Renin–angiotensin system blockade: a novel therapeutic approach in chronic obstructive pulmonary disease

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ABSTRACT

ACE (angiotensin-converting enzyme) inhibitors and ARBs (angiotensin II receptor blockers) are already widely used for the treatment and prevention of cardiovascular disease and their potential role in other disease states has become increasingly recognized. COPD (chronic obstructive pulmonary disease) is characterized by pathological inflammatory processes involving the lung parenchyma, airways and vascular bed. The aim of the present review is to outline the role of the RAS (renin–angiotensin system) in the pathogenesis of COPD, including reference to results from fibrotic lung conditions and pulmonary hypertension. The review will, in particular, address the emerging evidence that ACE inhibition could have a beneficial effect on skeletal muscle function and cardiovascular co-morbidity in COPD patients. The evidence to support the effect of RAS blockade as a novel therapeutic approach in COPD will be discussed.

INTRODUCTION

COPD (chronic obstructive pulmonary disease) encompasses a range of pathologies, including chronic bronchitis, bronchiolitis, emphysema and pulmonary vascular destruction. It is characterized by airflow limitation associated with an abnormal inflammatory response in the lungs to inhalation of noxious substances, including tobacco smoke and, in the developing world, biomass smoke. The airflow obstruction is not fully reversible and is usually progressive, causing breathlessness and limitation of daily activities. It is estimated that over 210 million people worldwide suffer from COPD, and WHO (World Health Organization) projections suggest that COPD will be the fifth leading cause of disability [1] and third most common cause of...
death worldwide by 2020 [2]. COPD is an umbrella term incorporating a number of distinct clinical phenotypes, including frequent exacerbators and emphysematous or airways predominant groups [3–5]. However, although COPD has been considered primarily in terms of its effects on lung parenchyma and airways, there is increasing evidence to suggest a multisystem disorder encompassing skeletal muscle dysfunction, cardiac disease, neurological impairment, osteoporosis and systemic inflammation [6–9]. An important illustration of this is the role of pulmonary rehabilitation, which improves health status and exercise capacity without influencing lung function in COPD patients [10,11]. Recent research implicates the RAS (renin–angiotensin system) in the pathogenesis of both pulmonary and extra-pulmonary manifestations of COPD. The present review outlines the evidence for RAS blockade as a potential novel therapeutic strategy in COPD and, in particular, explores the role of ACE (angiotensin-converting enzyme) inhibition in the treatment of the skeletal muscle and cardiovascular co-morbidities of the disease.

The RAS

A local RAS exists in many human tissues, including lung and skeletal muscle. ACE is a zinc metallopeptidase present in the circulating plasma and highly expressed in lung capillary blood vessels [12]. AngII (angiotensin II) receptors are also expressed in the lungs [13], and ACE expression is evident on the membrane of vascular endothelial cells in muscle [14]. The RAS, as illustrated in Figure 1, is mediated initially by renin which cleaves angiotensinogen to produce AngI (angiotensin I). ACE catalyses the conversion of AngI into AngII and the breakdown of vasoactive kinins. AngII stimulates sympathetic nerve terminals to release the vasoconstrictor noradrenaline (norepinephrine) and facilitates aldosterone secretion from the adrenal cortex, via AT1 receptors (AngII type 1 receptors). This enables ACE to exert an influence on salt/water retention and vascular tone. In addition, these effects are enhanced by the degradation of bradykinin, which, when active, can mediate the release of the vasodilator NO and prostaglandins [15]. AT2 receptors (AngII type 2 receptors) oppose some of AT1-receptor-mediated vasoconstrictor effects through local vasodilation. The human lung expresses both AngII receptor subtypes, whereas only the AT1 receptor is expressed in adult skeletal muscle [16]. The human ACE gene contains a functional polymorphism based on the presence [I (insertion)] or absence [D (deletion)] of a 287 base pair sequence in intron 16 on chromosome 17. Therefore three genotypes exist: II, ID and DD, and these have an approximate distribution of 25, 50 and 25 % respectively in a Caucasian population [17]. ACE activity is highest in the subjects homozygous for the D allele (DD), intermediate in the ID group and lowest in subjects homozygous for the I allele (II).

Figure 1 An overview of the RAS
This Figure was adapted from Christy S. Carter, Graziano Onder, Stephen B. Kritchevsky, Marco Pahor, Angiotensin-Converting Enzyme Inhibition Intervention in Elderly Persons: Effects on Body Composition and Physical Performance, Journals of Gerontology - Series A: Biological Science and Medical Sciences, 2005, 60, 11, p1437-46, by permission of Oxford University Press.
ACE inhibitors were initially developed from investigation of the venom of a Brazilian pit viper (*Bothrops jararaca*) in the late 1960s [18]. The Nobel Laureate Sir John Vane found that the venom’s effects, including extensive bleeding and a sudden fall in blood pressure, occurred through inhibition of ACE activity. From this discovery, an oral form of ACE inhibitor, captopril, was developed for the treatment of hypertension. This initial source of ACE inhibition highlights the actions of AngII as a vasoconstrictor and growth factor to counteract bleeding and initiate vessel wall repair [19]. However, although the RAS plays a key role in the stress response, chronic activation of this system in humans is thought to influence cardiopulmonary disease. In particular, evidence of an increase in cardiac and peripheral sympathetic activation in COPD patients [20,21] and the interaction between this impaired autonomic control and the RAS termed ‘neurohumoral activation’ has led to its implication in the pathogenesis of COPD [22].

When considering RAS modulation it is important to note that the local generation of AngII is also mediated via ACE-independent pathways. In particular, serine proteases, such as chymase and cathepsin G, have the ability to convert AngI into AngII within tissue systems [23]. Therefore, although ACE inhibition holds benefits, particularly in relation to preventing the degradation of bradykinin, blockade of the AT1 receptor is another key target for intervention. In addition, the protease cathepsin D can be utilized in place of renin for tissue conversion of angiotensinogen [24], further highlighting the inherent complexities within the local angiotensin-generating systems.

**RAS AND COPD**

Chronic inflammation of the central and peripheral airways is recognized as a central feature of COPD associated with lung remodelling, parenchymal destruction and the development of emphysema [25]. The RAS is potentially implicated in the pathogenesis of COPD through its involvement in inducing pro-inflammatory mediators in the lung [26] (Figure 2). AngII stimulates the release of cytokines including IL (interleukin)-6, TNF (tumour necrosis factor)-α and MCP-1 (monocyte chemotactic protein-1) [27]. In particular, alveolar macrophage-derived MCP-1 has been shown to activate tissue mast cells in response to acute alveolar hypoxia thereby triggering systemic inflammation [28]. AngII also has an immunomodulatory effect on T-cell responses which mediate the lung tissue injury associated with COPD [29]. Wong et al. [30] have recently shown that alveolar type I cells produce pro-inflammatory cytokines and express components of the RAS as part of an innate immune response to lung injury. That study found that this cytokine response was mediated by AngII and was inhibited by losartan, an AT1 receptor antagonist. Interestingly, in COPD patients, Bullock et al. [31] found a 5–6-fold increase in the AT1 receptor/AT2 receptor ratio in regions of marked fibrosis surrounding bronchioles, which correlated with the reduction in FEV1 (forced expiratory volume in 1 s). This supports a role for AngII in inducing bronchial constriction via the AT1 receptor [32].

The RAS can also generate ROS (reactive oxygen species) via the AT1 receptor, promoting mitochondrial dysfunction [33], which contributes to the oxidative stress and impaired redox signalling observed in COPD [34] (Figure 3). Podowski et al. [35] have recently studied RAS inhibition in an emphysema mouse model and in lung biopsies from COPD patients [35]. Cigarette smoking induced alveolar emphysematous injury and airway epithelial hyperplasia were associated with enhanced signalling of TGF (transforming growth factor)-β, a downstream mediator of AT1 receptor activation. Losartan improved oxidative stress markers, metalloprotease activation and elastin remodelling through TGF-β inhibition. These findings support work by Raupach et al. [36], who investigated the effects of the ARB (AngII receptor blocker) irbesartan on an emphysema mouse model, finding benefits in histological emphysema severity, lung compliance and exercise capacity following treatment. Interestingly, the potential modulation of TGF-β signalling has also been highlighted by emerging evidence of its interaction with non-coding RNA molecules, microRNAs, in the lung tissue of patients with COPD [37]. These microRNAs reduce mRNA half-life and translation and may therefore influence both pulmonary and extrapulmonary manifestations of COPD; recent evidence has identified miR-1 (microRNA-1) expression to be associated with smoking history, FEV1, fat-free mass index and 6-min walk distance in COPD patients [38]. Further research is required to understand the role of these microRNAs.
Figure 3  Actions of the RAS in COPD
Lines ending with a perpendicular segment represent inhibitory pathways. MAPK, mitogen-activated protein kinase.

and their possible interaction with the RAS in the pathogenesis of the disease.

**RAS AND FIBROSIS**

Pulmonary fibrosis is relevant to the pathogenesis of COPD in two ways; first, fibrosis is a component of airway remodelling in COPD [39], and secondly, it is now well recognized that a proportion of COPD patients have a syndrome of CPFE (combined pulmonary fibrosis and emphysema) with distinct clinical features [40]. Much of the clinical and experimental data, however, come from the study of IPF (idiopathic pulmonary fibrosis). Evidence for involvement of the pulmonary RAS in lung fibrosis comes from studies of bronchoalveolar lavage fluid from patients with the condition, showing elevated ACE levels [41]. In lung biopsies taken from IPF patients, Li et al. [42] found an increased level of angiotensinogen protein and mRNA, which localized to areas of epithelial apoptosis and myofibroblast foci. Furthermore, Königshoff et al. [43] have identified the localization of both AT₁ and AT₂ receptors to interstitial fibroblasts in fibrotic human lung samples. In vitro studies have shown AngII to be pro-fibrotic, causing an up-regulation of collagen gene expression in human lung fibroblasts [44]. Wang et al. [45–47] have demonstrated that activation of apoptosis, thought to be a critical event in developing fibrosis, via Fas [45,46] and TNF-α [47] is AngII-dependent. However, although there is evidence of a protective effect of ACE inhibition in animal models of pulmonary fibrosis [48], in a retrospective analysis of the effect of ACE inhibitors and statins on survival in 478 patients with IPF, Nadrous et al. [49] showed there was no difference in survival between those taking ACE inhibitors, statins or both compared with neither. This may be explained by the influence of local AngII-generating systems acting independently of ACE, as described above.

Potential alternative targets within the angiotensin system have also been highlighted by research exploring modulation of the ACE2/Ang-(1–7) [angiotensin-(1–7)]/Mas axis [50] (Figure 4). ACE2, a homologue of ACE, produces Ang-(1–7) from AngII, which then acts at the Mas receptor to produce effects that are largely opposite to those mediated by the AT₁ receptor, thus forming a counter-regulatory axis of the RAS. In a recent study using an AEC (alveolar epithelial cell) model of fibrosis, pre-treatment with Ang-(1–7) inhibited AEC apoptosis through action at the Mas receptor [51]. Further work on this axis in COPD and fibrotic lung disease may therefore provide novel targets for therapy. In addition, Montes et al. [52] have recently identified that lung fibroblasts express renin, which is up-regulated in IPF. They found that increased expression of TGF-β1 in renin-stimulated fibroblasts was not attenuated by losartan or captopril [52]. Direct renin inhibitors are available, but a clinical trial in COPD or pulmonary fibrosis is yet to be conducted.

**RAS AND PH (PULMONARY HYPERTENSION)**

Disruption of the pulmonary vasculature with consequent ventilation perfusion mismatch is a cardinal feature of COPD. PH is defined as an increase in mPAP [mean PAP (pulmonary arterial pressure)] ≥25 mmHg
at rest and can be primary or secondary in origin [53]. PH secondary to COPD is a consequence of pulmonary vascular remodelling and endothelial dysfunction characterized by an increase in ROS, cytokines and pro-thrombotic mediators, all of which may be influenced by the RAS [54]. The prevalence of PH remains difficult to quantify in COPD patients due to a lack of systematic screening studies [55]. In a study of 4930 COPD patients listed for lung transplantation undergoing right heart catheterization, PH occurred in 30.4 % of this population, with pulmonary venous hypertension present in an additional 17.2 % of patients [56]. Evidence for a role of the RAS also comes from monocrotaline animal models of PH, where the increase in right-sided pressure, right ventricular hypertrophy and vascular remodelling was associated with increases in the mRNA levels of renin, ACE, angiotensinogen, AT1 receptors and pro-inflammatory cytokines [57]. Orte et al. [58] have also shown that, in a group of patients undergoing heart–lung transplant for primary or secondary PH, there was an increase in endothelial ACE expression in the intra-acinar arteries, suggesting that increased local AngII production contributes to PH. As with pulmonary fibrosis, there is evidence that the ACE2 axis also has an important role in PH. In vitro studies have shown that Ang-(1–7) down-regulates the vasoconstrictive and pro-fibrotic actions mediated by the AT1 receptor [59]. In addition, evidence from the right ventricle of explanted hearts from primary PH patients undergoing transplantation suggests a protective up-regulation of ACE2 activity [60]. Animal models have supported this hypothesis with the overexpression of ACE2 found to prevent and reverse the increase in right ventricular systolic pressure [61]. This raises the possibility of targeting ACE2 as a therapy in COPD patients [62]; however, clearly caution is needed when extrapolating the findings from primary PH to that seen in COPD.

**RAS AND SKELETAL MUSCLE DYSFUNCTION**

Skeletal muscle dysfunction is a key systemic comorbidity in COPD. The weakness observed in COPD patients is most pronounced in the locomotor muscles [63,64] and at biopsy a classic disuse pattern of change is observed in the quadriceps with a shift towards a preponderance of ‘fast’ type II fibres [65,66], reduced capillarity [67] and oxidative capacity [68]. Importantly, reduced quadriceps strength in COPD is associated with reduced exercise capacity [69], impaired health status [70], increased healthcare use [71] and mortality independent of airflow obstruction [72]. Quadriceps weakness has also recently been shown to be a feature of early disease [73], and its development is likely to be multifactorial with inflammation and oxidative stress [74], thought to interact with physical inactivity [75,76]. IGF (insulin-like growth factor)-1 produced in response to GH (growth hormone), testosterone and mechanical stretch is thought to have a key role [77]. IGF-1 acts through the PI3K (phosphoinositide 3-kinase)/Akt pathway to inactivate FoxO (forkhead box O) transcription factors, thereby inhibiting the expression of two muscle-specific ubiquitin ligases, the atrogenes atrogin-1 and MuRF-1 (muscle RING-finger protein-1), to prevent muscle catabolism [78] (Figure 5). IGF-1 also activates mTOR (mammalian target of rapamycin) via PI3K/Akt signalling to promote muscle anabolism. Through modulation of this pathway, as well as the induction of pro-inflammatory cytokines and ROS species, AngII has potential relevance in the pathogenesis of muscle dysfunction in COPD. The evidence for an influence of the RAS on muscle atrophy in COPD comes from animal models, where infusion of AngII causes cachexia via an inhibitory effect on the IGF-1 system and stimulation of the ubiquitin–proteasome proteolytic pathway [79]. It has been shown that IGF-1 levels are reduced in COPD patients in the stable state compared with healthy controls [77]. Furthermore, in COPD patients undergoing pulmonary rehabilitation, increases in exercise capacity and fibre size are associated with the up-regulation of IGF-1 and a splice variant of IGF-1, MGF (mechano-growth factor) [80,81]. MGF is specifically produced in response to mechanical stretch and leads to muscle hypertrophy and satellite cell activation [82]. Recent work by Rezk et al. [83] in a mouse model has shown an increase in IGF-1 expression 7 days after AngII-induced diaphragm muscle atrophy, suggesting a potential involvement of IGF-1 in skeletal muscle regeneration following RAS-related injury.

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**Figure 4** The ACE 2 axis

Lines ending with a perpendicular segment represents an inhibitory pathway. This figure was reprinted from Current Opinion in Pharmacology, 6(3), Kuba, K., Imai, Y. and Penninger, J. M. Angiotensin-converting enzyme 2 in lung diseases, Pages 271–276, Copyright (2006), with permission from Elsevier.
Figure 5  Actions of AngII on skeletal muscle IGF and ubiquitin–proteasome signalling in COPD

Lines ending with a perpendicular segment represent inhibitory pathways. GSK3β, glycogen synthase kinase 3β; elf2B, eukaryotic initiation factor 2B; p70S6K, 70 kDa ribosomal S6 protein kinase; E4-BP1, eukaryotic initiation factor 4E-binding protein-1; PGC-1α, PPAR-γ co-activator-1α; TK, tyrosine kinase. This Figure was adapted from [142] with permission. © 2009 Biochemical Society.

Local IGF-1 expression also down-regulates NF-κB (nuclear factor κB) and pro-inflammatory cytokines, including TNF-α, IL-1B, HMGB-1 (high-mobility group protein-1) and macrophage MIF (migration inhibitory factor) [84]. NF-κB acts as a key downstream mediator of the inflammatory cytokine cascade, as well as being activated by other triggers including inactivity [85]. NF-κB is controlled via the IKK (inhibitor of NF-κB) complex and, in murine studies, targeted deletion of this complex was found to shift muscle fibre distribution towards a type I phenotype and improve muscle force [86]. AngII has been shown to induce muscle protein degradation via NF-κB [87] and, in addition, NF-κB has been associated with the overexpression of MuRF-1, leading to muscle atrophy [88]. As NF-κB activation occurs in the skeletal muscle of COPD patients with low body weight [89], this suggests a potential mechanism for RAS-related muscle atrophy.

PPARs (peroxisome-proliferator-activated receptors) may also have an important role in muscle atrophy in COPD [90], influencing skeletal muscle phenotype and angiogenesis [91]. These transcriptional co-factors mediate type II (anaerobic) to type I (aerobic) fibre shift and regulate mitochondrial activity, as well as muscle oxidative status [92]. Perindopril has been shown to protect against mitochondrial dysfunction and myopathy in skeletal muscle by preventing PPAR down-regulation [93], and this may represent an important target in COPD given that PPAR-δ protein content is decreased in the skeletal muscle of these patients [94]. In this context, the effects of RAS blockade have been studied in human skeletal muscle cells by investigating IGF-1R (IGF-1 receptor) phosphorylation following incubation with telmisartan, valsartan and lisinopril [95]. There was a 2-fold increase in phosphorylation with the ARBs and a 1.7-fold increase with ACE inhibition. The effects observed by AngII receptor blockade are likely to be mediated via activation of PPAR-γ, as IGF-1R phosphorylation was attenuated in the presence of a PPAR-γ antagonist. In particular, telmisartan enhances skeletal muscle endurance through activation of the PPAR-δ pathway [96] and has recently been proposed as a metabolic modulator in the context of performance-enhancing drugs in sport [97].

TGF-β signalling has also emerged as a potential mechanism for the RAS-mediated effects on muscle function. A key study by Cohn et al. [98] identified that elevated TGF-β activity led to a failure of muscle regeneration in fibrillin-1-deficient and dystrophin-deficient mice. They found that systemic antagonism of TGF-β using losartan restored muscle structure and function in both mouse models. This has particular relevance to TGF-β-associated muscle dysfunction in COPD, since myostatin, a negative regulator of skeletal muscle mass and member of the TGF-β family, has been shown to have a higher mRNA expression in the vastus lateralis of weak COPD subjects compared with controls [99] and exhibits an inverse relationship with quadriceps strength [100]. Myostatin may therefore represent a potential therapeutic target in COPD patients and, in this context, a myostatin antibody has already been trialled in patients with muscular dystrophy with some limited efficacy [101].

Cozzoli et al. [102] have also recently shown that enalapril treatment reduced AngII-dependent inflammation and oxidative-stress-related muscle damage in a dystrophic mouse model. Unlike AngII receptor blockade, ACE-specific inhibition maintains bradykinin production which, via the actions of NO and prostacyclin, can counteract AngII-mediated effects in skeletal muscle [103]. Bradykinin promotes the downstream signalling of insulin-dependent GLUT-4 (glucose transporter-4) in skeletal muscle, through the actions of NO [104]. NO also has a key role in inhibiting ROS, with fibre-type-specific NO shown to protect oxidative myofibres against cachectic stimuli through antioxidant gene expression [105]. Importantly, bradykinin is also synthesized in skeletal muscle during exercise [106] and therefore may influence responses to training. The potential synergistic effect of ACE inhibition with exercise was highlighted in a recent study using a rodent model to assess the effects of exercise training, perindopril or both interventions together over a 6-month period [107]. That study found that the combination treatment increased type I fibre type percentage in the gastrocnemius muscle when compared with exercise training alone [107]. An increase
in capillary density in the soleus and gastrocnemius muscles was also shown with the addition of ACE inhibition to exercise training, suggesting that perindopril may help promote the adaptive changes in response to exercise.

**ACE I/D POLYMORPHISM IN COPD**

A number of clinical studies have investigated a role for ACE expression in COPD by stratifying patients by ACE polymorphism. Busquets et al. [108] studied the distribution of the ACE polymorphism in 151 male smokers. They found that the DD genotype was more prevalent in smokers who developed COPD, being associated with a 2-fold increase in the risk for COPD. These findings provide a genetic link to support the existing evidence that ACE activity is both elevated in COPD [109] and is associated with lung function impairment [110]. Kanazawa et al. [111] performed right heart catheterization to assess the pulmonary vascular response to exercise challenge in COPD patients stratified by ACE genotype. They found that the DD genotype was associated with increased PAP and PVR (pulmonary vascular resistance) when compared with the II genotype group. In a separate study, COPD patients with a DD genotype had a reduced ratio of the change in oxygen delivery to increase in $\dot{V}_{O_2}$ (oxygen consumption) during exercise [112], suggesting an impairment in peripheral tissue oxygenation. The ACE polymorphism may also be related to low-grade systemic inflammation in COPD; a study of 72 stable COPD patients had an increase in serum high-sensitivity CRP (C-reactive protein) across genotypes DD > ID > II [113], suggesting that the RAS may contribute to the inflammatory response observed in COPD, as discussed above.

The ACE polymorphism also influences muscle phenotype, with greater endurance observed in patients homozygous for I allele (II) [114,115], and a higher proportion of type I fibres associated with this group [116]. In contrast, a power-oriented muscle phenotype is seen in subjects with a DD genotype [117,118], who interestingly also exhibit greater bradykinin degradation in comparison with the II genotype [119].

A recent study of 100 healthy older Caucasian males investigated the association between skeletal muscle strength, serum ACE activity and ACE polymorphisms [120]. Serum ACE activity was negatively associated with muscle strength, but, in this study population, no association was observed between ACE polymorphisms and muscle function. However, variations in the ACE genotype have been shown to influence quadriceps strength in COPD patients [121], suggesting a possible interaction between environmental factors and genetic predisposition. In a study of 103 stable COPD outpatients, presence of the D allele of the ACE gene polymorphism was associated with increased quadriceps strength, which was not observed in the control group. $B{K}_2R$ (bradykinin type 2 receptor) polymorphisms also influence quadriceps muscle strength in COPD with patients exhibiting the +9/+9 homozygous genotype, associated with lower $B{K}_2R$ expression, having a reduced fat-free mass and strength [122]. Of note, the ACE polymorphisms have also been shown to interact with the effect of vitamin D receptor genotypes on quadriceps strength in COPD [123], highlighting the potential complexity of the influence of genetic susceptibility in the muscle phenotype of these patients.

**RAS INHIBITION: INTERVENTIONAL TRIALS IN COPD**

A number of interventional trials have investigated the effects of RAS inhibition on COPD patients. A randomized double-blind cross-over trial studied the effects of captopril in 36 COPD patients using right heart catheterization and cycle exercise testing [124]. That study found that, in the treatment group, patients with the ID or II genotype had an improvement in mPAP and PVR after the cycle ergometric exercise. This suggests a treatment response in COPD that may be dependent on the ACE genotype. A smaller study in nine COPD patients with PH also found a reduction in mPAP and resistance following captopril administration [125]. However, in contrast with this, some studies have not found an effect of ACE inhibition on pulmonary haemodynamics [126], and Morrell et al. [127] were unable to show any beneficial effect of losartan in COPD patients with established PH. These contrasting results are most likely related to the small subject numbers studied, particularly given the known heterogeneity of the COPD population. Further larger trials and meta-analyses are therefore required to establish whether a true treatment effect on PAP exists.

More recently, a double-blind placebo-controlled study by Di Marco et al. [128] evaluated the effects of 4 weeks of treatment with enalapril on exercise performance in 21 COPD patients. Enalapril did not have an effect on the ventilatory response to exercise [$\dot{V}_e / \dot{V}_{CO_2}$ (expired minute ventilation/carbon dioxide output) slope] or on peak $\dot{V}_{O_2}$ . However, there was a significant improvement in oxygen pulse and peak work rate in the treatment group compared with placebo, suggesting an improvement in cardiopulmonary efficiency in COPD. ACE genotype did not significantly affect patient response to treatment. Andreas et al. [129] conducted a randomized placebo-controlled trial assessing the effect of 4 months of treatment with the ARB irbesartan in 60 COPD patients, finding a reduction in total lung capacity in the treatment group. Interestingly, they also observed a 10% increase in
quadriiceps strength in the treatment group. This was not statistically significant, but the study had not been powered for this end point and the patients were not stratified by ACE genotype or strength.

**CARDIOVASCULAR CO-MORBIDITY IN COPD**

Cardiovascular disease is now recognized as a key co-morbidity in COPD with a significant impact on mortality [9]. Epidemiological evidence suggests that more than 40% of COPD patients have concomitant cardiac disease, with chronic heart failure being the most common [130]. Indeed, the increased risk of ischaemic heart disease [131], subclinical left ventricular dysfunction [132] and elevated right ventricular pressures [133] in COPD have led to the suggestion that a more aggressive approach to the cardiovascular assessment and treatment of these patients may be justified [134–136]. The importance of cardiac involvement has recently been highlighted by the identification of troponin T [137] and NT-BNP (N-terminal pro-B-type natriuretic peptide) [138] as biomarkers in predicting risk of death for patients hospitalized with an exacerbation of COPD. In addition, low-grade systemic inflammation in the form of elevated CRP has been associated with an increased risk of cardiac ischaemia based on ECG scoring in moderate-to-severe COPD [139]. In this context, the potential mortality benefit of ACE inhibition has been assessed in a large retrospective study in elderly patients hospitalized for a COPD exacerbation [140]. The study identified that ACE inhibitor or ARB use, when controlling for demographics, co-morbidities and other medication, was significantly associated with a decreased 90-day mortality following their COPD hospital presentation [odds ratio, 0.55 (95% confidence interval, 0.45–0.66)]. These findings supports previous work by Mancini et al. [141], who performed a nested case-control study incorporating 946 COPD patients divided into two retrospective cohorts based on cardiac risk profile. They found that a combination of statin and ACE inhibitor or ARB was associated with a reduction in COPD hospitalization and mortality in both high- and low-cardiovascular-risk groups [141]. A greater understanding of the potential dual cardiopulmonary actions behind this effect will help to evaluate the role of these interventions in COPD disease modification.

**CONCLUSIONS**

In the present review we have highlighted the growing evidence for a role of the RAS in COPD. The importance of targeting systemic co-morbidities which may be under the influence of this system has been discussed, with particular focus on evidence to support direct pulmonary, skeletal muscle and cardiovascular benefits from ACE inhibition in COPD. However, further work is needed to establish the impact of RAS blockade as a novel treatment strategy in these patients with particular focus on whether an approach targeting the pulmonary disease, cardiac co-morbidity or addressing cardiac risk factors more widely holds greatest benefit. It is likely that only large randomized clinical trials, similar to those seen in cardiac populations, will enable us to elucidate the true therapeutic and survival benefits of this intervention.

**REFERENCES**


