SUMMARY: Mild-to-moderate pulmonary hypertension (PH) is a common complication of advanced chronic obstructive pulmonary disease (COPD). The presence of PH is associated with an increased risk of acute exacerbation and decreased survival.

Patients with COPD may present with severe elevation of pulmonary artery pressure (mean pulmonary artery pressure >35–40 mmHg). This is observed in end-stage disease, left heart disease or another COPD-associated respiratory disorder. A small proportion of patients may develop severe PH without any concomitant heart or lung disease other than COPD. These patients have unusual cardiopulmonary abnormalities with moderate airflow limitation, severe hypoxaemia, hypocapnia, a very low diffusing capacity of the lung for carbon monoxide and pulmonary haemodynamic characteristics similar to those of idiopathic pulmonary arterial hypertension (IPAH). Survival in this latter population of COPD is severely compromised. Right heart catheterisation (RHC) is mandatory when severe PH is suspected.

Management of PH in COPD relies on ruling out comorbidities, optimising therapy for COPD and long-term oxygen therapy. Specific treatment developed for IPAH should not be prescribed in COPD patients outside controlled trials or experienced PAH centre.

KEYWORDS: Chronic obstructive pulmonary disease, nitric oxide, pulmonary heart disease, pulmonary hypertension, respiratory insufficiency

Chronic obstructive pulmonary disease (COPD) is defined by persistent airflow limitation that is usually progressive [1]. This chronic lung disease is also characterised by frequent associated comorbid conditions and episodes of acute exacerbation. The important lesions in the lungs of patients with COPD are the alteration of distal airways, the development of emphysema and the occurrence of pulmonary vascular remodelling [2]. Once overlooked in patients with COPD, pulmonary vascular lesions and pulmonary hypertension (PH) are now recognised as central elements of disease pathogenesis [3] and are felt to be important in the development of the frequent comorbidities [4, 5].
The 4th World Symposium on PH defined group 3 as “pulmonary hypertension due to lung diseases and/or hypoxaemia” [6]. This group includes COPD. Due to the high prevalence of COPD, PH secondary to COPD is one of the most frequent causes of PH [7]. Besides the interesting links between the pathogenesis of COPD and PH, PH should be considered in COPD patients because it can impair exercise capacity and survival independently of the degree of airway obstruction [5, 7–9].

This chapter is devoted to PH due to COPD with the aim to cover definition, pathogenesis, haemodynamic characteristics, clinical impact, diagnostic strategy and management. The diagnosis and treatment of right heart failure during acute exacerbations of COPD will not be reviewed.

Definition

The current definition of PH is a mean pulmonary artery pressure ($P_{pa}$) $\geq$ 25 mmHg. Patients from groups 1, 3 and 4 of the current classification must also have a pulmonary capillary wedge pressure ($P_{pcw}$) $\leq$ 15 mmHg and a normal or reduced cardiac output [10]. A threshold value of 25 mmHg has been generally accepted because it is clearly abnormal and almost all observational studies and randomised controlled trials dedicated to PH have selected patients according to this cut-off value. Nevertheless, it has been acknowledged, and it is particularly true in COPD, that a mean $P_{pa}$ between 21 and 24 mmHg is also abnormal [11]. Further studies in this field are needed to better understand the clinical impact of this range of mean $P_{pa}$ values (currently classified as pre-PH) [12].

A second important issue to consider in terms of definition is “out of proportion” (or disproportionate) PH. Cut-off values of mean $P_{pa}$ $\geq$ 35 mmHg [13] and $\geq$ 40 mmHg [14] have been used in the literature to distinguish out of proportion PH. This expression appears in the current European Respiratory Society/European Society of Cardiology guidelines [15] and studies have shown different haemodynamic characteristics and greater mortality in this sub-population of COPD [13, 14]. The lack of a consensus definition hinders efforts to study this entity. We propose a definition based on our clinical experience. Any PH in patients with mild or moderate ventilatory compromise (forced expiratory volume in 1 second (FEV1) $\geq$ 50% of the predicted value), or a patient with a mean $P_{pa}$ $\geq$ 40 mHg, in the absence of comorbid illness, irrespective of severe ventilatory compromise. As pulmonary haemodynamics should be normal or near normal at rest in patients with a forced expiratory volume in 1 second $\geq$ 50% and because a mean $P_{pa}$ of 40 mmHg seems to be an important threshold, we suggest two criteria to define disproportionate PH in COPD.

Cor pulmonale is defined as right ventricular (RV) hypertrophy and dilatation, secondary to PH caused by lung diseases. However, cor pulmonale is not useful in clinical practice. First, the detection of RV abnormalities depends on the method employed and secondly, peripheral oedema, a clinical surrogate of cor pulmonale, might be observed in COPD patients with normal or low central venous pressure [16]. Exercise PH has been used in clinical research in COPD, although there is no consensus definition [15].

Therefore, only the definition of PH at rest (mean $P_{pa}$ $\geq$ 25 mmHg, $P_{pcw}$ $\leq$ 15 mmHg and normal or reduced cardiac output) is appropriate for routine assessment of pulmonary haemodynamics in COPD patients.

Pathogenesis of PH in COPD

As stated previously, PH in COPD is of the pre-capillary type associated with normal or low cardiac output. Therefore, PH is mainly due to an increase in pulmonary vascular resistance (PVR). Pulmonary vascular remodelling is the main factor of increased PVR in COPD. Pulmonary vasoconstriction, pulmonary pressure swings, reduction of the pulmonary vascular
bed and blood hyperviscosity are less significant causal factors. It has been shown that cigarette smoke induces pulmonary vascular remodelling at an early stage of COPD [5]. Pulmonary endothelial dysfunction and local inflammation are linked in COPD smokers with pulmonary vascular remodelling. Chronic alveolar hypoxia induces remodelling of small pulmonary arteries and arterioles in people living at high altitude and animal models of PH. Once considered the main factor of pulmonary vascular remodelling in COPD, hypoxia has been reconsidered because pulmonary vascular changes can be observed in patients who do not have hypoxaemia and because long-term oxygen therapy does not fully reverse PH in COPD. Nevertheless, in a site of local inflammation, as observed in the vicinity of small pulmonary arteries in patients with COPD, local hypoxia might be an important associated factor of pulmonary vascular remodelling.

### Pulmonary haemodynamic characteristics

PH in patients with COPD is of the pre-capillary type; therefore, $P_{pcw}$ is normal at rest when there is no associated left ventricular (LV) comorbidity. However, an increase in $P_{pcw}$ is frequently observed in patients with severe COPD of the emphysematous type [17] and when there is an associated LV dysfunction [18].

Due to the slow rate of progression of the RV afterload, the RV has time to adapt [19]. This slow development of PH explains why RV contractility is preserved and cardiac output at rest is in the normal range in patients in a stable condition.

In COPD, as well as in other chronic respiratory diseases, PH is usually of mild-to-moderate severity [5, 7]. This characteristic makes an important distinction from group 1 and from group 4 of the current classification (table 1) [20–22].

Although, PH is mild-to-moderate at rest, $P_{pa}$ increases noticeably during sleep, exercise and acute exacerbation. Large variations of pressure due to respiratory swings are also frequently observed in COPD [22]. An illustration of a typical recording of $P_{pa}$ is shown in figure 1.

Approximately 10–20% of patients with advanced COPD have been reported to have severe PH (mean $P_{pa} \geq 35$ mmHg). This could be observed in three clinical situations [13, 14]. First, few patients with very severe airflow limitation, severe hypoxaemia and hypercapnia present with a significant increase in mean $P_{pa}$ at rest and in a stable state. Secondly, patients with comorbid conditions, such as chronic venous thromboembolism, severe left-sided cardiac disease or an associated restrictive lung disease, may have severe PH. Finally, severe PH has also been

| Table 1. Comparison of pulmonary haemodynamics in three representative series of patients with pulmonary hypertension |
|---------------------------------|-----------------|-----------------|-----------------|
| First author [ref.]            | Group 1 PAH     | Group 3 COPD    | Group 4 CTEPH   |
| Age years                      | 674             | 797             | 34              |
| FEV1 % pred                    | 50 ± 15         | 67 ± 6          | 27 ± 7          |
| $P_{a,O_2}$ mmHg               | 27 ± 7          | 63 ± 10         | 43 ± 6          |
| $P_{a,CO_2}$ mmHg              | 63 ± 10         | 43 ± 6          |                 |
| Mean $P_{pa}$ mmHg             | 55 ± 15         | 23 ± 5          | 46 ± 13         |
| Cardiac index L·min⁻¹·m⁻²       | 2.5 ± 0.8       | 2.8 ± 1.0       | 2.1 ± 0.7       |

Data are presented as n or mean ± SD. In chronic obstructive pulmonary disease (COPD), the mean pulmonary artery pressure ($P_{pa}$) is less increased compared with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), and cardiac output is in the normal range in most of the COPD patients. Group 1: French registry of PAH; Group 3: National Emphysema Treatment Trial; Group 4: Toronto General Hospital; FEV1: forced expiratory volume in 1 second; % pred: % predicted; $P_{a,O_2}$: arterial oxygen tension; $P_{a,CO_2}$: arterial carbon dioxide tension.
observed in COPD patients with moderate airflow obstruction, severe hypoxaemia and hypocapnia. The latter condition has been termed out of proportion PH. Patients with this type of PH present with pulmonary haemodynamic alterations reminiscent of those seen in idiopathic pulmonary arterial hypertension (PAH). Table 2 shows FEV1 values, arterial blood gases and the pulmonary haemodynamic characteristics of COPD patients with disproportionate PH [13, 14]. Recent data from the National Emphysema Treatment Trial seems to indicate that severe PH at rest is very uncommon in patients with emphysema without significant comorbidities [22].

**Clinical impact**

**Dyspnoea on exertion and exercise tolerance**

The main mechanisms of dyspnoea in COPD are dynamic hyperinflation, increase in ventilatory demand, respiratory muscle weakness and, in the most severe patients, hypoxaemia and hypercapnia [24]. Therefore, it is difficult to know whether PH impacts on symptoms during exercise. Few physiological studies have shown that the increase in $P_{pa}$ during exercise may contribute to dyspnoea [25, 26]. More recently, a study compared COPD patients with severe PH and mild-to-moderate airflow limitation with patients who had less severe PH but more important airflow limitation and showed that the former group of patients had more exercise intolerance [14]. It has also been shown that patients with COPD and a mean $P_{pa} \geq 40$ mmHg had an exhausted circulatory reserve at the end of exercise contrasting with a ventilatory limitation in COPD patients without severe PH [8]. These observations suggest that pulmonary haemodynamics play a role on exertional dyspnoea in COPD patients with severe PH ($mean P_{pa} \geq 40$ mmHg), but probably not in patients with moderate PH or no PH.

**Table 2.** Comparison of chronic obstructive pulmonary disease patients with pulmonary hypertension (PH) without comorbid conditions that could cause disproportionate PH compared to patients with moderate or no PH.

<table>
<thead>
<tr>
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<th>Disproportionate PH</th>
<th>Disproportionate PH</th>
<th>Moderate or no PH</th>
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<tr>
<td>Subjects</td>
<td>16</td>
<td>11</td>
<td>30</td>
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<tr>
<td>FEV1 % pred</td>
<td>49 ± 12</td>
<td>50 (44–56)</td>
<td>29 (26–40)</td>
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<td>$P_{a}O_{2}$ mmHg</td>
<td>46 ± 16</td>
<td>46 (41–53)</td>
<td>64 (56–73)</td>
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<tr>
<td>$P_{a}CO_{2}$ mmHg</td>
<td>40 ± 11</td>
<td>32 (28–37)</td>
<td>44 (37–47)</td>
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<tr>
<td>Mean $P_{pa}$ mmHg</td>
<td>40 ± 10</td>
<td>48 (46–50)</td>
<td>21 (16–25)</td>
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</table>

Data are presented as n, mean ± SD or median (interquartile range). Remarkably, patients with disproportionate PH have less airflow limitation. FEV1: forced expiratory volume in 1 second; % pred: % predicted; $P_{a}O_{2}$: arterial oxygen tension; $P_{a}CO_{2}$: arterial carbon dioxide tension; $P_{pa}$: pulmonary artery pressure.
Exercise capacity

Two recent retrospective studies performed in advanced COPD patients found that high mean $P_{pa}$ was associated with a short 6-minute walking distance (6MWD) [27, 28]. In another study, patients with COPD and severe PH (mean $P_{pa} \geq 40$ mmHg) had lower maximal power during an incremental cardiopulmonary exercise test compared to patients with moderate or no PH while they had less airflow limitation [8]. In that latter study, end-tidal carbon dioxide tension, mixed venous oxygen saturation and the cardiac output–oxygen consumption slope were lower in COPD patients with severe PH. It has been shown that in the small population of patients with severe or disproportionate PH, 6MWD may be very low [29]. These observations showed that when mean $P_{pa}$ is $\geq 40$ mmHg in COPD, pulmonary haemodynamic impairment impacts exercise capacity. However, as stated before it must be emphasised that such a condition is uncommon and that a majority of COPD patients have exercise limitation due to limited ventilatory reserve.

Survival

Before the wide-scale introduction of long-term oxygen therapy (LTOT), it was shown that PH in COPD was an independent prognostic factor [30]. Nowadays, despite the fact that LTOT improves the survival of hypoxaemic patients, PH is still associated with lower survival rates [28, 31]. Importantly, an elevated $P_{pa}$ was also associated with an increased risk of severe acute exacerbation in COPD patients with moderate-to-severe airflow limitation [32].

In conclusion, it is often difficult to differentiate the clinical consequences of PH from those of airflow limitation in COPD. Nevertheless, it is important to detect associated conditions (such as left heart disease) or severe PH, which impact on the pulmonary circulation and may have clinical consequences in order to prescribe any recommended treatment. Recent data from emphysema patients participating in the National Emphysema Treatment Trial showed that even though pulmonary haemodynamics were more abnormal among patients with a reduced 6MWD and among those who died, age and pulmonary function abnormalities remained the primary drivers of functional capacity and survival [9].

Diagnostic strategy

Recognition of PH in COPD is difficult, especially in its mildest form because it is difficult to differentiate the clinical picture of PH from the underlying lung disease [33]. Cardiac auscultation is often hampered by thoracic distension or pulmonary sounds. Signs of right heart failure are rarely noticed in COPD except during severe acute exacerbation or in disproportionate PH. Peripheral oedema is frequent in the course of COPD, but rarely due to right heart failure. Chest radiography and ECG may be helpful but lack sensitivity. Spirometry, plethysmography, diffusing capacity of the lung for carbon monoxide and arterial blood gases do not allow an accurate prediction of PH. Nevertheless, symptoms, clinical signs and these usual tests are useful in raising suspicion of PH. Indeed, at this stage the main pitfall is to systematically exclude PH as a cause of severe dyspnoea on exertion and/or severe hypoxaemia. It must be mentioned that when these latter characteristics are identified in patients with COPD and are not adequately explained by the severity of compromise in lung function, it is of paramount importance to search for a comorbid condition and severe PH.

A fairly good noninvasive assessment of PH can be performed with Doppler echocardiography using several measurements. The association of measurements of maximal velocity of tricuspid regurgitation, pulmonary acceleration time, and indices of RV and LV dysfunction is important to exclude LV disease and raise suspicion of PH. However, Doppler echocardiography has been shown to lack sensitivity and specificity in patients with COPD [34, 35]. Therefore, clinicians should not stop searching for PH only on the basis of a negative echocardiography when PH is suspected.
Right heart catheterisation (RHC) is the gold standard for the diagnosis of PH. It allows the direct measurement of mean $P_{pa}$, $P_{pcw}$, right heart filling pressure and cardiac output. The main disadvantage of RHC is its invasive nature.

Brain natriuretic peptide (BNP) is mainly secreted by cardiomyocytes. Severe PH leads to an increase in plasma BNP [29]. However, since PH is generally mild to moderate and left heart disease is frequently associated with COPD, it is likely that BNP would lack specificity to detect PH in the whole population of COPD patients.

As stated previously, high mean $P_{pa}$ was associated with a short 6MWD in two retrospective studies [27, 28]. In these two studies, although statistically significant, the differences of 6MWD between patients having or not having PH were low with a standard deviation corresponding to four to five times the mean difference. COPD patients with PH might have more significant exercise desaturations. Although 6MWD does not clearly allow differentiation of patients with PH, unexpected low walking distance and severe desaturations should raise suspicion of PH.

The incremental maximal cardiopulmonary exercise test displays a specific pattern in patients with COPD and disproportionate PH [8, 36]. This profile, also observed in chronic heart failure, is characterised by very low maximal work, a larger ventilatory reserve at peak exercise and a low end-tidal partial pressure of carbon dioxide compared with COPD patients with mild-to-moderate PH or no PH.

Chronic pulmonary thromboembolism, associated restrictive lung disease or sleep-disordered breathing are relatively frequent conditions known to cause PH [14]. Symptoms and signs of these comorbidities could be covered by the clinical picture of COPD. Therefore, it may also be important to perform a measurement of static lung volumes, ventilation/perfusion scans, a thoracic computed tomography angiography and a sleep study.

In conclusion, although several tests may increase the suspicion for PH, RHC is mandatory to confirm a diagnosis of PH. However, due to its invasive nature this test should not be performed in all patients with COPD. Unfortunately, there is no unique test that may be used to appropriately select patients for RHC and a comprehensive evaluation should lead one to consider performing RHC in patients with COPD (fig. 2). It must be emphasised that severe PH or diastolic (left) heart failure are difficult to diagnose without performing RHC and, if left unrecognised and untreated, could have severe consequences for the patient.

**Treatments**

The objectives of PH treatment in COPD are to improve pulmonary haemodynamics, functional status and survival (table 3). Due to the complex interplay between lung mechanics, pulmonary haemodynamics and cardiac function, a single target is unlikely to be widely effective.

The underlying disease should be optimally treated. In particular, smoking cessation, among other positive effects, may help to lower the risk for PH [37, 38]. PH is not a contraindication to exercise training [39]; therefore, pulmonary rehabilitation can be performed in COPD patients with PH. However, when PH is severe it is wise to refer patients to an expert PH centre initially and monitor exercise training. When considering PH in patients with COPD it is important to consider and rule out comorbid conditions, such as left heart disease, sleep-disordered breathing, pulmonary embolism and interstitial lung disease. This is especially true of patients found to have severe or disproportionate PH and in patients with PH associated with mild-to-moderate COPD [7]. Their occurrence may help explain the PH and will have a significant impact on patient management.

Alveolar hypoxia is considered to be a cause of the elevation of PVR and $P_{pa}$ in COPD patients. One of the aims of oxygen therapy is the improvement of PH induced by chronic alveolar hypoxia. Pulmonary haemodynamic data were available at the onset in all patients and follow-up RHC was performed in a relatively high number of patients in the Nocturnal Oxygen Therapy Trial [40] and Medical Research Council studies [41]. These studies showed that $P_{pa}$: 1) increased in patients
who were not treated with oxygen therapy; 2) remained stable in patients who received LTOT for 12–15 hours per day; and 3) slightly decreased in patients treated with continuous LTOT (>18 hours per day).

COPD patients may have significant hypoxaemia during sleep even though daytime arterial oxygen tension is >60 mmHg [42]. It has been hypothesised that isolated sleep-related hypoxaemia could lead to permanent PH. If this were the case, prescription of nocturnal oxygen therapy would be justified. In fact, the present data related to sleep desaturation in COPD are not sufficient for justifying the use of nocturnal oxygen therapy in COPD patients who do not qualify for conventional LTOT [43]. A large ongoing multicentre trial of supplemental oxygen for patients with COPD and moderate hypoxaemia in North America will probably answer to this question [44].

Patients with an associated obstructive sleep apnoea syndrome or restrictive lung disease may need oxygen therapy plus continuous or bi-level positive airway pressure support [45]. This latter treatment is often necessary to stabilise chronic hypercapnic respiratory failure and may help to improve PH.

It is important to know whether any therapy, other than LTOT, acting on the pulmonary circulation is able to improve pulmonary haemodynamics and the clinical status of patients with COPD. To date, all attempts at using pulmonary vasodilators to improve outcomes in patients with COPD have been disappointing. Vasodilators, such as calcium channel blockers and urapidil, acutely decrease RV afterload but no long-term beneficial effect has been reported [5]. Similar results have been shown with angiotensin inhibitors [46]. Thus, calcium channel blockers, angiotensin inhibitors and \(\alpha_1\)-antagonists should not be prescribed to treat PH in patients with COPD.

At present, the main approach to treating patients with PAH is to correct, at least partially, the pulmonary endothelium dysfunction [47]. Given that the unbalanced release of endothelium-derived mediators has also been observed in PH due to COPD, drugs acting on or correcting the pulmonary endothelial dysfunction have been tested in patients with COPD. Inhaled nitric oxide and sildenafil have an acute positive effect on pulmonary haemodynamics [48, 49]. Sildenafil decreases mean \(P_{pa}\) and total PVR at rest and during exercise while worsening arterial hypoxaemia. A 3-month randomised trial of inhaled nitric oxide plus oxygen supplementation versus placebo plus oxygen supplementation showed a persistent improvement of mean \(P_{pa}\), PVR and cardiac output [50]. These results are promising but technical and safety issues are far from
being resolved. In a 3-month randomised controlled trial of COPD patients, some of whom had PH, bosentan did not improve 6MWD and was responsible for a worsening of gas exchange and deterioration in health-related quality of life [51]. Despite these limited data, patients with PH due to COPD in North America are being treated with medications that target the pulmonary vasculature [52]. No randomised controlled trial has been performed in patients with disproportionate PH in patients with COPD.

Recent pathophysiological studies have suggested an alteration of cellular lung repair in COPD, which could lead to PH [4]. As a consequence, medications such as 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, with a protective effect on vascular destruction and abnormal repair at the cellular level, require further study.

Lung volume reduction surgery (LVRS) is a treatment of severe emphysema. The National Emphysema Treatment Trial showed no significant increase in mean $P_{pa}$ 6 months after LVRS when the initial value was <35 mmHg [53]. Conversely, when the mean $P_{pa}$ is >35 mmHg lung transplantation may be considered in appropriately selected candidates without significant comorbidities.

In summary, optimising COPD management and ruling out comorbid conditions are essential components of evaluation. LTOT should be prescribed in all COPD patients with PH and with an arterial oxygen tension <60 mmHg. In patients with COPD and moderate PH, treatment with PH-specific therapy is not recommended in clinical practise and should be considered in the context of a clinical trial or an experienced PAH centre. Concerning patients with severe and disproportionate PH, lung transplantation may be considered in appropriately selected candidates as it provides the best opportunity for long-term benefit.

### Five unanswered practical questions

There are currently five unanswered practical questions about PH in COPD. 1) What is the prevalence of PH in the whole COPD population? 2) What level of PH has a clear impact on the clinical status? 3) What is the definition of disproportionate PH, taking into account pulmonary haemodynamic and lung function data? 4) What is the diagnostic strategy, with a high negative predictive value and an acceptable positive predictive value, to avoid unnecessary RHC? 5) In the population of COPD with PH, who might benefit from specific PAH therapy?
Conclusion

PH is a frequent complication of COPD. Even though frequently moderate, PH has an impact on functional capacity and survival in these patients. The impact of PH on exercise capacity is more significant when the mean $P_{oa}$ is $>40$ mmHg. Clinicians should suspect PH when dyspnoea on exertion and severe hypoxaemia cannot be explained by the severity of alterations in lung mechanics. Patients with moderate PH and who are hypoxaemic should be treated with LTOT and all other treatments according to current guidelines for the management of COPD. A subset of COPD patients, probably $<5\%$, develop disproportionate PH. This latter condition shares pulmonary haemodynamic similarities with PAH and mortality is significantly increased in these patients. Due to the severity of disproportionate PH in COPD and its scarcity, patients with this condition should be referred to an expert PH centre for management.

Statement of Interest

O.A. Minai is a member of the Scientific Advisory Board for Actelion, Gilead, United Therapeutics, Pfizer and Bayer, and is a member of the Speakers Bureau for Actelion, Gilead, United Therapeutics and Pfizer.

References


