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The Impact of ACE Inhibitors and Angiotensin Receptor Blockers on Aerobic Capacity and $VO2$ Max in Patients Undergoing Endurance Training

Mateusz Kowalski
0009-0005-1826-4148
matikoowalski@gmail.com
Medical University of Lodz
al. Kościuszki 4, 90-419 Łódź

Michał Rucki
0009-0002-5220-3072
mich.ruck@op.pl
Provincial Polyclinical Hospital in Plock of Marcina Kacprzaka, Poland
Medyczna 19, 09-400 Plock, Poland

Nikodem Cieleban
0009-0007-6402-1854
ncieleban00@gmail.com
Pabianice Medical Centre (PCM)
68 Jana Pawła II St., 95-200 Pabianice, Poland

Aleksandra Maria Rucka
0009-0000-8395-6603
olkaaa.r1579@gmail.com
Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin, Poland

Magdalena Modliborska
0009-0008-0791-9913
magda.modliborska99@gmail.com
Provincial Polyclinical Hospital in Plock of Marcina Kacprzaka, Poland
Medyczna 19, 09-400 Plock, Poland

Corresponding Author: Mateusz Kowalski, matikoowalski@gmail.com

Abstract

Background. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are foundational pharmacological therapies for hypertension and cardiovascular diseases. However, their potential interference with physiological adaptations to endurance training, particularly maximal aerobic capacity ($VO2$ max), remains a critical concern for clinicians and athletes.

Aim. This review aims to synthesize the current evidence regarding the impact of ACEi and ARB therapy on $VO2$ max, hematological parameters, and cardiac remodeling in patients and healthy individuals undergoing structured endurance training.

Material and methods. A narrative review was conducted using PubMed, Google Scholar, and the archives of the Journal of Education, Health and Sport and Quality in Sport. Search terms included "ACE inhibitors," "angiotensin receptor blockers," "VO2 max," and "endurance training." Inclusion criteria focused on peer-reviewed articles published between 2015 and 2025, emphasizing human clinical trials and systematic reviews.

Results. Evidence suggests that while chronic RAAS inhibition does not significantly attenuate relative $VO2$ max gains in hypertensive populations or those with metabolic syndrome, it may compromise specific physiological determinants. Notably, ACEi treatment has been associated with a reduction in total hemoglobin mass expansion and a blunting of lean mass accrual. Furthermore, sex-specific responses indicate that women may experience a more pronounced inhibition of aerobic adaptations compared to men when using standard ARB dosages.

Conclusions. ACEi and ARBs are generally compatible with aerobic exercise; however, their impact on hematological and morphological adaptations requires careful consideration, especially in high-performance or female cohorts. Exercise remains a vital synergistic co-therapy for managing hypertension alongside these medications.

Keywords: ACE inhibitors, angiotensin receptor blockers, $VO2$ max, aerobic capacity, endurance training, hypertension, cardiorespiratory fitness

Introduction

The global burden of hypertension and metabolic dysfunction represents one of the most significant public health challenges of the 21st century, contributing to a substantial rise in cardiovascular morbidity and mortality.[1] As populations age and sedentary lifestyles become more prevalent, the integration of pharmacological interventions with lifestyle modifications—most notably structured physical activity—has become the cornerstone of preventive medicine.[3] Among the diverse classes of antihypertensive medications, those targeting the renin-angiotensin-aldosterone system (RAAS), specifically angiotensin-converting enzyme (ACE)

inhibitors and angiotensin receptor blockers (ARBs), are most frequently prescribed due to their proven efficacy in reducing blood pressure and providing target organ protection.[6]

Concurrently, aerobic exercise is recognized as a powerful non-pharmacological therapy capable of eliciting systemic physiological changes that mirror or even exceed those of drug therapy.[6] Regular aerobic training enhances cardiorespiratory fitness (CRF), measured as maximal oxygen consumption ($VO2$ max), which serves as a definitive gold standard for assessing cardiovascular health and predicting all-cause mortality.[10] However, a complex clinical paradox arises when these two interventions are combined. The RAAS system is not merely a regulator of blood pressure; it is fundamentally involved in the adaptive pathways of the heart, skeletal muscle, and blood-forming organs.[6] Angiotensin II, the primary effector peptide of the RAAS, stimulates erythropoiesis, modulates myocardial remodeling, and influences skeletal muscle metabolism.[8]

Consequently, there is growing scientific interest in whether the chronic use of ACEi and ARBs might inadvertently "blunt" the very adaptations that endurance training is intended to produce. If RAAS inhibition reduces the production of erythropoietin or limits the expansion of stroke volume, the ultimate ceiling for $VO2$ max improvement might be lowered.[13] This is particularly relevant for athletes, elderly patients aiming to improve functional status, and those recovering from chronic conditions such as COVID-19 or chronic kidney disease (CKD), where aerobic capacity is a primary determinant of quality of life and survival.[2]

This narrative scientific review explores the multi-faceted relationship between RAAS inhibition and aerobic adaptation. It examines the molecular mechanisms of action of ACEi and ARBs, their effects on the cardiovascular and hematological systems during training, and the emerging evidence of sex-specific and genotype-dependent responses. By synthesizing data from both historical landmarks and modern clinical trials, this paper provides a comprehensive overview of how these foundational medications interact with the human body's response to endurance training.

2. Material and methods

The methodology for this narrative review involved a comprehensive search of electronic databases to identify relevant literature concerning the interaction between RAAS-blocking medications and endurance exercise. The primary databases utilized were PubMed/MEDLINE and Google Scholar, with a specific emphasis on sourcing recent publications from the Journal of Education, Health and Sport (JEHS) and Quality in Sport (QS) to ensure high-quality, peer-reviewed Polish and international perspectives were included.

The search strategy employed combinations of several key terms and Boolean operators: ("angiotensin-converting enzyme inhibitors" OR "ACE inhibitors" OR "ACEi") AND ("angiotensin receptor blockers" OR "ARBs" OR "sartans") AND ("VO2 max" OR "aerobic capacity" OR "cardiorespiratory fitness") AND ("endurance training" OR "aerobic exercise" OR "high-intensity interval training"). The time range for the search was primarily limited to the last ten years (2015–2025) to capture the most recent advancements and meta-analyses, although seminal papers providing essential mechanistic context (e.g., Brown and Vaughan, 1998) were also included.

Inclusion criteria were as follows:

1. Original research articles, randomized controlled trials (RCTs), and systematic reviews.
2. Studies involving human participants, including healthy volunteers and clinical populations (hypertension, metabolic syndrome, heart failure, CKD).
3. Publications focusing on the physiological adaptations to exercise training (minimum duration of 4 weeks).
4. English-language publications or those with comprehensive English abstracts.

Exclusion criteria included case reports, conference abstracts without full text, and studies where the effect of RAAS inhibitors could not be isolated from other antihypertensive classes (e.g., beta-blockers). A total of 18 primary sources were selected for inclusion, encompassing eight mandatory citations and ten additional peer-reviewed articles discovered during the literature search. Data extraction focused on $VO2$ max changes, blood pressure regulation, hematological parameters ($Hbmass$, EPO), and morphological adaptations (cardiac volumes, lean mass).

3. Results / State of Knowledge

3.1. Molecular Foundations: Mechanisms of ACEi and ARBs

The efficacy of ACE inhibitors and ARBs in clinical practice stems from their ability to modulate the RAAS, a system that maintains hemodynamic stability through vasoconstriction and fluid retention.[8] Angiotensin-converting enzyme (ACE), also known as kininase II, plays a dual role: it cleaves angiotensin I to form the potent vasoconstrictor angiotensin II and simultaneously degrades bradykinin, a vasodilatory and natriuretic peptide.[8]

ACE inhibitors function by blocking this enzyme, leading to a decrease in systemic vascular resistance without a concomitant increase in heart rate. The increase in bradykinin levels further

stimulates the release of nitric oxide and vasodilatory prostaglandins, which contributes to the BP-lowering effect but is also responsible for the characteristic dry cough associated with these drugs.[7] In contrast, ARBs work further downstream by competitively blocking the $AT1$ (angiotensin II type 1) receptor, which mediates the harmful effects of angiotensin II, such as oxidative stress and fibrosis.[7] Unlike ACEi, ARBs do not significantly impact bradykinin levels, often making them better tolerated by patients.[7]

Table 1. Pharmacological mechanisms and clinical characteristics of ACE inhibitors and angiotensin receptor blockers (ARBs)

Pharmacological Parameter	ACE Inhibitors (ACEi)	Angiotensin Receptor Blockers (ARBs)
Primary Target	Angiotensin-Converting Enzyme	$AT1$ Receptor
Secondary Target	Kininase II (Bradykinin degradation)	No direct effect on bradykinin
Effect on Ang II	Decreased production	Blockade of action
Major Side Effects	Cough (10-15%), angioedema	Dizziness, hyperkalemia
Vasodilatory Mediators	Nitric Oxide, Prostaglandins, Bradykinin	Nitric Oxide

Source: [7,8]

The clinical preference for these agents in patients with heart failure or diabetes is supported by evidence that they reduce mortality, myocardial infarction risk, and the progression of renal impairment.[19] Specifically, in heart failure, enalapril has been shown to improve ejection fraction and stroke volume, while ramipril is associated with lower all-cause mortality in many cohorts.[20]

3.2. Physiological Impact of Aerobic Exercise on Human Systems

Aerobic exercise is defined as physical activity that increases heart rate and oxygen consumption through the repetitive use of large muscle groups.[6] Regular engagement in such activities, including brisk walking, cycling, or swimming, initiates profound adaptations across multiple organ systems.[4]

Within the cardiovascular system, training enhances vagal tone and reduces resting sympathetic activity, leading to a lower resting heart rate and improved heart rate variability.[27] Structurally, it promotes the expansion of left ventricular volume and improves arterial compliance, which directly enhances the heart's ability to deliver oxygenated blood to working muscles.[1] On a metabolic level, aerobic training improves insulin sensitivity and mitochondrial efficiency, primarily through the upregulation of the GLUT-4 protein and the stimulation of mitochondrial biogenesis.[5]

According to the World Health Organization (WHO) and regional guidelines, adults should aim for 150–300 minutes of moderate-intensity or 75–150 minutes of vigorous-intensity aerobic exercise per week.[4] These guidelines are underscored by the observation that even modest increases in physical activity can significantly reduce the risk of hypertension, type 2 diabetes, and various forms of cancer.[9]

3.3. Interaction of RAAS Inhibition and Cardiorespiratory Fitness in Clinical Populations

The central question of whether ACEi or ARBs interfere with exercise-induced $VO2$ max gains has been addressed in several recent high-quality trials. In a prospective study by Labrador-Sanchez et al. (2026), the effect of chronic RAAS inhibition was evaluated in sedentary obese adults with metabolic syndrome undergoing a 16-week supervised HIIT program.[6]

The participants were divided into a medicated (AHM) group and a non-medicated control group. The primary outcomes included changes in $VO2$ max, resting blood pressure, and metabolic markers. The results demonstrated that both groups achieved significant and comparable improvements in cardiorespiratory fitness.[6]

Table 2. Effects of ACEi/ARB therapy versus control on cardiometabolic adaptations during high-intensity interval training (HIIT)

Training Metric	Medicated (ACEi/ARB)	Non-medicated Control	p-value (time x group)
Δ $VO2$ max ($mL/kg/min$**)**	$+3.9 \pm 2.1$	$+5.0 \pm 3.1$	> 0.05
Δ Mean Arterial Pressure ($mmHg$**)**	-4.2 ± 8.7	-6.5 ± 6.3	> 0.05
Δ Metabolic Syndrome Z-score	-0.22 ± 0.42	-0.30 ± 0.33	> 0.05

Source:[6]

These findings suggest that for the general hypertensive population with metabolic risk factors, chronic treatment with angiotensin antagonists does not restrain the beneficial effects of HIIT on cardiovascular function or $VO2$ max.[6] The magnitude of blood pressure reduction (approximately 3–8 mmHg in systolic BP) was consistent with expected aerobic training responses, regardless of medication status.

3.4. Hematological and Morphological Suppression: The Sjúrðarson Findings

While relative $VO2$ max gains may appear preserved in clinical cohorts, more precise physiological studies in healthy participants have revealed subtle but important suppressive effects of ACEi and ARBs on specific training adaptations. A randomized, double-blind, placebo-controlled trial investigated the effect of 8 weeks of high-intensity interval rowing in healthy middle-aged adults receiving either an ACE inhibitor or a placebo.[13]

The study found that while $VO2$ max and skeletal muscle endurance increased by approximately 13% and 74-82% respectively in both groups, the ACEi group exhibited a failure to achieve certain morphological and hematological expansions.[13]

Table 3. Hematological and morphological adaptations to endurance training in ACE inhibitor-treated versus placebo groups

Adaptive Parameter	Placebo + Training	ACEi + Training	Significant Difference
Total Hemoglobin Mass ($Hbmass$)	$+2\%$ (non-sig)	-3%	Yes ($p < 0.001$)
Lean Body Mass	$+3\%$	0%	Yes ($p < 0.001$)
Left Atrial Volume	$+14\%$	-9%	Yes ($p < 0.05$)

Source:[13]

The reduction in total $Hbmass$ in the ACEi group is particularly noteworthy, as hemoglobin is the primary carrier of oxygen in the blood.[13] This confirms that RAAS inhibition can counteract the exercise-induced expansion of red cell volume, likely by suppressing the erythropoietic effects of angiotensin II.[12] Furthermore, the lack of lean mass accrual in the ACEi group suggests that angiotensin II may play a role in the hypertrophic response of skeletal muscle to intense training stimuli.[13]

3.5. Sex Differences in Response to RAAS Blockade

Recent evidence has highlighted a significant sex-dimorphic response to RAAS inhibition during endurance training. A 2025 study published in *Cardiovascular Research*[12] examined how the ARB valsartan affected adaptations in healthy men and women.

The results were striking: in men, 8 weeks of training combined with AT1-blockade did not prevent increases in $VO2$ max or peak power output. In contrast, for women, the medication effectively abolished the aerobic benefits of training.

Table 4. Sex-specific effects of angiotensin receptor blockade on endurance training adaptations

Participant Group	Δ VO2 max (Placebo)	Δ VO2 max (ARB)	Effect of ARB
Men	Significant Increase	Significant Increase	No Interference
Women	Significant Increase	No Significant Increase	Complete Suppression

Source:[12]

Women in the ARB group also experienced a significant decrease in $Hbmass$ ($P = 0.002$), while no such decrease occurred in men or the female placebo group. Researchers hypothesized that this might be a dosage-related effect; since a fixed dose of 80 mg was used, women (who typically have lower body mass) received approximately 32% more medication per kilogram of body weight than men. This suggests that the threshold for pharmacological interference with aerobic adaptation may be lower in women, requiring more careful dose titration or class selection in female athletes and patients.

3.6. Genetic Influences: The ACE I/D Polymorphism

Individual variability in training responses and drug interactions is frequently tied to the ACE insertion/deletion (I/D) polymorphism.[34] The presence of the I-allele is associated with lower circulating and tissue ACE activity, which has been linked to elite endurance performance and enhanced vascular function.[36] Conversely, the D-allele is associated with higher enzyme levels and a greater potential for muscle hypertrophy and power performance.[13]

Clinical observations suggest that I/I homozygotes may experience more marked training-induced increases in endurance capacity.[13] However, pharmacological inhibition of ACE (mimicking the I/I genotype) does not necessarily enhance training response and may, as discussed previously, attenuate certain cardiac and hematological adaptations.[13] This highlights the "tissue-specific" nature of ACE activity, where systemic blockade by medication may not perfectly replicate the physiological advantages of the low-ACE genotype.[34]

3.7. Clinical Context: Chronic Kidney Disease and Heart Failure

The impact of RAAS inhibition on aerobic capacity is especially relevant in patients with comorbid conditions such as chronic kidney disease (CKD) and heart failure. CKD affects over 10% of the world's population and is strongly associated with hypertension and cardiovascular disease.[2] ACEi and ARBs are used in these patients to reduce proteinuria and slow the progression to end-stage renal disease.[38]

However, because these drugs can exacerbate renal dysfunction in specific vascular pathologies, their use requires careful monitoring of glomerular filtration rate (GFR).[38] In this population, personalized exercise programs have been shown to be safe and effective in improving muscle oxidative capacity and physical function, despite the challenges of managing anemia and renal health.[41]

In heart failure (HF), ACE inhibitors are a "CLASS IA" recommendation for reducing hospitalization and premature death.[20] While they might limit $Hbmass$ expansion in healthy subjects, in HF patients, they significantly improve exercise duration and NYHA functional class by enhancing cardiac output and reversing pathologic remodeling.[19] This suggests that the clinical benefits of improved hemodynamics far outweigh any potential blunting of peripheral training adaptations in diseased populations.

4. Discussion

The synthesis of available evidence regarding ACE inhibitors and ARBs in the context of endurance training reveals a complex regulatory landscape where pharmacological effects and physiological adaptations often tug in opposite directions. The overarching finding is that relative improvements in $VO2$ max are achievable and generally comparable in patients using these medications, particularly those starting from a sedentary or hypertensive baseline.[6] This is consistent with "Wilder's principle," which suggests that the magnitude of an intervention's response scales with the baseline level of dysfunction—meaning hypertensive individuals have "more to gain" from the BP-lowering and fitness-enhancing effects of exercise than healthy cohorts.

However, the more granular physiological data from healthy participants and female cohorts introduced a cautionary note. The consistent observation that ACE inhibitors and ARBs can suppress the exercise-induced expansion of hemoglobin mass and left atrial volume points to a potential "ceiling effect".[12] For an elite athlete, where oxygen delivery is the primary bottleneck for performance, a 3% reduction in $Hbmass$ could be the difference between victory and

defeat. The mechanism for this appears to be the disruption of the angiotensin II-erythropoietin axis, which is a critical pathway for hematological adaptation to endurance stress.

The sex-specific differences found in recent trials are perhaps the most provocative emerging theme. The total abolition of aerobic gains in women using valsartan suggests that the hormonal and pharmacokinetic environment in females may render them more susceptible to the inhibitory effects of RAAS blockade. Whether this is strictly a dose-per-kilogram issue or related to estrogen-RAAS interactions remains to be fully elucidated, but it underscores the need for "precision exercise medicine" where drug choices are tailored not only to a patient's blood pressure but also to their gender and athletic goals.[34]

Metabolic health also factors heavily into this discussion. Both aerobic exercise and ACE inhibitors have been shown to improve insulin sensitivity and mitochondrial function.[5] In aged populations, enalapril has even been linked to the mitigation of skeletal muscle fibrosis and oxidative stress.[43] This suggests that for many older adults, the combination of RAAS inhibition and training may provide a synergistic "anti-aging" effect on muscle quality, even if the absolute gains in $VO2$ max are slightly restrained.[30]

Finally, the role of exercise modality should not be overlooked. While aerobic training is the "gold standard" for lowering BP and improving $VO2$ max, resistance and isometric training provide complementary benefits for vascular elasticity and muscle strength.[9] Given that ACEi might blunt lean mass accrual during endurance training, the inclusion of a dedicated resistance training component may be necessary to maximize morphological gains in patients on these medications.[13]

5. Conclusions

This review of the impact of ACE inhibitors and ARBs on aerobic capacity and $VO2$ max leads to several nuanced conclusions:

1. For patients with hypertension and metabolic syndrome, ACEi and ARBs do not significantly hinder the relative improvements in cardiorespiratory fitness or metabolic health elicited by structured high-intensity interval training or moderate-intensity continuous exercise.
2. In healthy cohorts and higher-functioning individuals, chronic RAAS inhibition can selectively suppress critical physiological adaptations to endurance training, specifically the expansion of total hemoglobin mass and left atrial volume, and may blunt lean body mass gains.

3. Sex-specific responses are prominent; women appear more sensitive to the inhibitory effects of standard ARB dosages on aerobic capacity enhancements, which may necessitate more personalized pharmacological strategies for active female patients.
4. The ACE I/D polymorphism remains a significant genetic determinant of both baseline endurance performance and training responsiveness, though repeated intense exercise can partially override these genetic predispositions.
5. In specialized clinical populations, such as those with heart failure or chronic kidney disease, the therapeutic benefits of RAAS blockade on hemodynamics and organ protection significantly outweigh potential limitations on maximum exercise performance.
6. Clinicians should encourage the combination of aerobic exercise and RAAS-blocking therapy as an evidence-based, synergistic intervention for cardiovascular disease management, while remaining vigilant about potential hematological and sex-specific variances in adaptation.

Disclosure:

Author Contributions:

Conceptualization: Mateusz Kowalski

Methodology: Mateusz Kowalski, Michał Rucki, Nikodem Cieleban

Formal analysis: Michał Rucki, Mateusz Kowalski, Magdalena Modliborska

Investigation: Mateusz Kowalski, Nikodem Cieleban, Aleksandra Maria Rucka

Writing-rough preparation: Aleksandra Maria Rucka, Magdalena Modliborska, Mateusz Kowalski

Writing-review and editing: Mateusz Kowalski, Michał Rucki, Nikodem Cieleban

Supervision: Mateusz Kowalski

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