consequences. In such cases, combined right and left heart catheterization may be necessary. To differentiate between PAH and PH due to diastolic heart failure, the algorithm developed at the 4th World Symposium on PH in Dana Point may be helpful (Fig. 4).

If right heart catheterization is performed, all parameters that are important to fully characterize pulmonary hemodynamics have to be measured: pulmonary capillary wedge pressure (PCWP; alternatively LVEDP), pulmonary arterial pressure (PAP), right ventricular pressure (RVP), right atrial pressure (RAP), cardiac output (CO; determined by the thermodilution method or by the Fick's principle), and mixed venous oxygen saturation. Detailed oxymetry may be indicated to detect a possible shunt defect. In addition, the transpulmonary gradient (TPG) and pulmonary vascular resistance (PVR) must be calculated, especially if PH is associated with left heart disease. Institutions that are not able to fully determine the above mentioned parameters for technical reasons, should not perform right heart catheterization and, if necessary, refer patients to specialized centers.

Due to the fact that the measurement of pulmonary hemodynamics under stress conditions (exercise hemodynamics, volume challenge) is not sufficiently standardized, their significance in the diagnosis of PH associated with left heart diseases must be viewed critically. The same applies to pulmonary vasoreactivity testing in patients with post-capillary PH and increased TPG (reactive form), which is currently only relevant for scientific reasons. It should be the task of expert centers to standardize such tests in the near future, and to evaluate potential therapeutic consequences based on the test results.

5.3. Biomarkers

The measurement of brain natriuretic peptide (BNP) or N-terminal Pro-BNP (NT-proBNP) plasma levels may be helpful for the initial diagnosis of PAH, for the diagnosis of heart failure, and for follow-up investigations. Measurement of BNP or NT-proBNP levels for the diagnosis of left heart disease in the presence of PH and for the differentiation to PAH is mostly not useful, since both conditions are associated with elevated BNP or NT-proBNP levels [33]. On the other hand, normal BNP or NT-proBNP values largely – but not fully – rule out PH [37].

5.4. Pharmacological testing of pulmonary vasoreactivity before heart transplantation

In heart transplant candidates, a persistent increase in PVR to >2.5 Wood units and/or TPG to >15 mmHg are associated with an up to 3-fold increase in the risk for post-operative right ventricular failure and early post-operative mortality [38]. When the PVR can be lowered pharmacologically (e.g. with intravenous nitroprusside), this risk may be reduced [39]. (**Comment:** To identify transplant candidates with an increased risk for acute post-operative right ventricular failure, pharmacological testing with a pulmonary vasodilator is recommended in such patients if the PASP is >50 mmHg, the TPG is increased to >15 mmHg, or the PVR to >3.0 WU [40,41]. This type of test may, however, also lead to acute pulmonary edema due to the elimination of protective pulmonary vasoconstriction. At present, it should therefore be limited to transplant candidates and carried out at experienced centers.) The absence of consensus on a standardized protocol leads to the use of various agents for testing pulmonary vasoreactivity. These include inotropic agents, vasodilators, prostanoids, NO, and phosphodiesterase type-5 inhibitors. Acute post-operative right ventricular failure may also be observed in patients with normal pre-operative pulmonary hemodynamics, suggesting that other mechanisms may also be involved.

6. Treatment of PH associated with left heart failure

Currently, there is no specific therapy for the treatment of PH due to left heart disease. A number of drugs (including diuretics, nitrates, hydralazine, ACE inhibitors, AT_1 receptor antagonists, β-adrenoceptor blockers, inotropic agents) or interventions (LV assist device, valvular surgery, resynchronization therapy, heart transplantation) for heart failure may lower PAP to a certain extent through a drop in left-sided filling pressures [11]. Therefore, management of PH due to left heart disease should be aimed at the optimal treatment of the underlying left heart disease [1,2]. None of the agents recommended in left heart failure are contraindicated in concomitant PH [34]. Despite the treatment of left heart failure according to guidelines, PH often persists, so that additional treatment options may need to be pursued.

Few studies have examined the efficacy and safety of agents that are currently recommended in PAH in patients with left heart failure. Controlled studies evaluating the effects of chronic use of epoprostenol [42] and bosentan [43,44] in advanced heart failure showed no benefit. In case of intravenous epoprostenol, the study was even terminated early, because a higher mortality was documented in the investigational treatment group compared with conventional therapy. A small sized study recently suggested that

Table 4
Recommendations for PH due to left heart disease [1,2].

Recommendation	Class of recommendation	Level of evidence
The optimal treatment of the underlying left heart disease is recommended in patients with PH due to left heart disease	I	C
Patients with out of proportion PH due to left heart disease (Table 3) should be enrolled in randomized clinical trials targeting PH-specific drugs	IIa	C
Increased left-sided filling pressures may be estimated by Doppler echocardiography	IIb	C
Invasive measurement of PCWP or LVEDP may be required to confirm the diagnosis of PH due to left heart disease	IIb	C
Right heart catheterization may be considered if there are echocardiographic signs suggesting severe PH in left heart disease	IIb	C
The use of PAH-specific drug therapy is not recommended in patients with PH due to left heart disease	III	C

PH, pulmonary hypertension; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; PAH, pulmonary arterial hypertension.
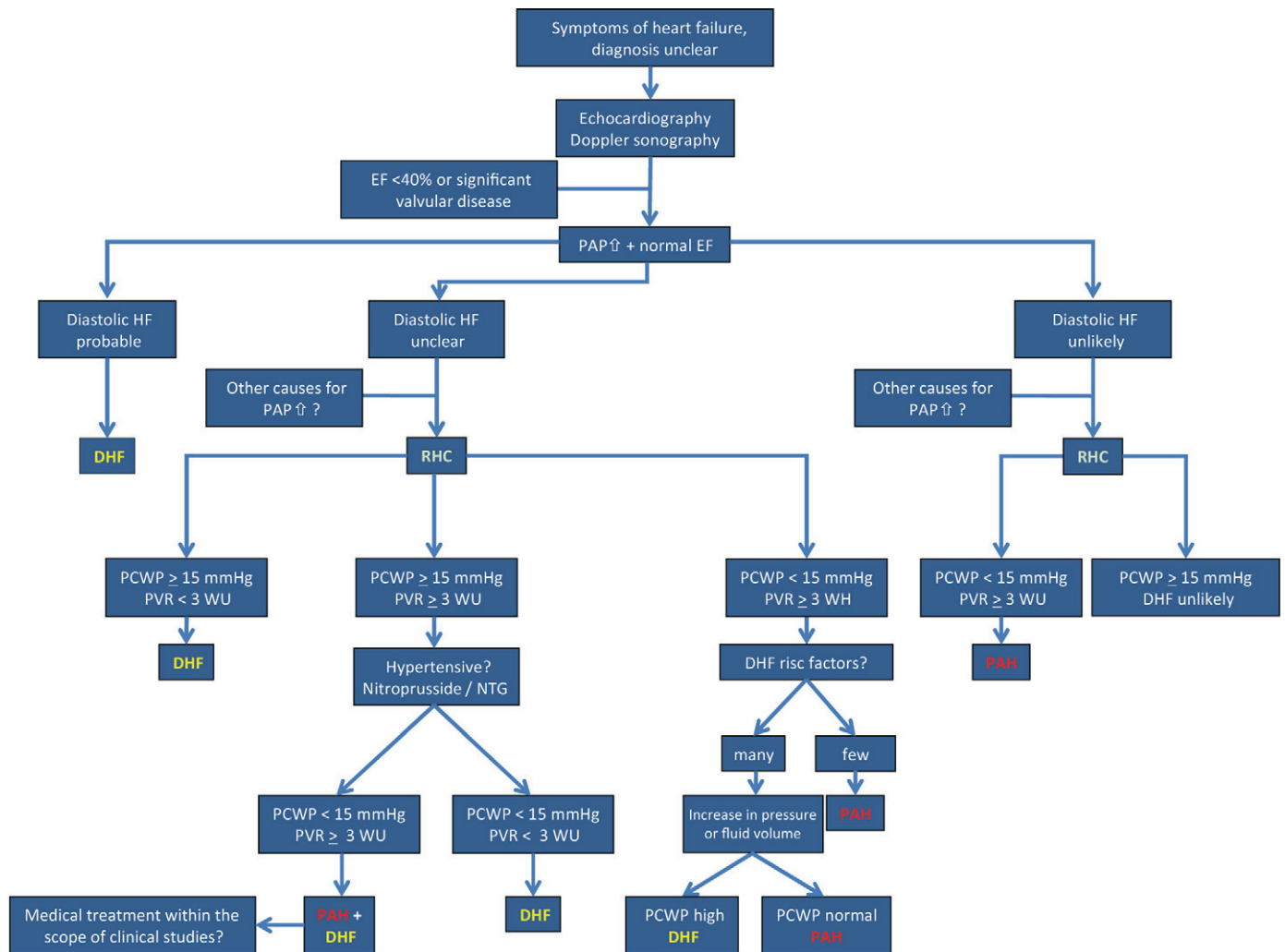
Fig. 4. Diagnostic algorithm for the differentiation between PAH and PH in diastolic heart failure (according to [8]). DHF, diastolic heart failure; EF, ejection fraction; HF, heart failure; NTG, nitroglycerin; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; WU, Wood units.

sildenafil may lead to an improvement in exercise capacity and quality of life in patients with PH due to left heart disease [45]. The history of medical therapy for heart failures is, however, full of examples where positive effects of drugs were documented on surrogate endpoints but eventually turned out to be detrimental and have a negative effect on hard endpoints such as mortality (e.g. phosphodiesterase type-3 inhibitors). Thus, the use of PAH-specific drugs (including PDE type-5 inhibitors) is not recommended for other forms of PH including PH associated with left heart disease until robust data from controlled long-term studies are available. It is also unclear if patients with normal or increased TPG would benefit from an additional treatment (Table 1). A sustained reduction of PH can be achieved in weeks to months in most patients successfully operated for mitral valve disease (valve replacement, reconstruction), even if PH represents a risk factor for surgery [28,29]. The ESC/ERS guidelines recommendations for PH due to left heart disease are summarized in Table 4.

Comment:

So far, there are no reliable data on the efficacy and safety of targeted drug therapy for PH owing to left heart disease which would justify the general use of PAH-specific drugs. This applies to systolic heart failure as well as to isolated left ventricular diastolic dysfunction. No data from clinical trials are available yet on diastolic heart failure. The data that are available on various classes of targeted PAH therapies

for the treatment of systolic heart failure may be summarized as follows:

Prostanoids: Even though a survival benefit was demonstrated for the prostacyclin analogue epoprostenol in patients with severe PAH [46], a therapeutic benefit was not documented in patients with congestive heart failure and post-capillary PH. The FIRST trial investigated whether the additional intravenous administration of epoprostenol would lead to an improvement of clinical symptoms and prognosis in 471 patients with severe chronic heart failure and reduced systolic LV function. Despite significant hemodynamic improvements with epoprostenol, the study was prematurely terminated due to an increased mortality in the treatment group [42]. However, in patients awaiting heart transplantation and in situations immediately after cardiosurgical interventions, the inhaled administration of the stable prostacyclin analogue iloprost demonstrated a short-term reduction of PVR without evidence of negative effects on pulmonary edema or volume overload [47,48]. Nevertheless, there are no data from controlled studies on inhaled prostanoids for patients with heart failure and PH.

Endothelin receptor antagonists (ERAs): In treatment studies with various dual (tezosentan, bosentan) endothelin receptor antagonists (ERAs) or selective endothelin type A (ET_A) receptor antagonist (darusentan), these agents did not prove clinically effective in patients with heart failure, irrespective of the presence of PH. In acute decompensated heart failure, the intravenous administration of tezosentan

led to an improvement of hemodynamic parameters but failed to improve clinical symptoms and prognosis [49]. One study with bosentan (2 × 250 mg/day orally) in patients with chronic heart failure (REACH-I) was terminated early because of elevated liver enzymes in the treatment group. At the time the study was terminated, there was no difference between the bosentan and placebo group with regard to clinical severity [43]. In the ENABLE I/II studies, bosentan was administered at a lower dose (2 × 125 mg/day orally) in patients with congestive heart failure (NYHA class III or IV). After a 9-month observational phase, bosentan treatment was also not associated with improvements of clinical severity or mortality [44,50]. While in patients with heart failure, an increase in cardiac index was documented with the ET$_A$R-selective ERA darusentan in the HEAT study [51], the EARTH study showed that a 6-month treatment with darusentan (10–300 mg/day) did not have an effect on left ventricular remodeling, clinical symptoms, and mortality [52].

Phosphodiesterase type-5 inhibitors: A number of clinical pilot studies indicated the potential efficacy of PDE type-5 inhibitors, especially sildenafil, in patients with systolic heart failure and PH [45,53–58]. Sildenafil at a dose of 50 mg acutely improved pulmonary hemodynamics (decrease of PVR and mean PAP, increase of cardiac output) [45], and chronic treatment with sildenafil (25–75 mg tid) over 3 to 6 months led to a significant improvement of various parameters such as exercise capacity, respiratory efficiency, oxygen uptake, endothelial function, quality of life, and hemodynamic parameters including a decrease in PVR [45,55,57]. The hemodynamic profile observed in these studies indicates relative pulmonary selectivity of sildenafil, since left ventricular filling pressure, systemic blood pressure, and heart rate remained largely unaffected. Even though these observations are quite promising, they can presently at best be viewed as preliminary hints for the potential efficacy of PDE type-5 inhibitors in heart failure and concomitant PH, which have to be confirmed in larger, randomized controlled trials.

In view of these data, the working group agrees with the recommendations of the European guidelines not to recommend treatment with targeted PAH drugs in patients with left heart failure and PH. This applies regardless of the type of left heart failure (systolic/diastolic). Instead, the main goal is to establish and maintain a guideline-oriented treatment of the underlying heart failure [34].

When interpreting the above study results it should be pointed out, however, that the patient selection in most of the above-mentioned studies was probably not adequate when the current state of knowledge is considered. For example, the clinical studies with ERA in patients with heart failure were conducted regardless of concomitant PH. The studies with sildenafil may have been conducted in patients with heart failure and PH but in most cases, PAP was only slightly elevated. Invasive measurements revealed that the mean PAP in the study by Lewis and co-workers was only 30 ± 2 mmHg [45], and in the patients assessed by Guazzi and co-workers, the PASP estimated with echocardiography was only 33.7 ± 3.1 mmHg [57]. Furthermore, the filling pressures of the left ventricle – measured either directly or as PCWP – were not documented at all [57] or were not considered sufficiently for the interpretation of the collected data [45,55]. The European PH guidelines now distinguish for the first time between a purely passive pressure increase in the pulmonary circulation due to elevated filling pressures of the left heart with consecutively elevated PCP and PAP, but normal TPG (purely pulmonary venous or post-capillary PH), and an additional, reactive pressure increase due to functional (vasoconstriction) or structural (remodeling) changes in the pulmonary vascular bed (reactive, "out of proportion" PH with pre-capillary component) (see Table 1 and Fig. 2). This aspect, which may be of major importance, has not been taken into consideration in the previous studies on the evaluation of PAH drugs in heart failure. It may, however, have therapeutic implications since it is conceivable that the existing pre-capillary component in patients with increased TPG can be affected by targeted therapies. Given the fact that

pulmonary hemodynamics and right ventricular function are of major prognostic relevance in patients with left heart failure [4,5,13,21,22,26], such effects may be of importance for improvement of both clinical symptoms and survival. Indeed, at least some examples that indicate therapeutic efficacy in such cases already exist. Furthermore, a recent study demonstrated that optimization of heart failure treatment by additional monitoring of PAP substantially reduced the rate of heart failure-related hospitalizations in patients with CHF [59]. Hence, patients with left heart failure who have severe PH while already receiving optimized treatment for heart failure (over a sufficient period of time using the respective target doses) may have to be viewed separately, especially when the TPG is significantly increased. In some of such cases, it may be challenging or even impossible to determine if a patient is suffering from left heart failure with resulting PH or from PAH with concomitant but not causative left heart failure. It is quite possible that in individual cases – although moderate left heart disease may be present – PAH is the predominant disease which dominates the clinical symptoms and thus may represent an indication for targeted PAH therapy. In addition, a chronic increase of pulmonary venous pressure in systolic or diastolic heart failure could constitute a trigger mechanism for the development of pre-capillary PH. Since patients with a PCWP >15 mmHg have so far been excluded from studies for PAH treatment, there is currently no evidence on the clinical benefit of these agents in such patient groups. A major task of clinical research is the re-evaluation of the efficacy and safety of targeted PAH drugs (ERA, PDE type-5 inhibitors, prostanoids) in selected patients with heart failure, PH, and increased TPG or PVR, and also to investigate the efficacy and safety of other agents (e.g. sGC stimulators, nitrates). Randomized controlled trials with various compounds that have different mechanisms of action are currently under way (e.g. LEPHT, CAESAR). Importantly, the European guidelines on PH strongly recommend that patients with heart failure and out of proportion PH should be included in such trials (see Table 4). However, some studies are currently not recruiting, and a number of patients will not meet the inclusion and exclusion criteria so that enrollment in a study is not always an option. If a patient meets the above-mentioned criteria of a pronounced, reactive PH, and is not eligible for a clinical trial, the decision regarding targeted PH therapy lies within the discretion of the treating physician. At this time, such compassionate treatments should however exclusively be initiated at expert centers.

Until today, there is no evidence-based therapy on the reduction of morbidity and mortality in diastolic heart failure. Current data suggest that PH may be a pathophysiological correlate of symptomatic diastolic heart failure (as compared to pure myocardial hypertrophy in hypertensive heart disease), and that the presence and extent of PH has important impact on survival [26]. Accordingly, control of pulmonary hemodynamics in patients with symptomatic diastolic heart failure and documented PH appears as a promising therapeutic approach so that the investigation of the efficacy and safety of PAH-drugs seems plausible in diastolic heart failure. In this regard, a recent placebo-controlled study demonstrated in a limited number of patients with HFpEF and PH that the PDE5 inhibitor sildenafil (50 mg tid) improved pulmonary hemodynamics and right ventricular function, and also led to a decrease in the PCWP and improved LV function [60]. Furthermore, the results of the RELAX study (phosphodiesterase-5 inhibition to improve clinical status and exercise capacity in diastolic heart failure) which investigates the efficacy of sildenafil in a larger population of patients with diastolic heart failure [61], may be expected with interest.

In addition to the lack of evidence on the efficacy of PAH drugs, potential detrimental effects of pulmonary vasodilators must be taken into consideration in patients with left heart failure and PH. For instance, a decrease in PVR commonly results in an improvement of right ventricular function which potentially may lead to a further elevation of left atrial pressure in patients with heart failure [62]. Furthermore,

evidence indicates that PDE type-5 inhibitors such as sildenafil exert direct positive inotropic effects in the hypertrophied right heart [63]. Treatment studies in patients with chronic heart failure have shown that such an effect was associated with arrhythmogenic effects and increased mortality [64]. At this point, it is again emphasized that the initial improvement of hemodynamics and clinical symptoms with intravenous epoprostenol in the FIRST study was accompanied by excess mortality in the treatment group [42].

These considerations underline once more the need for sufficiently large randomized trials with a sufficient observational period to investigate the efficacy and safety of PAH-drugs in selected patients with heart failure and PH, and to confirm or refute a positive effect on hard end-points (mortality). The uncritical use of such agents in patients with left heart failure is strongly discouraged at this time.

Specific recommendations of the working group on the treatment of PH due to left heart disease

- *The treatment of patients with PH owing to left heart disease consists of evidence-based, guideline-oriented therapy of the underlying left heart disease. In general, targeted treatment of PH with "PAH drugs" is not recommended.*
- *In the majority of cases, the pathology and pathophysiology of PH owing to left heart disease is clearly different from PAH. By lowering left ventricular filling pressure, a significant reduction of the mean PAP and PVR can be achieved in many cases.*
- *It is conceivable that in individual cases, left heart disease could "trigger" the development of PAH (in analogy to other diseases such as collagen vascular disease, HIV infection, or portal hypertension). In patients with slight to moderate left heart disease but substantially elevated PAP, PH can dominate the clinical symptoms. In some cases, it may be challenging or even impossible to distinguish the clinical symptoms from PAH.*
- *The evaluation of therapeutic approaches which specifically target the pulmonary circulation, as well as the identification of patients who may benefit from such therapies, is the objective of currently ongoing and future clinical trials.*
- *In rare and justified exceptions in which a considerable precapillary component is the key aspect of the disease and the clinical symptoms, PAH therapy may be considered after the patient has been informed in detail. This, however, requires a comprehensive diagnostic work-up including right and left heart catheterization; in such exceptional cases, treatment decisions should exclusively be made at expert centers (definition according to the European guidelines [1,2]). Patients should meet the following criteria:*
  - *(i) PH confirmed by invasive assessment, with PAP substantially exceeding the values normally seen in left heart diseases (markedly increased TPG or PVR);*
  - *(ii) no remediable cause of (diastolic) heart failure (CHD, valvular disease);*
  - *(iii) evidence-based, guideline-oriented treatment of chronic heart failure for a sufficient period of time (usually >6 months), using the respective target dosages;*
  - *(iv) exclusion of other causes of PH, including severe lung disease and CTEPH.*
- *If patients may be eligible for targeted PH treatment, the primary objective is the enrollment of patients into clinical trials. Large expert centers and patient associations (in Germany: pulmonale hypertonie e.V.; phev) will provide information on this.*
- *Even if patients meet the above criteria and thus suffer from PH with a relevant pre-capillary component, they have so far not been enrolled into clinical trials on PAH therapy because of the elevated left ventricular filling pressure (PCWP >15 mmHg). Accordingly, the safety and efficacy of "PAH drugs" is not sufficiently characterized in such cases, so that treatment attempts should exclusively be made at expert centers. Close monitoring especially in the initial phase is warranted, and invasive follow-up examinations may be plausible.*

- *Unlike in PAH, it is not yet known if the specific PAH drugs have a positive effect on disease progression in patients with PH owing to left heart disease. Hence, in the above mentioned exceptional cases, a treatment attempt should initially be made over a limited period of 3–6 months in order to decide then, after careful re-evaluation, whether an objective clinical improvement was achieved that would justify the continuation of therapy. Otherwise, the treatment should be discontinued. This approach and individual treatment goals should be discussed with the patient and documented before such treatment is initiated.*
- *The uncritical use of targeted PAH drugs outside of the above-mentioned exceptional cases is strongly discouraged.*

Closing remarks

This consensus document aims to discuss specific aspects of PH owing to left heart disease in greater detail than could be provided in the European guidelines. The recommendations of the Cologne Consensus Conference question a few hemodynamic definitions and deviate from the European guidelines with regard to treatment recommendations in selected exceptional cases. Regarding the pathology and pathophysiology of PH and possible therapeutic consequences, a detailed classification of PH in left heart diseases seems plausible and is thus provided here.

The members of this working group observe with great concern that targeted PAH therapies are increasingly used in patients for whom these drugs are not indicated, and in whom the efficacy and safety has not been carefully assessed. This uncritical use was particularly observed in patients with heart failure and PH. In many of these cases, the treating physicians do not seem to be aware of the difference between PAH and other forms of PH. In individual cases, patients who do not have PAH are therefore treated with drugs that are not indicated, while other patients who are actually suffering from PAH are denied comprehensive treatment at specialized centers. In addition, the unjustified use of targeted PAH drugs results is an economic burden to health care systems.

The uncritical use of PAH drugs is strongly discouraged since no sufficient efficacy and safety data is available for patients with heart failure. However, the validity of the available data, especially from negative studies, is critically assessed because of the patients enrolled. Since the presence and extent of PH in patients with heart failure appears to be of major relevance for survival, and since there is limited clinical evidence indicating that individual patients may benefit from PAH therapies, specialized expert centers, industry, and authorities should be encouraged to jointly carry out the corresponding clinical studies. The authors emphasize that on no account the above recommendations on possible treatment indications in exceptional cases with severe PH must lead to an increased and undifferentiated use of PAH drugs in patients with PH associated with left heart disease.

Conflicts of interest

S. Rosenkranz: Remunerations for lectures and/or consultancy for Actelion, BayerSchering, GSK, Lilly, Novartis, Pfizer and United Therapeutics.

D. Bonderman: Remunerations for consultancy for Bayer-Schering.

M. Buerke: Remunerations for lectures and/or consultancy for Actelion, BayerSchering, GSK, Lilly, Novartis, and Pfizer.

R. Felgendreher: Honorarium from Actelion.

H. ten Freyhaus: none.

E. Grünig: Remunerations for lectures and/or consultancy for Actelion, BayerSchering, GSK, Lilly, and Pfizer.

F. de Haan: none.

C. Hammerstingl: Honorarium from Actelion and GSK.

A. Harreuter: none.

W. Hohenforst-Schmidt: Remunerations for lectures for Actelion, BayerSchering, GSK, Pfizer, Novartis, and United Therapeutics.

I. Kindermann: Honorarium from Actelion.

M. Kindermann: none.

F.-X. Kleber: Remunerations for lectures and/or consultancy for Actelion, BayerSchering, GSK, Lilly, Pfizer, and United Therapeutics.

M. Kuckeland: none.

W.M. Kübler: Financing of pre-clinical studies by Pfizer and BayerSchering.

D. Mertens: Remunerations for lectures and/or consultancy for Actelion, BayerSchering, GSK, Lilly, and Pfizer.

V. Mitrovic: Remunerations for lectures and/or consultation of BayerSchering.

C. Opitz: Remunerations for lectures and/or consultancy for Actelion, BayerSchering, GSK, Lilly, and Pfizer.

A. Schmeisser: Remunerations for lectures for Actelion, Pfizer, and GSK.

U. Schulz: Remunerations for lectures and/or consultancy for Actelion, BayerSchering, GSK, Lilly, and Pfizer.

R. Speich: none.

W. Zeh: none.

J. Weil: Remunerations for lectures and/or consultancy for Actelion, BayerSchering, GSK, Novartis, Pfizer.

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