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Impact of antihypertensive drugs on male fertility: mechanistic insights from experimental and clinical evidence

Impacto dos medicamentos anti-hipertensivos na fertilidade masculina: perspectivas mecanísticas a partir de evidências experimentais e clínicas

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Abstract: Systemic arterial hypertension (SAH) is a highly prevalent chronic condition associated with significant adverse cardiovascular outcomes. In parallel, a progressive decline in seminal quality and male fertility rates has been observed, raising concerns about the impact of SAH and chronic antihypertensive therapy on male reproductive function. Physiological systems involved in blood pressure regulation, such as the renin–angiotensin and adrenergic systems, also play key roles in spermatogenesis, steroidogenesis, and sperm function. This literature review critically analyzed the effects of major antihypertensive drug classes on male fertility, integrating experimental and clinical evidence. Findings indicate distinct reproductive profiles among drug classes: aldosterone antagonist diuretics and beta-blockers are associated with hormonal alterations, sexual dysfunction, and impaired semen parameters; calcium channel blockers interfere with sperm physiology by disrupting calcium homeostasis; and angiotensin-converting enzyme inhibitors may exert unfavorable effects, particularly through testicular oxidative stress. In contrast,

angiotensin II receptor blockers demonstrate heterogeneous, context-dependent effects, with potential cytoprotective actions under specific conditions. In conclusion, hypertension management in men of reproductive age should consider potential reproductive impacts, reinforcing the need for individualized therapy and integrated cardiovascular and reproductive care.

Keywords: Spermatogenesis, Testicular oxidative stress, Renin–angiotensin system, Sexual dysfunction, Semen parameters.

Resumo: A hipertensão arterial sistêmica (HAS) é uma condição crônica altamente prevalente e associada a desfechos cardiovasculares relevantes. Paralelamente, observa-se declínio progressivo da qualidade seminal e da fertilidade masculina, suscitando questionamentos sobre o impacto da HAS e do uso crônico de anti-hipertensivos na função reprodutiva. Sistemas envolvidos no controle pressórico, como a renina–angiotensina e o adrenérgico, também participam da regulação da espermatogênese, esteroidogênese e função espermática. Esta revisão analisou criticamente os efeitos das principais classes de anti-hipertensivos sobre a fertilidade masculina, integrando evidências experimentais e clínicas. Os achados indicam perfis distintos entre as classes: diuréticos antagonistas da aldosterona e betabloqueadores associam-se a alterações hormonais, disfunção sexual e prejuízo seminal; bloqueadores dos canais de cálcio interferem na fisiologia espermática ao alterar a homeostase do cálcio; e inibidores da enzima conversora de angiotensina apresentam possível efeito desfavorável, relacionado ao estresse oxidativo testicular. Em contraste, bloqueadores do receptor de angiotensina II exibem efeitos heterogêneos, com potencial ação citoprotetora em contextos específicos. Conclui-se que o manejo da HAS em homens

em idade reprodutiva deve considerar impactos reprodutivos, reforçando a individualização terapêutica e a integração entre saúde cardiovascular e fertilidade.

Palavras-chave: Espermatogênese, Estresse oxidativo testicular, Sistema renina–angiotensina, Disfunção sexual, Parâmetros seminais.

Introduction

Systemic arterial hypertension (SAH) is one of the main risk factors for cardiovascular morbidity and mortality and represents a major global health challenge[1]. Analogous to the difficulties in achieving adequate blood pressure control, recent decades have witnessed a marked decline in semen quality and global male fertility rates. This trend raises critical questions regarding how chronic exposure to pharmacological interventions – particularly antihypertensive agents – may impact spermatogenesis and male fertility[2].

The renin–angiotensin system (RAS) and the adrenergic system play fundamental roles not only in hemodynamic regulation but also in testicular physiology, influencing steroidogenesis and sperm function[2]. Drugs such as angiotensin II receptor blockers (ARBs), including losartan, are widely used in the management of SAH[3]. However, evidence suggests that chronic activation of α1-adrenergic receptors and the angiotensin II axis may impair testicular vasomotion. The dynamic regulation of vascular tone and blood flow within testicular arterioles, thereby inducing tissue hypoxia and compromising sperm integrity[2].

Oxidative stress has been proposed as one of the central mechanisms underlying male infertility associated with antihypertensive therapy. Exposure to certain classes of antihypertensive drugs in experimental models has demonstrated an imbalance between reactive oxygen species production and testicular antioxidant capacity, resulting in cellular damage and reproductive dysfunction[4]. Conversely, the role of drugs such as losartan appears to be complex and, in some contexts, protective. Studies indicate that it may reduce germ cell apoptosis under conditions

such as varicoceles[5] and improve post-thaw sperm quality due to its antioxidant properties and modulation of mitochondrial activity.

Despite the well-established efficacy of combination therapies, such as perindopril and amlodipine, in reducing blood pressure[1]. The literature still lacks a robust synthesis correlating the long-term clinical use of these agents with fertility outcomes. Understanding which antihypertensive classes present higher cytotoxic risks and which may offer a safer reproductive profile is essential for the clinical management of men of reproductive age.

This literature review aims to analyze the impact of the main classes of antihypertensive drugs on male fertility. By synthesizing experimental and clinical evidence, this work examines hormonal alterations, the role of oxidative stress, and changes in semen quality to guide therapeutic decisions that preserve the reproductive health of hypertensive patients.

Methodology

This study consists of a narrative literature review conducted through structured, non-systematic searches in the PubMed/MEDLINE, Scopus, and Web of Science databases. The search strategy was guided by thematic relevance and aimed to identify experimental and clinical evidence regarding the impact of antihypertensive drugs on male reproductive function. The following descriptors and their combinations were used: “systemic arterial hypertension”, “male fertility”, “spermatogenesis”, “antihypertensives”, “beta-blockers”, “calcium channel blockers”, “angiotensin-converting enzyme inhibitors”, “angiotensin receptor blockers”, “oxidative stress”, and “seminal parameters”. Boolean operators (AND, OR) were applied according to the specific requirements of each database. Studies published in the last 10 years were considered eligible. Experimental studies (in vivo and in vitro), observational clinical studies, and systematic reviews addressing the effects of the main classes of antihypertensive agents on male reproductive function were included. Articles focusing exclusively on female fertility or that did not directly address male reproductive outcomes were excluded.

Study selection was based on relevance to the objectives of the review and on each study's contribution to understanding the underlying pathophysiological mechanisms. Data were analyzed descriptively and critically, with emphasis on integrating mechanistic experimental findings and clinical evidence.

Aplications of Antihypertensive Agents on the Main Axes of Male Reproductive Function

Male reproductive function depends on the harmonious integration of hormonal, vascular, metabolic, and cellular axes that act in a coordinated manner to ensure steroidogenesis, spermatogenesis, and sperm maturation. Recent evidence demonstrates that systems classically associated with hemodynamic regulation, such as the RAS and the adrenergic system, play an active role in the testicular microenvironment by modulating perfusion, cellular metabolism, and germ cell survival[2,6]. Therefore, antihypertensive drugs that interfere with these systems may directly or indirectly influence different axes of male reproductive function, based predominantly on experimental and observational evidence.

Within the hypothalamic–pituitary–gonadal axis, adequate testosterone production is essential for the maintenance of spermatogenesis. Certain diuretics, particularly spironolactone, exhibit a well-established antiandrogenic effect in human, primarily through competitive antagonism of androgen receptors in target tissues and interference with the peripheral actions of testosterone and dihydrotestosterone. These mechanisms may negatively affect the regulation of testicular function and the maintenance of the microenvironment required for spermatogenesis. Consequently, chronic exposure to this drug has been associated in clinical and experimental studies with reduced androgenic activity and potential alterations in male reproductive parameters. Similarly, beta-blockers have been associated in observational human studies with changes in sexual function and reduced availability of free testosterone, likely through peripheral mechanisms, indirectly impacting male reproductive function and contributing to erectile dysfunction, decreased libido, and potential impairment of sperm production[7].

Regarding the vascular and testicular microcirculatory axis, adequate perfusion is essential for the delivery of oxygen and nutrients to germ cells. Systemic arterial hypertension promotes endothelial dysfunction, persistent vasoconstriction, and reduced testicular microcirculation, culminating in tissue hypoxia and deterioration of semen quality[8] as demonstrated in experimental animal models. Drugs that modulate sympathetic tone, such as alpha-blockers, have demonstrated in experimental studies the ability to attenuate these effects by reducing excessive activation of α1-adrenergic receptors, partially restoring testicular vasomotion and reducing sperm damage[2]. In contrast, selective blockade of the RAS by angiotensin receptor blockers (ARBs), such as losartan, may normalize systemic blood pressure without necessarily fully reversing pre-established microvascular damage in the testis, indicating an effect dependent on disease stage[2].

Within the redox and mitochondrial axis, oxidative stress emerges as one of the main convergent mechanisms of reproductive toxicity associated with antihypertensive therapy. Experimental studies in animal models indicate that exposure to certain classes, including angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, and calcium channel blockers, may increase reactive oxygen species production and reduce testicular antioxidant capacity, with elevated markers such as malondialdehyde and decreased glutathione levels[4]. This pro-oxidative environment may compromise sperm membrane integrity, mitochondrial function, and DNA stability, and has been associated in experimental and observational studies various experimental models and observational studies with impaired sperm motility, viability, and fertilizing potential.

In the axis of ionic signaling and sperm function, calcium channel blockers exert a direct effect by inhibiting calcium influx through L-type channels, an ion essential for hyperactivation of sperm motility and the acrosome reaction. Inhibition of these processes compromises fertilization both *in vivo* and *in vitro*[8]. These findings reinforce that certain pharmacological classes act directly on sperm physiology beyond their systemic effects.

Finally, antihypertensive agents may simultaneously act on multiple axes of male reproductive function, with effects varying according to pharmacological class, dose, treatment duration, and the patient's clinical context. An integrated understanding of these mechanisms is fundamental to guide safer therapeutic choices in men of reproductive age, allowing effective blood pressure control while preserving male fertility[9,10].

Classification of Antihypertensive Drugs

Pharmacological treatment of arterial hypertension is widely used among adult populations, including men of reproductive age. The different classes of antihypertensive medications present distinct mechanisms of action, targeting specific systems such as the renin–angiotensin–aldosterone system, calcium channels, adrenergic receptors, and renal tubular transport mechanisms (diuretics). These pharmacological differences may result in variable effects not only on blood pressure control but also on male reproductive physiology, influencing sex hormone levels, spermatogenesis, testicular function, and overall fertility[7,9].

Diuretics

Diuretics are widely used as first-line therapy for arterial hypertension. Their primary mechanism involves modulation of renal sodium and water excretion, resulting in reduced plasma volume and blood pressure[11]. They are classified as thiazide diuretics, loop diuretics, potassium-sparing diuretics, and aldosterone receptor antagonists, according to their site and mechanism of action within the nephron. Thiazide diuretics, such as hydrochlorothiazide and chlorthalidone, inhibit sodium–chloride cotransport in the distal convoluted tubule. Loop diuretics, such as furosemide, act on the ascending limb of the loop of Henle. Potassium-sparing diuretics, such as amiloride, and aldosterone antagonists, such as spironolactone, reduce potassium excretion in the collecting tubule[7,11].

Regarding their effects on the male reproductive system, spironolactone in clinical practice, spironolactone is administered in doses ranging from 25–100

mg/day; the reported reproductive effects are generally described after prolonged exposure (3 to 6 months of continuous treatment).These effects are associated with its structural similarity to steroid hormones. Spironolactone acts as a potent androgen receptor antagonist and inhibits the enzyme 17α-hydroxylase, which is essential for testosterone synthesis[7]. In contrast, animal studies use higher doses than those used in humans for shorter exposure periods (days to weeks), amplifying endocrine and spermatogenic changes when compared to clinical observations.

Adrenergic Antagonists

Adrenergic antagonists constitute a heterogeneous class of drugs widely used in the treatment of arterial hypertension and other cardiovascular and urological conditions. These agents act by blocking α- or β-adrenergic receptors, thereby reducing the effects of norepinephrine and epinephrine on the cardiovascular system[9,12].

Considering that adrenergic signaling plays a relevant role in both vascular function and male reproductive mechanisms, the use of these drugs may affect male sexual function, including libido, sexual performance, and ejaculatory parameters, depending on the pharmacological subclass of antihypertensive agents used[2,7,11]. The known effects are mostly derived from observational clinical studies, pharmacovigilance reports, and experimental models. These data are quite heterogeneous in terms of exposure, dose, and duration. In clinical practice, they are commonly prescribed in varying doses (e.g., propranolol 40–160 mg/day, metoprolol 50–200 mg/day, and atenolol 25–100 mg/day), with adverse sexual effects appearing after weeks to months of continuous therapy, although susceptibility varies considerably among individuals. These potential adverse effects appear to depend not only on pharmacological differences within each class but also on individual patient factors, including comorbidities and concomitant medication use. Experimental and mechanistic studies, including in vitro and animal models, utilize supratherapeutic or stress-induced dosages and shorter exposure periods, which may not fully replicate chronic clinical use in hypertensive

patients. Careful evaluation of these risks is therefore essential when prescribing adrenergic antagonist therapy, particularly in men of reproductive age or in those with preexisting sexual complaints[7,11,12].

Beta-Blockers

The literature indicates that chronic use of beta-blockers, such as propranolol and atenolol, may exert a negative impact on male reproductive function through multiple mechanisms. Clinically, these drugs have been associated with erectile dysfunction, reduced libido, and alterations in male sexual function, which may be partly explained by decreased peripheral sympathetic activity and changes in the availability of free testosterone. These effects can negatively influence quality of life and treatment adherence[7,11]. This association is mainly supported by observational clinical studies where exposure conditions are heterogeneous across studies, particularly regarding dose and treatment duration.

Beta-blockers can be classified according to their selectivity for β-adrenergic receptor subtypes. Non-selective beta-blockers antagonize both β1 receptors (predominantly located in the heart) and β2 receptors (present in bronchial and vascular smooth muscle and other tissues), whereas selective beta-blockers preferentially act on β1 receptors[12].

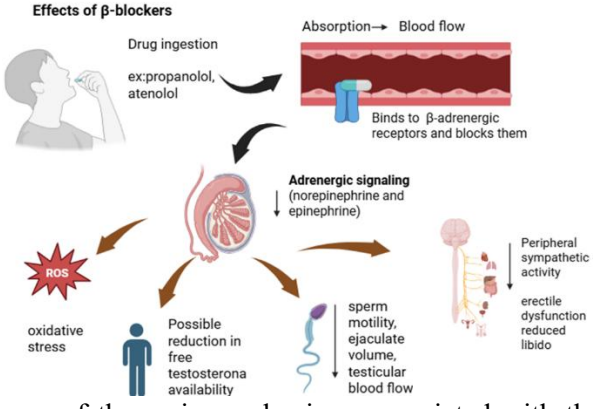
Examples of non-selective beta-blockers include propranolol, nadolol, and timolol, which exert broader effects on cardiovascular and peripheral systems. In contrast, selective beta-blockers such as metoprolol, atenolol, bisoprolol, and esmolol have predominant affinity for the β1 receptor and therefore produce fewer effects on β2 receptors, minimizing bronchospasm, peripheral vasoconstriction, and metabolic alterations[12,13].

Additionally, clinical and experimental evidence suggests that men exposed to beta-blockers may present alterations in semen parameters, mainly characterized by reduced sperm motility. These findings are primarily derived from a systematic review of the literature, rather than from controlled experimental or clinical interventional trials. Decreased ejaculate volume, and a lower proportion of

spermatozoa with normal morphology compared to non-exposed individuals[7]. The reported reproductive changes, including decreased ejaculate volume and a lower proportion of sperm with normal morphology, are generally described in the context of chronic exposure (≥3 months), although the exact duration limits remain inconsistent across studies.

Furthermore, experimental studies indicate that exposure to antihypertensive agents, including beta-blockers, is associated with increased production of reactive oxygen species within the testicular microenvironment, promoting oxidative stress. This imbalance may compromise cellular membrane integrity, mitochondrial function, and sperm DNA stability, contributing to deterioration of semen quality and reduced male reproductive potential[4]. These findings are derived primarily from animal models, in which exposure is often acute or subchronic and involves induced hypertension, which limits direct extrapolation to chronic therapeutic use in humans.

Figure 1. Effects of beta-blockers on male reproductive function and the testicular microenvironment.



Representative diagram of the main mechanisms associated with the impact of chronic beta-blocker use on male reproductive function. Inhibition of β-adrenergic receptors is related to a reduction in peripheral sympathetic activity, associated with complaints of erectile dysfunction and decreased libido, as well as possible alterations in the availability of free testosterone. Furthermore, impairment of seminal parameters is observed, characterized by reduced sperm motility, ejaculatory volume, and the proportion of spermatozoa with normal morphology. Exposure to beta-blockers is also associated with increased production of reactive oxygen species in the testicular microenvironment, favoring oxidative stress, compromising the integrity of cell membranes, mitochondrial function, and sperm DNA stability, causing deterioration in semen quality. The images were created using Biorender.

Alpha-Blockers

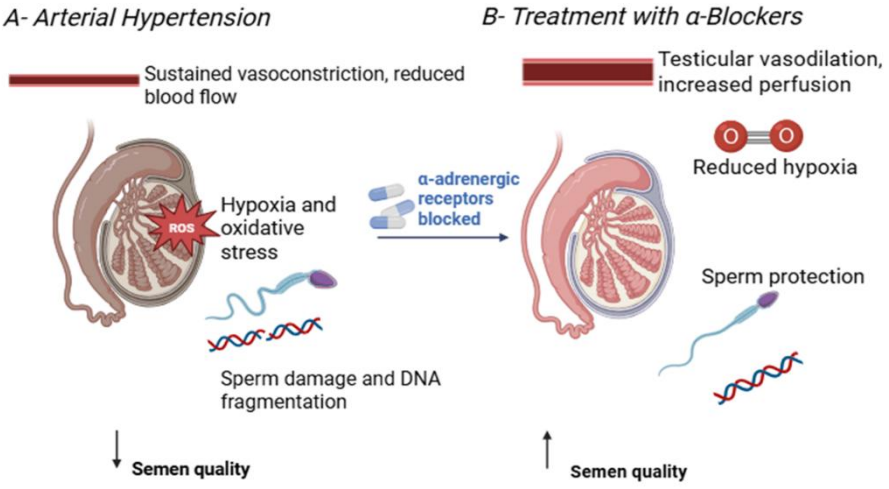
Alpha-blockers (e.g., doxazosin and tamsulosin) are associated with retrograde ejaculation, ejaculatory dysfunction, and an increased risk of ejaculatory disorders, particularly with agents highly selective for the α_1A receptor subtype, such as silodosin[14]. These findings are mostly from observational studies demonstrating a dose-dependent increase in ejaculatory dysfunction in standard antihypertensive regimens, with adverse effects arising during short- to medium-term exposure (weeks to a few months of continuous use). In addition, recent evidence suggests that these drugs may exert a protective role in the testicular microenvironment under hypertensive conditions.

Excessive activation of α1-adrenergic receptors in hypertensive individuals has been associated with impaired testicular vasomotility. An experimental study demonstrated that systemic inhibition of these receptors attenuates sperm damage and testicular hypoxia in animal models[2]. These findings suggest that, under chronic hypertensive conditions, exaggerated activation of these receptors contributes to sustained vasoconstriction within the testicular vascular bed, leading to reduced local blood flow and increased oxidative stress in the gonadal microenvironment. Interruption of this signaling pathway through this class of medications has been associated, particularly in experimental models, with partial improvement of testicular microcirculation, increased tissue perfusion, and attenuation of local hypoxia[2].

This study corroborates previous evidence linking systemic arterial hypertension to structural and functional alterations in testicular microcirculation. These changes include impaired vasomotility, vascular remodeling, and increased hypoxia markers, accompanied by reduced semen quality and greater sperm DNA damage in animal models[6]. Importantly, these preclinical findings are derived mainly from rodent models, whereas clinical evidence from systematic reviews and meta-analyses suggests that the most consistent and well-established effect of α-blockers in humans is ejaculatory dysfunction rather than improvement in reproductive outcomes, reinforcing the gap between mechanistic and clinical

observations. Therefore, alpha-blockers may exhibit dual effects: while they may induce ejaculatory alterations in some patients, they may also improve testicular perfusion and reduce sperm damage under chronic hypertensive conditions. However, the proposed beneficial effects of alpha-blockers on testicular perfusion are largely inferential and based on extrapolation from preclinical data, rather than direct clinical evidence in hypertensive human populations.

Figure 2. Effect of α-blockers on the testicular microenvironment.



Illustrative diagram of the effects of arterial hypertension and α-adrenergic receptor blockade on testicular microcirculation. (A) In arterial hypertension, sustained vasoconstriction is observed in the testicular vascular bed, with reduced blood flow, increased hypoxia and oxidative stress, associated with increased sperm damage and DNA fragmentation, leading to reduced semen quality. (B) Treatment with α-blockers promotes the inhibition of α_1-adrenergic receptors, resulting in testicular vasodilation, increased perfusion, reduced hypoxia and sperm protection, with improved semen quality. The images were created using Biorender.

Calcium Channel Blockers

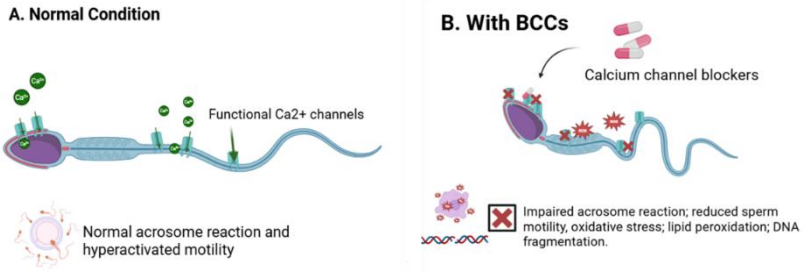
Calcium channel blockers (CCBs), such as amlodipine and nifedipine, are widely prescribed due to their high efficacy in controlling arterial hypertension. This class of antihypertensive agents acts by inhibiting L-type calcium channels located in vascular smooth muscle and the myocardium, resulting in arterial vasodilation and reduced peripheral vascular resistance. However, in the context of male fertility, these drugs raise concerns because calcium is a central ion in the

regulation of sperm physiology[7,8]. Evidence regarding the reproductive effects of CCBs derives from a combination of limited in vitro, preclinical, and observational clinical studies. There is no standardization regarding dose or treatment duration in most studies. In clinical practice, they are commonly administered at antihypertensive doses (e.g., amlodipine 5–10 mg/day and nifedipine 30–90 mg/day in extended-release formulations).

Studies indicate that CCBs may impair calcium influx through specific channels in the sperm membrane. This interference may lead to fertilization failure both in vitro and in vivo, as calcium is essential for the acrosome reaction and for sperm motility hyperactivation[7,8]. Importantly, a substantial proportion of mechanistic evidence is derived from in vitro fertilization models, in which spermatozoa are directly exposed to calcium channel antagonists under controlled laboratory conditions, often at concentrations that may exceed physiological systemic levels, limiting direct extrapolation to in vivo therapeutic exposure.

Furthermore, alterations in intracellular calcium homeostasis may promote the production of reactive oxygen species[4]. Systemic use of these drugs in animal models has been associated with lipid peroxidation of the sperm membrane and reduced activity of major testicular antioxidant systems, resulting in cellular damage within testicular tissue and significant impairment of semen parameters, including decreased sperm motility, reduced sperm concentration, diminished cell viability, and histopathological alterations in the seminiferous tubules. Consequently, these effects contribute to deterioration of spermatogenic function and reduction of male reproductive potential[4].

Figure 3. Representation of the effects of calcium channel blockers on Ca^{2+} homeostasis and sperm function.



Under physiological conditions (A), functional Ca^{2+} channels located in the sperm membrane allow controlled calcium entry, necessary for capacitation, hyperactivation of motility, and proper occurrence of the acrosomal reaction. In the presence of calcium channel blockers (B), there is a reduction in Ca^{2+} influx, compromising these processes, which is associated with decreased sperm motility, impaired acrosomal reaction, increased oxidative stress, intensified lipid peroxidation, and greater susceptibility to DNA fragmentation, negatively impacting the fertilization potential of spermatozoa. The images were created using Biorender.

Angiotensin-Converting Enzyme Inhibitors

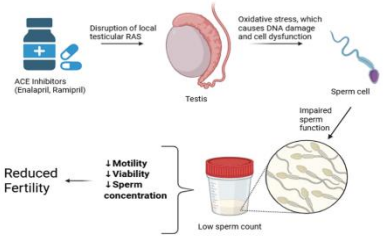
Angiotensin-converting enzyme inhibitors (ACEIs), such as enalapril and ramipril, exert their pharmacological effects by inhibiting the conversion of angiotensin I to angiotensin II, in addition to reducing bradykinin degradation. Although this class is widely used in the treatment of arterial hypertension, modulation of the local renin–angiotensin system—particularly within testicular tissue—may significantly affect male reproductive physiology[2,6,9]. The main hypothesis supporting the negative impact of ACEIs on male fertility involves functional disruption of the testicular renin–angiotensin system associated with intensified oxidative stress in the gonadal microenvironment[4]. The effects of ACE inhibitors on the male reproductive system are predominantly derived from preclinical and observational clinical studies. In clinical practice, they are commonly prescribed at standard antihypertensive doses ranging from 2.5 to 40 mg/day depending on the drug class. Exposure is mostly chronic; however, semen-related outcomes are rarely primary outcomes in these studies, which limits causal inference.

Experimental evidence from an animal study indicates that chronic exposure to ACEIs, particularly ramipril, promotes redox imbalance in testicular tissue, characterized by a significant increase in malondialdehyde (MDA) levels, a classic marker of lipid peroxidation, concomitant with reduced activity of endogenous antioxidant systems, such as reduced glutathione (GSH) and superoxide dismutase (SOD)[4]. In these experimental settings, exposure is typically subchronic and may involve induced hypertension models in rodents, with drug dosing not directly equivalent to human therapeutic regimens, which limits extrapolation to long-term clinical use. Considering that the sperm plasma membrane is rich in polyunsaturated fatty acids and that spermatozoa possess limited antioxidant repair capacity, this pro-oxidative environment favors structural membrane damage, mitochondrial dysfunction, and sperm DNA fragmentation, directly compromising cell viability and motility.

Functionally, these biochemical alterations translate into measurable impairments in semen parameters. Lipid peroxidation of the sperm membrane and mitochondrial dysfunction induced by oxidative stress compromise ATP production, membrane fluidity, and cellular integrity, resulting in reduced sperm motility, viability, and concentration[4]. In addition, epidemiological data suggest that continuous ACEI use is associated, in observational studies, with a statistically modest yet clinically relevant increase in the risk of male infertility, estimated at approximately 9% after adjustment for potential confounding factors[7]. Furthermore, inhibition of bradykinin degradation promoted by these drugs may potentially alter blood–testis barrier permeability, raising the hypothesis of indirect interference with spermatogenesis and sperm maturation, although this mechanistic pathway still lacks robust clinical confirmation.

Thus, despite their well-established efficacy in blood pressure control, ACEIs may present a potentially unfavorable profile from a male reproductive perspective, particularly during prolonged treatment, in which maintenance of a pro-oxidative testicular environment may contribute to progressive deterioration of semen quality[4,7].

Figure 4. Proposed mechanisms underlying the impact of angiotensin-converting enzyme inhibitors (ACEIs) on male reproductive function.



The image illustrates that drugs such as enalapril and ramipril, by inhibiting the conversion of angiotensin I to angiotensin II, promote disruption of the local renin-angiotensin system (RAS) in testicular tissue. This modulation can trigger increased oxidative stress in the gonadal microenvironment, characterized by elevated reactive oxygen species and lipid peroxidation, with consequent DNA damage and sperm cell dysfunction. Considering the high concentration of polyunsaturated fatty acids in the sperm membrane and its limited antioxidant capacity, the pro-oxidant environment favors membrane damage, mitochondrial impairment, and reduced ATP production. Functionally, these processes result in decreased sperm motility, viability, and concentration, culminating in reduced male fertility. The images were created using Biorender.

Angiotensin II Receptor Blockers

Angiotensin II receptor blockers (ARBs), such as losartan, exert their antihypertensive effects through selective antagonism of angiotensin II AT1 receptors. Considering that the local renin–angiotensin system (RAS) plays a central role in the regulation of spermatogenesis, testicular microcirculation, and sperm function, pharmacological interference with this pathway presents a more complex and highly context-dependent profile of effects[2]. Unlike angiotensin-converting enzyme inhibitors (ACEIs), ARBs preserve angiotensin II activity at other receptor subtypes, resulting in a less uniform impact on male fertility[9].

In experimental models using spontaneously hypertensive rats (SHR), treatment with losartan consistently normalized systemic blood pressure; however, this isolated intervention proved insufficient to fully reverse chronic hypertension-induced damage to testicular tissue. The study by Machado et al.[2] demonstrated that, despite adequate blood pressure control, reductions in sperm concentration and acrosomal integrity persisted, suggesting that AT1 receptor blockade, when initiated after the establishment of vascular and structural testicular alterations, may be too late to fully restore reproductive function. These findings support the hypothesis

that systemic arterial hypertension promotes prolonged RAS activation, leading to constriction of testicular arterioles, chronic tissue hypoxia, and vascular remodeling, alterations that are not completely reversed solely through AT1 antagonism.

Conversely, the literature highlights a potential cytoprotective effect of losartan under specific conditions of testicular stress. Experimental studies have shown that the drug may reduce germ cell apoptosis in varicocele models, attenuating cell loss induced by hemodynamic and inflammatory stress[5]. More recent investigations also suggest that losartan exerts a modulatory effect on sperm mitochondrial function, contributing to maintenance of mitochondrial membrane potential, reduction of reactive oxygen species production, and preservation of motility, particularly under extracorporeal stress conditions, such as semen cryopreservation[15].

Thus, ARBs exhibit a heterogeneous and context-dependent reproductive safety profile. While selective AT1 receptor blockade may be insufficient to reverse damage established by chronic hypertension, it may offer cytoprotective and mitochondrial benefits in acute or controlled settings. These data reinforce the notion that the effects of ARBs on male fertility depend on the timing of intervention, the severity of testicular vascular dysfunction, and the clinical context in which the drug is administered[2,5,15].

Clinical Considerations

Systemic arterial hypertension (SAH) represents one of the major contemporary public health challenges and is strongly associated with increased cardiovascular morbidity and mortality worldwide[1]. In addition, both hypertension itself and antihypertensive therapy have been associated with adverse changes in semen parameters and male reproductive function in recent clinical studies[16], raising growing concern about the impact of SAH and prolonged antihypertensive use on male fertility.

The renin–angiotensin system (RAS) and the adrenergic system are not limited to hemodynamic regulation; they actively participate in testicular physiology, steroidogenesis, and spermatogenesis[2]. Excessive activation of these systems in hypertensive individuals may impair the testicular microenvironment, contributing to alterations in sperm quality. This impairment has been increasingly documented, with studies reporting hormonal changes and alterations in testicular metabolism, including testosterone deficiency, in hypertensive men[16,17].

Among antihypertensive classes, particular attention should be given to antiandrogenic diuretics, β-blockers, and angiotensin-converting enzyme inhibitors (ACEIs), due to their potential impact on male fertility. Angiotensin II receptor blockers (ARBs) may exhibit cytoprotective effects in specific contexts, with reproductive outcomes varying according to the stage of hypertension and the patient's clinical profile[2,5,15]. Furthermore, recent systematic reviews indicate that the use of certain antihypertensive agents may modify semen parameters, although the mechanisms appear heterogeneous and depend on the specific drug class and duration of treatment[7].

Despite the widespread use of highly effective combination therapies for blood pressure control, such as the association of ACEIs and calcium channel blockers[1], further studies are needed to clarify their long-term reproductive effects. It is also important to emphasize that hypertension itself, even prior to pharmacological intervention, has been associated with impaired sperm motility, reduced ejaculate volume, and decreased total sperm count in large cohorts of men evaluated for fertility[16].

In clinical practice, an integrated approach is recommended, considering male fertility as a relevant outcome. This includes pre-treatment counseling regarding potential reproductive risks, especially in young men or those planning future conception. Monitoring of semen parameters and hormonal profiles may be useful in selected cases to detect early alterations and guide therapeutic adjustments.

Conclusions

The available evidence indicates that antihypertensive agents exert distinct effects on male fertility, varying according to pharmacological class, mechanism of action, and pathophysiological context. The main axes affected include the hypothalamic–pituitary–gonadal axis, testicular microcirculation, redox homeostasis, and sperm ionic signaling, with direct impact on steroidogenesis, spermatogenesis, and sperm function. Diuretics with antiandrogenic activity, beta-blockers, and calcium channel blockers show more consistent associations with hormonal alterations and sperm dysfunction, whereas angiotensin-converting enzyme inhibitors (ACEIs) demonstrate a potentially unfavorable profile during prolonged treatment, particularly due to induction of testicular oxidative stress. In contrast, angiotensin II receptor blockers (ARBs) exhibit context-dependent effects; although they may not reverse established damage, they may present cytoprotective properties under specific conditions. Therefore, the management of hypertension in men of reproductive age should consider not only blood pressure control but also the reproductive profile of antihypertensive agents, aiming to balance cardiovascular protection with preservation of male fertility.

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