

Current perspectives on treatment of hypertensive patients with chronic obstructive pulmonary disease

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Abstract: Systemic hypertension and chronic obstructive pulmonary disease (COPD) frequently coexist in the same patient, especially in the elderly. Today, a wide variety of antihypertensive drugs with different mechanisms of action are available to the prescribing physician. In addition, combination drugs for hypertension are becoming increasingly popular. Certain antihypertensive drugs can affect pulmonary function. Therefore the management of such patients can present therapeutic challenges. We have examined the literature pertaining to the use of antihypertensive drugs in patients with systemic hypertension and coexisting COPD. Although data are often limited or of poor quality, we have attempted to review and then provide recommendations regarding the use of all the specific classes of antihypertensive drug therapies including combination drugs in patients with COPD. The antihypertensive agents reviewed include diuretics, aldosterone receptor blockers, beta blockers, combined alpha and beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II antagonists, calcium channel blockers, alpha-1 blockers, centrally acting drugs, direct vasodilators, and combinations of these drugs. Of these classes, calcium channel blockers and angiotensin II antagonists appear to be the best initial choices if hypertension is the only indication for treatment. However, the limited data available on many of these drugs suggest that additional studies are needed to more precisely determine the best treatment choices in this widely prevalent patient group.

Keywords: blood pressure, hypertension, COPD, treatment, antihypertensive drugs

Introduction

There is a high prevalence of both systemic hypertension and chronic obstructive pulmonary disease (COPD) in the adult population. COPD affects about 6% of the US adult population and is associated with high morbidity and mortality.¹ However, the real prevalence may be much higher than 6%, as half the patients with airflow limitation are asymptomatic, and thus COPD is not detected.² Prevalence of COPD increases with age, from 3.2% among those aged 18–44 years to 11.7% among those aged ≥ 65 years. Systemic hypertension is much more prevalent than COPD, with 27.6% of the US adult population carrying the diagnosis.³ The prevalence of hypertension also increases with advancing age, with more than half of people 60–69 years of age and approximately three-fourths of those 70 years of age and older diagnosed with this condition.⁴

Data from the Medical Outcomes Study show that the prevalence of COPD in adult outpatients with systemic hypertension is similar to that in the general population.⁵ This would mean that there are about three million adults in the US with COPD who also have systemic hypertension. As a result, the management of hypertension in a patient

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with COPD is a common problem faced by a physician, especially when taking care of older adult patients.

Smoking tobacco is a major risk factor in the development of both systemic hypertension and COPD, and the Framingham Study has shown that smoking can increase the impact of hypertension as a risk factor in the development of cardiovascular disease.^{6,7} Epidemiological studies have suggested that ventilatory impairment measured by impaired forced expiration as seen in patients with COPD is an independent predictor of future cardiovascular events.^{8,9}

The American College of Cardiology Foundation/American Heart Association 2011 expert consensus document on hypertension in the elderly recommends that blood pressure should be lowered to less than 140/90 mmHg in adults younger than 80 years who are at high risk for cardiovascular events.¹⁰ On the basis of data from the Hypertension in the Very Elderly trial,¹¹ these guidelines recommend that systolic blood pressure should be reduced to 140 to 145 mmHg, if tolerated, in adults aged 80 years and older. Since we have no reason to believe that treatment of patients with concomitant COPD should have different therapeutic targets than for other hypertensive patients, patients with COPD and hypertension should be treated according to these guidelines.^{10,12–17}

Today, a wide variety of antihypertensive drugs with different mechanisms of action are available to physicians. Some antihypertensive drugs can have an adverse impact on pulmonary function and therefore the management of patients with COPD and hypertension can present certain therapeutic challenges. The goal of this review is to conduct an analysis of the literature and provide recommendations regarding antihypertensive drug treatment in patients with COPD.

Search strategy

We searched using electronic databases (MEDLINE [1966 to March 2013], EMBASE and SCOPUS [1965 to March 2013], and DARE [1966 to March 2013]). Additionally, abstracts from national and international cardiovascular meetings were searched. Where necessary, the relevant authors were contacted to obtain further data. The main data search terms were “antihypertensive drugs,” “blood pressure,” “COPD,” “hypertension,” “therapy,” and “treatment.”

Review of specific classes of antihypertensive agents

A large number of drugs are currently available to treat hypertension. Table 1 provides a list of the commonly used antihypertensive classes.

Table 1 Oral antihypertensive classes

Class	Examples
Thiazide diuretics	Hydrochlorothiazide, chlorthalidone
Loop diuretics	Furosemide, bumetanide, torsemide
Potassium-sparing diuretics	Amiloride, triamterene
Aldosterone receptor blockers	Spirolactone
Cardioselective beta blockers	Metoprolol, nebivolol, bisoprolol
Noncardioselective beta blockers	Propranolol
Beta blockers with intrinsic sympathomimetic activity	Pindolol, acebutolol
Combined alpha and beta blockers	Carvedilol, labetalol
Angiotensin-converting enzyme inhibitors	Captopril, enalapril, lisinopril, ramipril
Angiotensin II antagonists	Candesartan, losartan, valsartan
Calcium channel blockers: non-dihydropyridines	Diltiazem, verapamil
Calcium channel blockers: dihydropyridines	Amlodipine, felodipine, nifedipine
Alpha-1 blockers	Doxazosin, prazosin, terazosin
Central alpha-2 agonists and other centrally acting drugs	Clonidine, methyldopa
Direct vasodilators	Hydralazine, minoxidil

Thiazide diuretics

Based on the findings in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),¹⁸ the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and others have concluded that low-dose thiazides should be used as the initial drug treatment of most patients with uncomplicated hypertension.^{6,18} There is a dearth of good outcome data from clinical studies designed to examine the effects of thiazide diuretics used as antihypertensive agents in patients with COPD. However, a recent study of patients with hypertension and COPD requiring two antihypertensive drugs, combination therapy that included a thiazide diuretic was associated with a significantly lower risk of hospitalization for congestive heart failure (CHF) among patients without a prior diagnosis of CHF.¹⁹ This study was a retrospective cohort of Veterans Administration Medical Center patients.¹⁹ The use of a thiazide diuretic in combination therapy in this study was not associated with a difference in risk of COPD exacerbations.

Thiazide diuretics have no adverse effect on airway function and can be used effectively in patients with COPD.²⁰ However, the potential for serious hypokalemia must be recognized.²¹ This problem is related to the ability of inhaled beta-2 receptor agonists like albuterol to drive potassium into the cells, and of oral corticosteroids, which

are used for COPD exacerbations, to slightly increase urinary potassium excretion.²² In patients with COPD and chronic hypercapnia, there is another potential problem with the use of thiazide diuretics. This is the metabolic alkalosis induced by thiazide diuretics, which can suppress the ventilatory drive, potentially worsening the degree of hypoxemia and hypercapnia.²³ With careful monitoring of electrolyte, hypercapnia, and oxygen levels, the use of thiazide diuretics is probably safe. Hypokalemia from thiazides is dose-dependent.

Thus, overall, it is probably safe to administer low doses of thiazide diuretics to nonedematous hypertensive patients with COPD. Low-dose treatment may be both effective and less likely to cause undesirable side effects such as hypokalemia and metabolic alkalosis.

Loop diuretics

Among patients with normal renal function, loop diuretics have a lesser antihypertensive effect than the thiazide diuretics. This may be related to the shorter duration of action of most loop diuretics when compared to the thiazides. However, loop diuretics may be useful in patients with COPD who have resistant hypertension, are volume overloaded, and have an estimated glomerular filtration rate of <30 mL/min/m². In addition, inhaled furosemide has shown some early promise as a dyspnea-relieving intervention in COPD.²⁴

Patients with COPD who have chronic respiratory acidosis or are receiving corticosteroids or beta-agonists and do get treated with potassium-wasting loop diuretics should undergo close monitoring of electrolyte levels and be considered for therapy with potassium supplements. In addition, these drugs can increase hematocrit as well as lead to hemodynamic compromise in patients who are preload dependent in the setting of right heart failure.

Potassium-sparing diuretics

The potassium-sparing diuretics triamterene and amiloride have minimal antihypertensive effect and are not widely used as initial therapy for primary hypertension.²⁵ However, these drugs may provide some antihypertensive benefit when added to multidrug regimens in patients with resistant hypertension.²⁶ There are no specific contraindications or concerns about the use of these drugs in patients with COPD.

Aldosterone receptor blockers

Aldosterone receptor blockers can provide significant antihypertensive benefit when added to multidrug regimens in patients with resistant hypertension.^{27,28} These drugs

have a clear role to play in patients with established heart failure; in addition, they may play a role in preventing the development of heart failure in patients with hypertension as suggested by a mouse study.²⁹ There are no specific contraindications or concerns about the use of these drugs in patients with COPD. Spironolactone should be used as an add-on agent for treatment of resistant hypertension in patients with COPD.

Beta blockers

Adrenergic receptors of airway smooth muscle are primarily of the beta-2 subtype.³⁰ Beta-2 receptor activation by beta-2 agonists like albuterol causes bronchodilation by increasing adenylyl cyclase activity and inhibiting the cholinergic pathway. Therefore, nonselective beta blockers like propranolol can cause bronchoconstriction in susceptible individuals.³¹ As a result, the safety of beta blocker therapy in patients with COPD has been a common and longstanding concern. Traditional dogma has stated that beta blockers are contraindicated in COPD because of their bronchoconstrictive properties and “competition” with beta-2 agonists.³² Therefore many physicians have avoided prescribing beta blockers in patients with COPD.^{33,34}

However, selective beta-1 blockers like atenolol and metoprolol, which have a 20-fold greater affinity for beta-1 receptors than beta-2 receptors, are less likely to induce bronchoconstriction. A meta-analysis concluded that, in patients with COPD, single-dose or long-term treatment with selective beta blockers did not have a significant effect on forced expiratory volume in 1 second (FEV₁), beta-agonist response, inhaler use, or respiratory symptoms.³⁵ Even in patients with COPD who had reactive airway disease, the use of selective beta blockers was only associated with a small decrease in FEV₁ and a similar small increase in beta-agonist response with the first dose, both of which normalized with continued treatment.³⁶ Cardioselective beta-1 blockers such as metoprolol, bisoprolol, or nebivolol may be beneficial in COPD. Atenolol does not reduce cardiovascular events in patients with hypertension. Nonselective beta blockers such as propranolol may induce bronchospasm and should not be used in patients with COPD. Beta blockers with intrinsic sympathomimetic activity cause less reduction in pulmonary function tests than propranolol but have not been compared to cardioselective agents.

There is good evidence that the use of beta blockers reduces mortality in post-myocardial infarction patients with COPD or those undergoing major vascular surgery.³⁷ There is also some evidence that the use of beta blockers

in patients with COPD may actually reduce the risk of exacerbations and improve survival.³⁸ However, a recent time-dependent analysis from Sweden suggests that beta blockers decrease survival in oxygen-dependent COPD.³⁹ Similarly, in a randomized, double-blind, crossover trial, cardioselective beta blockers worsened airway obstruction in COPD patients.⁴⁰ Formgren reported that the cardioselectivity of certain beta blockers can be lost at higher doses.⁴¹

Among the cardioselective beta blockers, bisoprolol may have the least effect on pulmonary function in patients with COPD.^{42,43} These studies show that treatment with atenolol produced a statistically significant increase in airway resistance when compared to bisoprolol and placebo. However, neither atenolol nor bisoprolol produced any significant changes in the more commonly used parameters of pulmonary function such as peak expiratory flow rate (PEFR), FEV₁, and forced vital capacity (FVC).

Nebivolol is also an effective alternative in COPD patients.⁴⁴⁻⁴⁶ Nebivolol is a third-generation beta-adrenergic receptor antagonist with high beta-1 selective adrenergic receptor antagonism and vasodilating properties that induces a substantial decrease of arterial pressure in hypertensive subjects while preserving their left ventricular function. Respiratory effects of nebivolol have been widely investigated in animal models, in healthy volunteers, and in clinical trials carried out on patients suffering from bronchial asthma and COPD.⁴⁴⁻⁴⁶ In contrast to older compounds, nebivolol, which modulates the endogenous production of nitric oxide and affects oxidative cascade, proved clinically well tolerated in terms of respiratory outcomes in this type of subject. Moreover, due to the substantial dissociation between its cardiac and pulmonary activity, nebivolol confirmed a very good safety profile when regularly administered to hypertensive subjects with obstructive respiratory comorbidities.⁴⁴⁻⁴⁶

Therefore, despite some conflicting data, selective beta-1 blockers appear to be relatively safe to use as an antihypertensive in stable COPD patients with irreversible or partially reversible airway obstruction and may in fact have some other additional benefits. However, if time permits, it would be safer to start a beta blocker at a small dose and carefully monitor for side effects as the dose is increased. During such initiation, patients with COPD should be carefully monitored for new symptoms (eg, dyspnea, exercise intolerance, cough) or changes in medication-use patterns (eg, increased need for a beta-agonist inhaler) that should

then prompt reevaluation about the use of the drug. In a similar vein, the safety of starting beta blocker therapy in a patient during an exacerbation of COPD is not known, and so these agents should not be used during an exacerbation if hypertension is the only indication.

It needs to be emphasized that atenolol, despite its relatively safe profile in COPD patients, has very limited effectiveness in the treatment of hypertension, including a small or even negative influence on central blood pressure, arterial stiffness (pulse pressure), vascular resistance/remodeling, and prevention of target organ damage, and therefore should be avoided.^{46,47}

Beta blockers with intrinsic sympathomimetic activity (ISA)

There is evidence that treatment with beta blockers with ISA is associated with downregulation of beta-2 receptors.⁴⁸ This is consistent with data from an analysis that shows that continued treatment with beta-1 blockers with ISA did not produce the increase in beta-2 agonist response that was seen with beta-1 blockers without ISA.⁴⁹

These agents decrease blood pressure and systemic vascular resistance, while the heart rate and cardiac output at rest are maintained. Beta blockers with ISA may therefore be used in clinical situations where non-ISA beta blockers are relatively contraindicated, such as sinus bradycardia, sick sinus syndrome, and Raynaud-like symptoms.

While it has been demonstrated that beta blockers with ISA, such as pindolol, have a less marked effect on pulmonary function than nonselective beta blockers without ISA, such as propranolol, there is no data comparing these drugs to beta-1 selective blockers without ISA. Therefore, the recommendations regarding the use of these drugs for the treatment of hypertension in patients with COPD have to be similar to those made above regarding the use of beta blockers.

Combined alpha and beta blockers

Recent experience indicates that combined nonselective beta and alpha blockade with carvedilol is well tolerated in patients with COPD who do not have reversible airway obstruction. Alpha-adrenergic blockade may promote mild bronchodilation that offsets nonselective beta blockade-induced bronchoconstriction in patients with obstructive airway disease.^{50,51}

The effect of carvedilol on lung function was compared to the selective beta blockers metoprolol and bisoprolol in

35 patients with COPD and heart failure. FEV₁ was lowest with carvedilol and highest with bisoprolol (carvedilol 1.85 [95% confidence interval (CI): 1.67–2.03]; metoprolol 1.94 [95% CI: 1.73–2.14]; bisoprolol 2.0 [95% CI: 1.79–2.22]), although the 6-minute walk distance was not different.⁵² On the other hand, in a report of 14 patients with COPD treated with carvedilol 25 mg twice daily for heart failure, no changes were noted in FEV₁, vital capacity, or peak oxygen consumption with exercise.⁵³ Similarly, labetalol up to 1200 mg/day caused no significant changes in FEV₁ or forced expiratory flow (FEF 25%–75%) in a small series of eleven patients with COPD and hypertension.⁵⁴

All current evidence on combined nonselective beta and alpha blockade is observational or based on small studies. It is not yet clear whether this class of beta blockers is better tolerated due to the alpha blockade or merely because the nonselective beta blockers themselves are well tolerated. In view of the fact that not enough is known about their effect on respiratory function, nonselective agents that include alpha-adrenergic blockade should probably not be considered as an antihypertensive in a patient with COPD.⁵⁵ However, carvedilol can be considered if such a patient has coexisting heart failure. The evidence is weaker for use of carvedilol and labetalol in patients with COPD than it is for use of cardioselective agents or beta blockers with intrinsic sympathomimetic activity.

Angiotensin-converting enzyme (ACE) inhibitors

The most common side effect of therapy with ACE inhibitors is cough, which develops in 5%–20% of patients.⁵⁶ The cough is typically described as dry, irritating, and persistent, but rarely productive. The possibility that this cough may represent an asthma equivalent has been suggested by the demonstration of bronchial hyperresponsiveness in some affected patients, but this has not been a consistent finding.^{57,58}

On the other hand, one study found that prior use of ACE inhibitors was associated with decreased mortality in older COPD patients hospitalized for exacerbation.⁵⁹ There is also some emerging evidence that ACE inhibition may have a beneficial effect on skeletal muscle function and cardiovascular comorbidity in COPD patients.⁶⁰ There are some indications that increased renin–angiotensin–system activity may contribute to the pathogenesis and progression of COPD. A small study from Japan showed that captopril, at a dose of 25 mg, was associated with lower exertional

pulmonary artery pressure, lower pulmonary vascular resistance, higher mixed venous oxygen saturation, and lower lactate levels in selected COPD patients.⁶¹

At present, and based on the available evidence, ACE inhibitors should probably not be used as first-line antihypertensive therapy in patients with COPD. However, these agents are certainly not contraindicated in these disorders as long as the clinician is aware of the relatively uncommon complication of worsening airflow obstruction. When it is desirable to block the renin–angiotensin system, administration of an angiotensin II antagonist may be a better alternative because ACE inhibitor treatment may cause harm.

Angiotensin II antagonists

Angiotensin II antagonists do not appear to induce cough. Furthermore, among patients with symptomatic asthma, one study found no increase in bronchial hyperreactivity with their use.⁶² In a study from Germany, angiotensin II antagonists were well tolerated in patients with stage III and IV COPD, although they did not improve respiratory muscle strength or exercise capacity as had been anticipated.⁶³ Analysis of a Canadian database showed that angiotensin II antagonists improved both cardiovascular and pulmonary outcomes, especially when combined with statins.⁶⁴ Therefore, based on the relatively limited data available, it appears to be safe to use these agents to treat hypertension in patients with COPD.

Calcium channel blockers: non-dihydropyridines

The non-dihydropyridine calcium channel blockers are negative chronotropes, inotropes, and dromotropes. They should be used with caution in patients with heart failure and in combination with medications that produce similar hemodynamic effects. Therefore, these agents tend to be more commonly given for rate control in patients with atrial fibrillation or for control of angina than for isolated hypertension. Regardless, they can be used safely in patients with COPD.

Calcium channel blockers: dihydropyridines

Initially, the dihydropyridine calcium channel blockers were thought to be potentially harmful in patients with COPD by worsening ventilation–perfusion matching and increasing hypoxemia.⁶⁵ A subsequent study confirmed a very mild

worsening of hypoxemia, but this was more than offset by an improvement in central hemodynamics.⁶⁶

These drugs have also been shown to be excellent agents for the treatment of hypertension in patients with asthma. They have the theoretical advantages of opposing muscle contraction in tracheobronchial smooth muscle and possibly reinforcing the bronchodilator effect of beta agonists. A number of studies have shown modest improvement or no significant clinical benefit of calcium antagonists in asthma.^{67–69} Based on all of the above, the dihydropyridine calcium channel blockers appear to be excellent agents for the treatment of hypertension in patients with COPD.

Alpha-1 blockers

A megastudy of terazosin showed that it maintained its antihypertensive efficacy and was well tolerated by patients with COPD.⁷⁰ Similarly, a study from Scotland concluded that doxazosin is an effective oral antihypertensive drug, which did not exacerbate preexisting airflow limitation in patients with COPD.⁷¹ Based on the above, it would appear that there are no specific concerns regarding the use of alpha-1 blockers as antihypertensives in patients with COPD. However, alpha-1 blockers are not front-line drugs for the treatment of hypertension.

Central alpha-2 agonists and other centrally acting drugs

Clonidine and other alpha-2 receptor agonists like methyldopa should be used with caution in asthmatics. While these agents do not change baseline air flow in asthmatics, they have been shown to increase bronchial reactivity to inhaled histamine.⁷²

There is no safety data available regarding the use of these drugs in patients with COPD. However, clonidine has been used as a second-line agent for smoking cessation and so may be able to play a dual role in active smokers with hypertension and COPD.⁷³

Direct vasodilators

There is little specific information available regarding the use of direct vasodilators such as hydralazine in COPD. However, if an asthma-like reaction occurs with these drugs, one should always consider the possibility that the tartrazine dye within the drug preparation may be the culprit. In a small study, hydralazine was shown to increase minute ventilation, alveolar ventilation, and arterial partial

pressure of oxygen when administered to patients with COPD.⁷⁴ Based on the limited literature available, it appears that there are no specific safety concerns regarding the use of direct vasodilators as antihypertensives in patients with COPD.

Combination drugs

Most patients with hypertension require more than one antihypertensive drug to provide adequate hypertensive control.⁷⁵ Table 2 provides a list of the commonly used combination drugs for hypertension. A recent study by Herrin et al concluded that, in patients with hypertension and COPD requiring two antihypertensive agents, combination therapy that included a thiazide diuretic was associated with a significantly lower risk of hospitalization for CHF in patients without a prior history of CHF.¹⁹ There is also evidence that giving two or more drugs in fixed-dose combinations improves adherence and reduces costs compared to single-pill formulations.

Summary

Although hypertension and COPD are commonly seen in the same patients, especially in the elderly, there is relatively little or poor data regarding the use of many antihypertensive drugs in such patients. We have summarized the information that is currently available about these drugs in this review, and Table 3 is an attempt to provide some recommendations regarding their use in patients with hypertension and COPD. If hypertension is the only indication for using these drugs, then, based on a review of the currently available data, dihydropyridine calcium channel blockers and angiotensin II antagonists appear to be the best initial choices, although there are limited data on the use of dihydropyridine calcium

Table 2 Possible combination drugs for hypertension

Combination type	Examples
ACE inhibitors and calcium channel blockers	Amlodipine–benazepril, enalapril–felodipine
ACE inhibitors and diuretics	Lisinopril–hydrochlorothiazide
Angiotensin II antagonists and diuretics	Losartan–hydrochlorothiazide
Beta blockers and diuretics	Bisoprolol–hydrochlorothiazide
Centrally acting drug and diuretic	Methyldopa–hydrochlorothiazide
Diuretic and diuretic	Triamterene–hydrochlorothiazide

Abbreviation: ACE, angiotensin-converting enzyme.

Table 3 Summary of comments and recommendations regarding use of antihypertensive agents in patients with chronic obstructive pulmonary disease

Class	Comments/recommendations
Thiazide diuretics	Low doses are probably effective and safe.
Loop diuretics	Should not be used as an antihypertensive except in patients with advanced renal disease who do not respond to thiazide diuretics.
Potassium-sparing diuretics	Not a first-line agent. Limited data but no specific contraindications.
Aldosterone receptor blockers	Not a first-line agent. Limited data but no specific contraindications.
Beta blockers	Some conflicting data, but cumulative evidence supports safety. Historical underutilization probably not justified. Probably not a first-line agent if hypertension is the only indication. Propranolol and atenolol should not be used.
Beta blockers with intrinsic sympathomimetic activity	Limited data but probably similar to beta blockers.
Combined alpha and beta blockers	Should probably not be used if hypertension is the only indication.
Angiotensin-converting enzyme inhibitors	Should not be used as a first-line agent because of the associated cough.
Angiotensin II antagonists	Limited data but no safety concerns.
Calcium channel blockers: non-dihydropyridines	Can be used safely.
Calcium channel blockers: dihydropyridines	First-line agent.
Alpha-1 blockers	No safety concerns.
Central alpha-2 agonists and other centrally acting drugs	Limited data but there may be some safety concerns.
Direct vasodilators	Limited data but no safety concerns.

channel blockers in the treatment of hypertension in patients with COPD. Low-dose thiazide diuretics can also be considered. However, more studies are clearly needed in order to provide greater clarity about the large number of antihypertensive drugs available to physicians today treating patients with both these conditions.^{76–78}

Disclosure

The authors report no conflicts of interest in this work.

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