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Review Article

Antihypertensive Therapy in Athletes

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Abstract

COCIS guidelines first permitted the use of antihypertensive drugs in competitive sports in 1995. Since then, the choice of the ideal drug for athletes has become one of the greatest challenges for doctors.

Many classes of antihypertensive drugs interfere with athletic performance as they act on pathophysiological mechanisms involved in sporting activities. The ideal drug should control blood pressure both during exercise and at rest, not cause orthostatic hypotension, cover 24 hours with a single dose, not interfere with the cardiac response to exercise, nor cause arrhythmias. It should also not cause electrolyte imbalance or interfere with energy substrates, nor should it affect blood distribution to skeletal muscle. Finally, it must not be considered to be a doping agent. The first line drugs of choice are Ace (Angiotensin Converting Enzyme) inhibitors and Angiotensin II receptor blockers, due to their minimal interactions with athletic performance. Alternatively dihydropyridine calcium channel blockers or alpha lithics can be used. Beta blockers and diuretics should be avoided due to their numerous interactions with the physiological mechanisms involved in the control of physical exercise and because they are prohibited by doping regulations. It may be useful, for those who have not achieved the desired effect with first-line drugs, to use pre-established antihypertensive combinations.

Keywords: Antihypertensive Therapy; Sport; Physical Exercise

Introduction

Hypertension is the most common condition to be identified in health checks for athletes, particularly in the category of masters athletes.

For athletes aged 20 to 29, the prevalence of hypertension is 14.4% for males and 6.2% for females, while in those aged 30 to 39 it rises to 21.2% and 9.9% respectively [1].

The Italian guidelines relating to medical fitness for sport have permitted the use of antihypertensive drugs for competitive athletes since 1995, and since then antihypertensive therapy has played a fundamental role in managing the condition of athletes suffering from arterial hypertension.

As well as addressing blood pressure levels, the assessment and risk stratification of the overall cardiovascular risk is essential when managing hypertension in athletes. It is therefore vital to take into account the patient's gender and age, whether they smoke and whether they suffer from diabetes, obesity, dyslipidaemia or have a family history of early cardiovascular events.

Furthermore, it is fundamentally important to assess the athlete's arterial blood pressure also during exercise by means of an ergometric test. If the subject is classified as "low cardiovascular risk" the ESC (European Society of Cardiology) guidelines recommend an initial non-pharmacological therapeutic approach, with lifestyle changes for a period of at least 3 months (lowering salt intake, reducing body weight, avoiding alcohol and stopping smoking, together with a suitable exercise program). In case of grade 3 hypertension (i.e.: "high cardiovascular risk" or "very high") it is advisable to start medical therapy promptly [2].

The correct pharmacological management of hypertension has a particularly relevance for athletes involved in competitive sports, where, as well as reducing blood pressure, it also needs to consider the limitations imposed by anti-doping regulations and the influence of the drug on performance.

Choice of Medication

The biggest challenge faced in the management of hypertension in athletes is being able to control blood pressure levels, both at rest and during exercise, without affecting performance and only using drugs approved by the World Anti-Doping Agency (WADA).

Many classes of antihypertensive drugs can interfere with athletic performance, as they act on physiological mechanisms that affect sporting performance and have significant impacts on metabolism and muscle function.

The characteristics of the ideal drug for hypertensive athletes are shown in Table 1,2.

ACE Inhibitors

ACE inhibitors are the first line drug of choice for the management of hypertension in athletes [3].

Some studies have demonstrated a slight reduction in both systolic and diastolic blood pressure during exercise in patients receiving captopril [4], enalapril [5,6] and saralasin [7]; heart rate remains unchanged [4] and peripheral vascular resistance is reduced by all ACE inhibitors [4,6,8].

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Table 1: Characteristics of the ideal drug for hypertensive athletes.

The drug must:
· Control BP both at rest and during exertion;
· Not reduce the cardiac response to exercise;
· Have no arrhythmogenic effect;
· Not cause interference with the distribution of blood to the muscle;
· Not cause interference with energy substrates;
· Not be a substance prohibited by doping regulations;
· Not cause orthostatic hypotension; (already physiologically present at the end of exercise);
· Must not cause electrolyte imbalance;
· Cover 24 hours with a single dose;
· Have no significant side effects;

These drugs do not affect VO_2 max or exercise tolerance (both sub-maximal and maximal) and this feature makes them particularly suitable for use with patients who undertake physical activity [5]. Some studies also suggest that elderly (non-heart failure) patients taking ACE inhibitors experience a lower reduction in walking speed, hand grip and knee extension strength than patients taking other hypertensive medication or not receiving any therapy [9].

In 2007 Sumukadas et al. found that treatment with perindopril in elderly patients with functional impairment and without heart failure can increase exercise capacity in a way that is similar to a 6-month training program. The pathophysiological mechanism underlying this phenomenon is probably linked to metabolic changes at the muscular level [10,11].

It is known that ACE inhibitors induce a shift in myosin heavy chains towards slow, aerobic isoforms, which are related to improved physical performance [12].

These drugs also increase insulin sensitivity, glycogen storage and glucose uptake by the muscle; they have a limiting effect on the proinflammatory mechanism triggered by angiotensin and increase the concentration of bradykinin and nitric oxide.

This causes the suppression of the inflammatory cascade and an increase in muscular vascular permeability leading to an increase in the intake of glucose and amino acids, and consequently better muscle metabolic efficiency [11].

However, recent studies by Sumukadas et al. seem to indicate that the addition of these drugs, in elderly patients with functional impairment undergoing training, does not lead to any improvement in the ability to perform physical exercise compared to the training program alone [13].

Angiotensin II Receptor Blockers

Like ACE inhibitors, Angiotensin II Receptor Blockers (ARBs) are one of the first line antihypertensive drugs for athletes [3]. They both share many of the same metabolic and haemodynamic characteristics, as they act on the same molecular pathway.

In numerous studies, ARBs have also shown beneficial effects on physical performance, especially in the elderly.

A study by Vescovo et al. reports that a 6-month treatment with losartan significantly increases VO_2 max and the ventilatory threshold on the cardiopulmonary test [12]. On the other hand, De Rosa et al. showed in 2009 how the use of candesartan improves the VO_2 peak in cardiopulmonary tests in hypertensive grade 1 or 2 patients with secondary ventricular hypertrophy, compared to control subjects (placebo) [14].

This class of drugs could also have a beneficial effect on muscle recovery after injury. Indeed, the administration of 30 mg/day of losartan immediately after trauma seems to improve the recovery of muscle strength. This property perhaps depends on an overexpression of follistatin, a positive regulator of skeletal muscle growth [15].

In a study conducted on mice, chronic administration of telmisartan has been shown to cause an increase in slow twitch muscle fibres, prevent body weight loss, improve endurance and post-exercise oxygen consumption. These effects were absent in genetically modified mice lacking peroxisome Proliferator Activated Receptor (PPAR). Consequently, the increase in muscle function and exercise tolerance seems to be due to the activation of PPAR and the AMPK pathway (adenosine monophosphate activated protein kinase) [16].

These effects of Telmisartan could, however, lead to the illicit use of this drug in doping, and PPAR agonists are indeed classified by the WADA as metabolic modulators. Telmisartan is not mentioned on the list of these substances, but its effects and the metabolic pathways it acts on suggest that it should be considered to be in this category [17].

It is important to remember that high intensity physical exercise can cause negative effects on the cardiovascular system, including platelet activation; these effects are more pronounced in hypertensive patients.

A 2014 study demonstrated a reduction in platelet activation following high-intensity sporting activity in hypertensive patients who were treated with 160 mg of valsartan and who had well controlled blood pressure [18]. From a metabolic point of view, ARBs cause a significant reduction in circulating glucose levels by antagonizing the effect of angiotensin II on the mechanisms of insulin signal transduction.

These drugs therefore reduce insulin resistance and accentuate the uptake and use of glucose by muscles and other tissues in a similar way to ACE inhibitors. In this regard Fujimoto et al. have shown that

Table 2: Main effects of the different classes of antihypertensive drugs.

Parameters	ACE Inhibitors	Sartans	Calcium Channel Blockers		Central Alpha Agonists	Alpha Blockers	Beta Blockers		Diuretics
			Phenylalkylamines	Dihydropyridines			Selective	Non selective	
Blood pressure									
BP at rest	reduction	reduction	reduction	reduction	reduction	reduction	reduction	reduction	reduction
Systolic during exercise	slight reduction			significant reduction	reduction	reduction	reduction	reduction	reduction
Diastolic during exercise	slight reduction			significant reduction	reduction	reduction	reduction	reduction	reduction
Athletic performance									
Endurance	unchanged	increase			reduction		reduction	significant reduction	
Anaerobic threshold		increase		reduction				reduction	
VO_2 max	unchanged	increase	unchanged	unchanged	unchanged			reduction	
Hemodynamic parameters									
Heart rate during exercise	unchanged	unchanged	slight reduction	unchanged	reduction		significant reduction	significant reduction	
Cardiac output during exercise			non significant reduction	unchanged	unchanged	unchanged	reduction	reduction	
Peripheral vascular resistance	reduction			reduction	unchanged	reduction	reduction	reduction	reduction
Metabolism									
Glycaemia	significant reduction	significant reduction		significant increase			reduction	significant reduction	
Glycogenolysis	reduction	reduction		increase			reduction	significant reduction	
Beta-oxidation							reduction	significant reduction	
Insulin resistance	reduction	reduction		increase					
Electrolyte imbalance									yes
Doping substance	no	no	no	no	no	no	yes	yes	yes

the administration of Telmisartan increases glucose uptake and the expression of the GLUT4 (glucose transporter type 4) protein on adipocytes [19].

There is also experimental evidence that suggests that angiotensin II promotes osteoclastic activity and bone resorption. Consequently, it has been hypothesized that ARBs and ACE inhibitors may have a protective effect against osteoporosis in the elderly.

However, contrary to what was expected, a 2012 study on elderly American subjects demonstrated a bone density-reducing effect caused by ACE inhibitors, but not by ARBs. Nonetheless, there was no evidence of a significant increase in fractures in patients receiving this therapy [20]. Although ACE inhibitors and ARBs are considered as the first line drug of choice for athletes, it should be remembered that they should be avoided in women of childbearing age due to possible teratogenic effects in the case of pregnancy [2].

It is likely that direct renin inhibitors can have effects on physical activity similar to ARBs, however their use by athletes has not yet been adequately researched, and therefore their use is not recommended [3].

Calcium Channel Blockers

Calcium Channel Blockers (CCB), in particular dihydropyridines, are considered the medicine of choice for athletes who cannot take either ACE inhibitors or ARBs [3]. This class of drugs has shown significant success in reducing systolic-diastolic blood pressure during exercise, probably attributable to the effect of the drug on peripheral arterial resistance; [21-24]. Non-dihydropyridine CCB, however, have negative inotropic and negative chronotropic effects that can lead to the impairment of sporting performance.

Some studies have shown that verapamil has more pronounced negative inotropic effects than other drugs in the same class, but both verapamil and diltiazem cause a slight decrease in heart rate during exercise [23,25], without significant changes in cardiac output [26]. During cardiopulmonary tests, diltiazem does not significantly modify VO_2 max [24].

From a metabolic point of view, a lipolysis stimulating effect would be expected (attributable to the stimulation of alpha 2 adrenergic receptors) [27], however it has been shown that free fatty acids do not increase during administration of verapamil [28].

For the class of dihydropyridine CCB, prolonged treatment with nifedipine does not increase heart rate, cardiac output or systolic volume during exercise [23,29]. Nifedipine also appears capable of increasing the fraction of myocardial shortening during high-intensity exercise, reducing the diastolic volume due to the action on peripheral resistance [21,26].

According to a study undertaken in 2001, nifedipine was found

to have a good effect on resting blood pressure, but also has an effect on the blood pressure response to exercise when compared to benidipine and the placebo. This has been linked to nifedipine being faster acting, which affects the body's ability to implement compensation mechanisms. Furthermore, nifedipine was seen to increase Plasma Renin Activity (PRA), causing the activation of the Renin-Angiotensin-Aldosterone System (RAAS), which could be the cause of cardiovascular events [30]. However, these negative effects were not seen in subjects receiving benidipine [31].

From a metabolic point of view, a significant hyperglycaemia inducing effect was observed during sustained effort (60% VO_2 max). This effect can be attributed to the inhibition of insulin function and the stimulation of catecholaminergic and IGF (Insuline-like Growth Factor action), which result in an increase in hepatic glycogenolysis [32].

In the cardiopulmonary test the Anaerobic Threshold (AT) was reduced after administration of nifedipine (in a single dose), while VO_2 max and maximum power reached during exercise remained unaltered [33].

For these reasons, dihydropyridine CCB are considered the medicine of choice for hypertensive athletes who cannot take ACE inhibitors or ARBs. Nonetheless, their usefulness in controlling pressure during isometric exercise remains controversial.

Verapamil and diltiazem can be used in case of intolerance to dihydropyridines [3].

Alpha Agonists/Blockers

In hypertensive patients the administration of clonidine or methyldopa causes a reduction in blood pressure and heart rate during exercise [34,35].

Clonidine does not affect vascular resistance or induce reduction in cardiac output [36].

Treating normotensive patients with methyldopa reduces plasma renin activity and increases aldosterone [37].

In terms of exercise tolerance, this drug does not change VO_2 max during cardiopulmonary tests even though it seems to negatively affect the duration of exercise (decreased by 3.9%) [35].

Prazosin causes a reduction in the increase in blood pressure during exercise and reduces resting pressure, but it does not affect the Stroke Volume (SV) [3,8].

For patients who cannot take the drugs mentioned above, an alternative is the use of doxazosin; however this can lead to orthostatic hypotension at the end of exercise, in particular if exercise is interrupted abruptly.

Beta Blockers

Beta blockers are particularly unsuitable drugs for treating hypertensive athletes.

From a haemodynamic point of view they reduce the systolic and diastolic pressure both at rest and during physical exercise [37,39-47]. This characteristic is typical of selective drugs [39,43,45,47], of non-selective ones [37,42,44,47], of those with intrinsic sympathomimetic action [46,48] and of those with combined action (alpha and beta blockers) [41].

All drugs in this class cause a reduction in stroke volume, left ventricular function (SV reduced by 18-25%) [49,50] and peripheral resistance [48].

Furthermore, the known negative chronotropic effect of these molecules causes a reduction in HR (Heart Rate) during exercise of 20-30% [45,50,51].

This bradycardising effect is less pronounced in drugs with intrinsic sympathomimetic actions [46,48].

Beta blockers also have a significant impact on metabolism, due to the reduction of glycogenolysis and beta oxidation processes normally induced by the sympathetic nervous system [52].

In particular, non-selective drugs cause a more marked reduction in glycogenolysis and lipolysis than selective drugs. This effect is seen particularly in the reduction in endurance time during aerobic exercise. In this sense, the molecule that has shown the greatest negative effect is propranolol [52-54]. In this regard, the use of propanolol leads to a reduction in VO_2 max of 6-14% [55-58] (which it is more pronounced in patients with a good level of fitness) [51] and an 11% reduction in the anaerobic threshold after 3 months of therapy [59].

An early increase in blood lactate during physical activity has also been demonstrated, probably due to a delay in adapting the cardiovascular system to the demands of the muscles. With the use of propanolol, for example, there is an increase in blood lactate in the initial minutes of exercise and then a decrease in them after 25 minutes of exercise (to 65% of VO_2 max), compared to control subjects [60].

The decrease in lactate after 25 minutes of exercise is probably linked to the fact that glycogenolysis is stimulated by the activation of beta receptors [61].

Some studies also show that the expected increase in VO_2 max after aerobic training in subjects who took propranolol was not found [62]. However, other studies contradict these findings [63].

In any case, the concentration of muscle mitochondrial enzymes after a period of training does not seem to increase as expected in subjects treated with this drug [64,65].

For all these reasons, beta blockers are not suitable drugs for anti-hypertensive therapy in athletes.

It should also be remembered that these drugs are not recommended in cases of bradycardia (bpm <50) and second-degree atrioventricular block (characteristics commonly found in athlete's hearts), in cases of third-degree atrioventricular block or in dexterity-based sports where doping rules prohibit their use.

When it is necessary to use Beta blockers, it is preferable to use a combination of alpha-beta blockers as this causes less impairment of muscle vascularization and has less of an effect on maximum oxygen consumption [66].

Separate consideration should be given to nebivolol, a latest generation beta blocker with very high cardioselectivity (B1/ß2>

300) [67] which is associated with a significant effect in reducing peripheral resistance.

The vasodilatory property of the molecule is not expressed by blocking the α1 receptors, as happens with labetalol and carvedilol, but by the direct action of the drug on the enzyme nitric oxide synthetase (eNOS) [68]. Nitric oxide plays a key role in endothelial function by causing vasodilation, reducing the expression of endothelial receptors for proinflammatory and adhesion molecules, as well as the suppression of signalling pathways for the triggering of inflammatory processes [69,70].

In this regard, a study conducted on obese patients subjected to intense physical exercise highlights how the administration of this active ingredient for 8 weeks at therapeutic doses results in a reduction in pro-inflammatory cytokines and leptin and an increase in adiponectin, exerting a protective effect against the inflammatory stress induced by intense physical exercise [71].

Several studies have also documented a significant improvement in diastolic function. The SENIORS study [72] showed that nebivolol is well tolerated in elderly patients with heart failure with both preserved and reduced ejection fraction.

Some studies on patients with heart failure and preserved ejection fraction have found good control of systolic blood pressure and heart rate both at rest and at peak exertion after treatment with nebivolol. However, the expected increase in VO_2 max was not observed [73].

Diuretics

Diuretic drugs are banned by the World Anti Doping Agency, and therefore they cannot be used by athletes who compete.

Diuretics help in the clearance of any illicit substances, affecting the results of anti-doping tests; furthermore, in sports that are divided into weight categories (such as combat and weightlifting sports) they can help athletes qualify for a lower weight category.

Therapy with thiazides reduces systolic Blood Pressure (BP) at rest and during exercise by about 20% -30% and diastolic BP by 15-20%, with a simultaneous reduction in peripheral arterial resistance [74].

These drugs also favour the onset of electrolyte imbalances such as hypokalaemia and hypomagnesaemia, which can be a factor in triggering cardiac arrhythmias. An increase in ventricular premature beats was seen in patients receiving hydrochlorothiazide compared to control subjects [75,76].

Diuretics can also lead to dehydration in athletes who undertake prolonged aerobic exercise in hot climates and interfere with thermoregulation. According to a 2000 study, dehydration induced by pre-exercise diuretics causes a greater imbalance in thermoregulation during physical exercise [77]. The decrease in plasma volume caused by the diuretic causes the activation of the sympathetic nervous system with a consequent increase in the release of norepinephrine and stroke work and a reduction in cutaneous blood flow with impaired heat dispersion [77].

According to a 2005 study, acute dehydration caused by diuretics (with consequent loss of body mass of 2-2.5%) does not affect the performance of maximum power and sprint, consequently the diuretic would not provide the expected effect of improved athletics performance in these categories of sports [78]. Similarly, the factors that affect aerobic performance in instances of moderate dehydration have no impact on results in sprinting and in activities where explosive strength is required [78].

Pharmacological Combinations

Unfortunately, only limited information is currently available about the hemodynamic effects and the implications for physical exercise of combinations of drugs.

A 2011 study was conducted in this regard examining the association of lisinopril (40 mg/day) with a beta blocker (carvedilol 20, then 40 mg/day) and ARBs (valsartan 160 then 320 mg/day).

By adding valsartan or carvedilol to the ACE inhibitor, a reduction in stroke work was observed with different mechanisms (vasodilation and a reduction of preload with ARBs, reduction in heart rate with the beta blockers). During exercise, valsartan maintained the reduction in central systolic pressure and peripheral resistance and the increase in blood pressure; carvedilol did not. Neither drug affected the response to exercise or carotid flow.

Although a greater cardio-depressive effect of the combination with carvedilol was expected, the study revealed a comparable heart rate and stroke work reduction effect with both drug combinations [79].

The combination of telmisartan and nifedipine seems to have a good anti-hypertensive effect in controlling BP during sub-maximal exercise at high altitude, counteracting the excess pressure increase at altitude found in the hypertensive patients [80].

The combination of enalapril and hydrochlorothiazide reduces systolic pressure by 12.6% at peak exercise without changing the VO_2 max and the level of fatigue perceived during maximal and sub-maximal exercise [5].

It is noteworthy to observe that drug combinations including beta-blockers or diuretics can not be used by competitive athletes.

Conclusion

When we consider anti-hypertensive therapy for athletes, the choice of active ingredients to be used is complex and must take into account numerous considerations.

For these reasons, the first line choice of anti-hypertensive drugs for athletes are ACE inhibitors and ARBs.

Alternatively, dihydropyridine CCB and alpha blockers can be used, as they do not affect sporting performance.

Diuretics should always be avoided: apart from being considered to be doping agents in all sports, they also induce haemodynamic and electrolyte alterations that can lead to arrhythmias and reduce the athlete's performance.

Beta blockers reduce heart rate, alter the haemodynamic response to exercise, cause metabolic impairment and reduce exercise tolerance, so their use should be limited to cases where there are no other options, and in these cases nebivolol is to be preferred.

To promote patient compliance, it may be useful for those who have not achieved the desired effect with first line drugs, to use pre-established antihypertensive combinations (sartans or ACE inhibitor/calcium channel blocker) as recommended by the ESC/ESH (European Society of Cardiology / European Society of Hypertension) guidelines.

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