

Standard Therapies for Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) was first described in 1891 in a case report by Romberg [1]. The term “primary pulmonary hypertension” (PPH) was first used in 1951 when Dresdale and colleagues [2] reported clinical features and hemodynamics of 39 patients. Until approximately two decades ago, before the development of specific PAH therapies, such as prostacyclin analogs, endothelial receptor antagonists, and phosphodiesterase-5 inhibitors, PAH (especially idiopathic [IPAH] or PPH form of PAH) was considered a disease that was universally fatal with a median survival of 2.8 years [3]. An explosion of research and drug development has resulted in the development of several specific PAH therapies (see other articles elsewhere in this issue) [4–21]. Therapies such as oxygen supplementation, calcium channel blockers (CCBs), anticoagulation, digoxin, and diuretics have been in use since long before the development of the newer specific PAH agents. These therapies have been referred to as “standard PAH therapies” or “conventional PAH therapies” [22]. The concept of these standard therapies originated from the experience with other pulmonary and cardiac diseases with similar—but not identical—manifestations in terms of symptoms (eg, edema in congestive left heart failure and

use of diuretics) or physiologic observations (eg, hypoxemia in emphysema and use of oxygen supplementation therapy, low cardiac output in left ventricular [LV] systolic dysfunction and use of digoxin, high blood pressure in essential systemic hypertension and use of vasodilators, prothrombotic tendency in venous thromboembolism and use of anticoagulation). These practices were subsequently adopted in the treatment of PAH and right heart dysfunction and failure. None of these therapies is supported by well-designed placebo-controlled trials. Some of these practices are based on marked symptomatic relief or improvement with short-term use (eg, diuretics for edema) or by observations based on acute testing in the laboratory setting (eg, improvement in cardiac output by single administration of digoxin) [23] or from autopsy findings [24–26] (eg, in situ microthrombi in lungs of patients who have PAH and use anticoagulation). Therapies such as anticoagulation have been supported by a few retrospective studies [27,28] and an uncontrolled, single-center prospective study [29], especially in IPAH [30]. This raises the ethical question of the appropriateness of performing a placebo-controlled trial in these patients. On the other hand, the short-term benefits from diuretics are so obvious that it virtually obviates the need for a clinical trial to validate such benefit. For these reasons it seems unlikely that any large, prospective, clinical trials will examine the role of the standard therapies used in PAH in the near future. Such trials are needed, however.

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Especially lacking are data about use of standard therapies in PAH other than IPAH (associated [APAH]). It may be possible that in specific populations, these therapies may not be helpful, that they may be less helpful than they are currently considered, or that they may be even harmful.

In a prospective, controlled study of patients who had PAH and Eisenmenger syndrome, the use of oxygen supplementation in hypoxemic patients was not associated with any improvement in hematologic variables, quality of life, or survival [31]. A recent retrospective chart review of French patients who had IPAH showed that only 6.8% of all patients who had IPAH could be maintained on CCB therapy alone without any need for augmentation of therapy by a newer agent [32]. This is an example in which retrospective [33] and noncontrolled prospective [29,34] data led to enthusiasm, first about the use of acute vasoreactivity testing for assessing prognosis in PPH and second about the excessive use of CCBs in patients who have PAH. It should be noted that the initial studies [29,34], which reported that the “responders” had an excellent (94%) 5-year survival on CCBs, had mean fall in mean pulmonary artery pressure (mPAP) of 39% to 48% and mean fall in pulmonary vascular resistance (PVR) of 53% to 60%. The acceptance of relatively less stringent criteria for favorable acute vasoreactivity response [35–37] was at least partly caused by the fact that at that time the only alternative to CCB therapy was continuous intravenous prostacyclin therapy. Because currently several oral and inhaled therapies are available and it is known that as many as 46% of “acute responders” eventually will fail, CCB monotherapy [32], the need for and emphasis on performing acute vasoreactivity testing, and the use of CCBs as primary therapy for IPAH has changed [32]. Reliance on CCBs in such patients and not using specific PAH therapies may or may not be in patients’ best interest.

This article reviews current recommendations and widely accepted practices regarding the use of standard therapies in PAH and presents the evidence available to support these practices. The primary purpose of this article is to provide clinicians with relevant information to be able to make informed therapeutic decisions in clinical situations in which data regarding standard therapies are lacking, relative contraindications to these therapies exist, or the

therapies are poorly tolerated or adverse events occur.

Oxygen therapy

The value of long-term oxygen supplementation therapy in patients with PAH has not been evaluated by well-designed clinical trials. Recommendations and guidelines for oxygen therapy in patients who have PAH have been extrapolated from the clinical data available for chronic obstructive pulmonary disease (COPD). Pathophysiologically, hypoxemia is a potent stimulus for pulmonary vasoconstriction [38]. In COPD patients who have hypoxemia, two well-designed, prospective, randomized, non–placebo-controlled trials [39,40] have shown that there is marked improvement in long-term survival with the use of supplemental oxygen (Table 1) [31,39,40].

One trial [40] studied 87 patients who had COPD and a history of right heart failure (RHF) along with arterial oxygen partial pressure <60 mm Hg. Patients were randomly assigned to receive 15 h/d of oxygen supplementation therapy or no therapy. Five-year mortality rate in the oxygen treatment group was 46% versus 67% in control group (number needed to treat to save one life in approximately five). The study also showed an increase in PVR in the control group over the study period but no increase in PVR in the oxygen therapy group. The study was not powered to evaluate this parameter, however.

The other prospective, randomized, controlled study of 203 patients who had chronic hypoxemic COPD showed that in patients who were hypoxemic at rest during the daytime, the use of nocturnal oxygen supplementation (12 h/d) was associated with a higher 3-year mortality rate (42% versus 22%) when compared with the group that used continuous (at least 19 h/d) supplemental oxygen [39]. The number needed to treat to save one life was approximately five. The survival advantage was more pronounced in patients with less severe pulmonary hypertension at baseline (mean pulmonary arterial pressure <27 mm Hg). Continuous oxygen supplementation therapy improved long-term survival in patients who had COPD with significant hypoxemia (PaO_2 <55 mm Hg at rest) even if there was no significant improvement in pulmonary hemodynamics with acute oxygen supplementation. Patients with low baseline PVR had an improved mortality on continuous oxygen supplementation therapy, but the patient with high baseline PVR did not experience

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