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THE EFFECTS OF AMLODIPINE ON EXERCISE PERFORMANCE IN MILD TO MODERATE ESSENTIAL HYPERTENSIVES

Thesis submitted for the degree of Masters in Medicine. MSc.(MED)

by

Hunter C Gillies

MBChB, BSc. (MED)(HONS) Sport Science.

Bioenergetics of Exercise Research Unit of The Medical Research Council

and The University of Cape Town.

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DECLARATION

I, Hunter Campbell Gillies, do hereby declare that the experiments presented in this thesis were conceived and executed by myself and, apart from the normal guidance from my supervisor, I have received no assistance.

No part of this thesis has been submitted in the past, or is being, or is to be submitted for a degree in the University or any other University.

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ABSTRACT

The effect of the long acting dihydropyridine calcium channel antagonist, amlodipine, on the exercise performance of hypertensive patients is not known. The aim of this study was to determine the effects of amlodipine on maximal (MAX), prolonged submaximal (PSX) and on skeletal muscle function (SMF) in patients with mild hypertension. In a double-blind randomised crossover trial, ten physically active hypertensive patients performed i) graded exercise to exhaustion for determination of maximal oxygen consumption (VO_{2max}), peak heart rate (HR) and systolic blood pressure (SBP); ii) PSX at 75% VO_{2max} to determine, cardiorespiratory responses, cardiac output (Q), blood lactate [La], free fatty acid [FFA], glucose [G] concentrations and ratings of perceived exertion (RPE), and iii) tests of isometric SMF including maximal voluntary contraction (MVC) and time to fatigue (TTF) during repetitve isometric MVC's. Tests were performed following two week ingestion of amlodipine (5 mg daily) or placebo seperated by a two week washout period. Resting SBP was decreased following ingestion of amlodipine (142 ± 13 vs 133 ± 12 mmHg; vs placebo; [mean ± SD]; $P<0.05$). However, VO_{2max} (31 ± 5 vs 33 ± 5 $mlO_2.kg.min^{-1}$; amlodipine vs placebo), peak heart rate (167 ± 12 vs 165 ± 16 $b.min^{-1}$; amlodipine vs placebo) and peak SBP (181 ± 21 vs 170 ± 16 mmHg; amlodipine vs placebo) were not reduced following ingestion of amlodipine. Submaximal cycling time, VO_2, Q, BP, HR, ventilation, RPE, [FFA], [La^-] and [G] during PSX were unaltered following ingestion of amlodipine. Similarly ingestion of amlodipine did not alter tests of isometric SMF. These data suggest that: i) ingestion of amlodipine lowers resting SBP but does not alter the normal haemodynamic response during

exercise; ii) MAX, PSX exercise performance and SMF are unaltered following ingestion of amlodipine in athletic hypertensive patients. These findings suggest that the regulatory mechanisms which maintain haemodynamic homeostasis during maximal and submaximal exercise are not influenced by ingestion of amlodipine in athletic hypertensive patients.

LITERATURE REVIEW

Introduction

A lack of regular aerobic exercise is currently listed as one of the major risk factors for cardiovascular mortality. The most recent report of the joint national comittee on detection , evaluation and treatment of high bloood pressure (JNC V) lists regular physical activity as one of the lifestyle modifications to be instituted in the primary prevention and management of hypertension. With the Calcium antagonists and angiotensin converting enzyme (ACE) inhibitors now joining the diuretics and beta-blockers as acceptable first line therapy in the treatment of hypertension, it is important that the hypertensive individual is managed according to his or her needs and experiences (50, 63).

Clearly, the physically active hypertensive is such an individual that needs the appropriate 'tailoring' of therapy. Whilst effective in lowering the maximum blood pressure during exercise, much current data on the effect of beta blockade appears to indicate a reduction in exercise performance and an alteration in the physiological response. Beta blockade can effect the biochemical and physiological response to exercise at many levels. Both cardioselective and non selective beta blockers impair exercise performance, however it is likely that submaximal performance is impaired to a greater degree by non selective beta blockade (18, 29, 55, 62, 65, 68, 70). Briefly, the proposed mechanisms whereby beta blockade limits exercise performance include:

i) **Central Haemodynamics.**

Heart rate and systolic blood pressure at rest and during exercise are decreased by beta blockers (7, 13, 17). Much of the current data indicates that beta blockade decreases cardiac output at rest and during both maximal and submaximal exercise by between 5 - 15% (7, 9, 23). The reduction in exercise performance and increased fatigue has historically been attributed to these central haemodynamic changes. However, further analysis would question this hypothesis. First, a relative reduction in cardiac output during exercise is not a consistent finding (48). Beta blockers with intrinsic sympathomimetic activity limit the reduction in cardiac output, however, both maximal and submaximal exercise performance are impaired to the same degree as that with other beta blockers (19, 38). Second, various beta blockers alter maximal exercise performance even though they have no significant effect on cardiac output or total peripheral resistance measured during submaximal exercise (48). Therefore, it is unlikely that central factors alone could impair exercise performance.

ii) **Peripheral Haemodynamics.**

The majority of studies on peripheral blood flow in exercising limbs with beta blockade demonstrate a decrease in blood flow to exercising muscle (22, 37, 45). However, the arteriovenous oxygen content difference is increased such that submaximal oxygen consumption ($V0_2$) is unchanged during submaximal exercise (22). The reduction in skeletal muscle blood flow is likely to be worse with the non selective beta blockers where unopposed alpha mediated vasoconstriction would occur under catecholamine stimulation during exercise (22, 45). Therefore, it is likely that blood flow to working muscle is affected by beta blockade but oxygen delivery is possibly unaltered (22). However, it is possible that diminished blood flow during exercise could allow for the accumulation of cellular metabolites, such as lactate and potassium, and thus impairing performance.

iii) **Lipolysis.**

Beta blockade inhibits adipose tissue lipolysis and therefore attenuates the increase in plasma free fatty acids that would normally occur during prolonged exercise and thereby possibly altering skeletal muscle substrate metabolism (35, 55, 65, 66).

iv) **Glycolysis.**

During submaximal exercise under beta blockade, plasma lactate concentrations tend to be higher with a lower relative oxygen consumption ($V0_2$) when compared to placebo (70). The relative respiratory exchange ratios are higher after the ingestion of beta blockers suggesting a greater dependance on carbohydrate as an energy substrate. Therefore if there were a reduction in hepatic glycogenolysis due to beta 2 receptor blockade, this might result in a decrease in plasma glucose concentration and thereby impair exercise performance (55). However, it would appear that low plasma glucose concentrations are found only in fasting subjects undergoing submaximal exercise and normally fed subjects undergoing high intensity exercise (65). Assuming that athletes are generally well fed, those subjects participating in high intensity exercise under beta blockade may be at risk of developing hypoglycaemia, however, the evidence for impaired glycogenolysis in skeletal muscle is indirect and glycogenolysis is probably maintained by mechanisms independant of the beta receptor (55).

v) **Hormonal effects of beta blockade.**

The increase in plasma adrenaline concentration is augmented by beta blockade during exercise whereas the increase in plasma noradrenaline concentration during submaximal

exercise is unchanged (11, 24, 46). Kindermann et al (1982) reported significant increases in plasma concentrations of noradrenaline, adrenaline, growth hormone, glucagon, and cortisol during submaximal exercise following β_1 - selective blockade compared to placebo.

Serum insulin and oestradiol concentrations are unaffected whereas serum testosterone concentration is decreased by β_1 - selective blockade during submaximal exercise (35). Growth hormone concentrations during exercise are increased by selective and non selective β blockade (35).

It is possible that the increase in the concentration of adrenaline, growth hormone, glucagon and cortisol allows for the mobilisation of alternative fuel sources, such as carbohydrates, as free fatty acid metabolism is impaired by beta blockade (35, 55).

vi) **Ventilation.**

It is possible that the respiratory response to exercise is affected by beta blockade. Both cardioselective and non selective beta blockers would appear to attenuate the normal increase in tidal volume with increasing work rate, the latter to a greater degree than the former, highlighting the importance of beta $_2$ mediated bronchodilation (33). However, minute ventilation and carbon dioxide production (VCO_2) are unaltered due to an increase in breathing frequency (33). Therefore it is possible that the maintenance of minute ventilation, at the cost of an increase in breathing frequency, might result in an increase in the work of breathing under beta blockade.

vii) **Thermoregulation.**

During prolonged exercise beta blockade may interfere with the regulatory mechanisms involved in controlling body temperature thereby affecting performance. Increased sweat losses and the elevation of pulmonary artery temperature has been documented in exercising subjects under non selective beta blockade (27).

In summary, the commonly prescribed beta blockers undoubtedly affect exercise performance. When both exercise programmes and pharmacological agents are prescribed to hypertensive patients, who are not limited by ischaemic heart disease, it is essential that an agent which does not impair the ability to exercise adequately, is selected.

As a result there is a need to find more appropriate agents for the use in physically active individuals i.e. ones that reduce peripheral resistance whilst allowing a normal physiological and metabolic response to exercise. The use of either angiotensin converting enzyme (ACE) inhibitors or calcium channel antagonists would appear to be more appropriate. However, both groups of anti-hypertensives have been reported to impair exercise performance (17, 26, 67). Acute dosing with ACE inhibitors has shown a decrease in maximal and prolonged submaximal performance, as well as altering substrate metabolism during submaximal testing (17, 67). The recognition for the need of twenty four hour blood pressure control has enhanced the popularity of the long acting calcium channel antagonists such as amlodipine. The once daily dosing, smooth onset of action and limited vasodilatory side effects give these drugs an advantage over the shorter acting calcium antagonists such as nifedipine. However, few data are available on how these drugs affect performance and in particular their effect on prolonged submaximal performance in hypertensive individuals. The literature concerning calcium antagonists and exercise performance as well as the physical and metabolic response to exercise will be the focus of this review.

Calcium Antagonists:

The Calcium antagonists can be classified into two main groups, those of the verapamil type (phenylalkylamines and benzothiazepines) and those of the nifedipine type (dihydropyridines). Both groups lower blood pressure by acting on vascular smooth muscle and decreasing the total peripheral resistance, however, they also have a cardiodepressive effect which is seen predominantly in those drugs of the verapamil type whereas the nifedipine type or dihydropyridines have a predominant vasodilating action with little or no cardiodepressive effect (36).

A review of the studies of calcium antagonists and their effects on the physiological response to exercise is presented below. The data are clarified if the two types of exercise, incremental graded (maximal) and prolonged submaximal exercise; and the types of dosing; acute versus chronic, are considered seperately.

i) Maximal exercise performance

Historically maximal exercise performance has been assessed by determining the VO_{2max}, maximal workload achieved (WL_{max}) or time taken to exhaustion. Noakes et al (1990) question the predictive value of $V0_{2max}$ as regards performance (51). Their findings suggest that peak treadmill running speed is a better predictor of performance than $V0_{2max}$. Therefore the interpretation of $V0_{2max}$ data should be viewed with circumspection if correlations are made to performance. For completeness all the data traditionally measuring maximal exercise performance as $V0_{2max}$ will be presented.

The exercise studies can be grouped into those that used acute (single) doses of drug and those in which long term administration was used (table 1).

Table 1. Performance during incremental graded exercise tests after the ingestion of various calcium antagonists. The frequency of the dose i.e either acute (stat) or long term administration is indicated.

Study	Drug	Dose	Exercise Type	Performance
Gordon et al 1986	Nifedipine	10 mg stat	IGE	↓
	Diltiazem	60 mg stat	IGE	→
	Verapamil	80 mg stat	IGE	→
Derman et al 1992	Nifedipine	20 mg stat	IGE	↓
Raffestin et al 1985	Nifedipine	20 mg stat	IGE	→
	Diltiazem	90 mg stat	IGE	→
Kindermann 1986	Nifedipine	40 mg daily	IGE	→
	Diltiazem	180 mg daily	IGE	→
Petri 1986	Verapamil	120-360 mg daily	IGE	→
Yamakado et al 1983	Diltiazem	180mg daily	IGE	→
Luurila et al 1987	Diltiazem	216 mg daily	IGE	→

Symbols represent no change (→) or a decrease (↓) in performance. Abbreviations: IGE, incremental graded exercise.

Gordon et al noted a significant reduction in VO_{2max} and performance time in normotensive subjects using cycle ergometry after a single dose of nifedipine 10 mg, however, after 60 mg diltiazem and 80 mg verapimil neither of these parameters were significantly altered (26). Raffestin et al (1985) using a single dose of nifedipine 20 mg and diltiazem 90 mg did not detect a change in the $V0_{2max}$ or maximum power output

after cycle ergometry in healthy individuals (58). Derman et al (1992) after a single dose of nifedipine 20 mg showed a significant decrease in time to exhaustion and peak work load achieved, however, the VO_{2max} was unchanged in normotensive subjects (17).

The duration of drug administration in the 'long term' studies varied from three times daily for three days (Petri 1986) to once daily for one month (Luurila 1987). After the administration of nifedipine 40 mg daily and diltiazem 180 mg daily Kindermann failed to show a difference in the VO_{2max} or maximal treadmill speed (35). Petri (1986) after long term administration of verapimil 120 mg to 360 mg demonstrated no change in VO_{2max} (57). In hypertensive patients, Yamakado et al (1983) failed to show a change in performance on treadmill testing after long term administration of diltiazem 180 mg daily (71). Luurila et al (1987) demonstrated no change in peak work load achieved using diltiazem, mean dose 216 mg per day, versus placebo in hypertensive subjects after long term administration (44).

A review of the data thus far is inconclusive in the findings that the calcium antagonists as a class attenuate maximal exercise performance. However, the majority of studies that used long term administration of such drugs did not show a reduction in performance data in both hypertensive and normotensive subjects. It would appear to be those studies that used acute dosing, and predominantly with nifedipine, that showed a decrease in one of the parameters traditionally used to measure performance. With invasive intra arterial blood pressure, cardiac output and peripheral resistance monitoring, Omvik and Lund Johansen (1993) detemined that the physiological changes that occur after the acute ingestion of a wide variety of antihypertensives is different to that after long term ingestion. After acute dosing various counter regulatory processes are stimulated, however these responses may be attenuated over time with long term therapy (54). This acute alteration in physiology may contribute towards explaining why the findings of

acute dose studies frequently differ from the studies performed after long term ingestion, furthermore, applying the findings of the acute dose studies to hypertensive patients on long term therapy may be inappropriate.

ii) Submaximal exercise performance :

Relatively few studies have been undertaken looking at the effects of calcium antagonists on the ability to perform prolonged submaximal exercise (table 2).

Table 2. Performance during prolonged submaximal exercise tests after the ingestion of various calcium antagonists. The frequency of the dose i.e either acute (stat) or long term administration is indicated.

Study	Drug	Dose	Exercise Type	Performance
Raffestin et al 1985	Nifedipine	20 mg stat	PSME (60% $V0_{2max}$)	→
Kindermann 1986	Nifedipine	20 mg b.d	PSME (75% $V0_{2max}$)	→
	Diltiazem	60 mg t.d.s	PSME (75% $V0_{2max}$)	→
Selvey et al 1994	Isradipine	2.5 mg b.d	PSME (75% $V0_{2max}$)	↓

Symbols represent no change (→) or a decrease (↓) in performance. Abbreviations: PSME, prolonged submaximal exercise. t.d.s, three times daily. b.d, twice daily.

Raffestin et al used nifedipine 20 mg in subjects cycling at 60% of their VO_{2max} for 45 minutes. All of these subjects completed both the placebo and nifedipine trial (58). He noted no difference in oxygen consumption. Kindermann et al studied the effects of nifedipine 20 mg twice daily and diltiazem 60 mg three times daily on prolonged exercise performed at 75% of VO_{2max} for 50 minutes on a treadmill. In this study, all of the subjects completed the 50 minutes and there was no difference in the rating of

perceived exertion when compared to placebo (36). These two trials are limited by the fact that the prolonged exercise was stopped at 45 minutes (Raffestin) and 50 minutes (Kindermann). It is possible that if the subjects were allowed to continue until the point of fatigue an effect on performance might have been demonstrated. However, Kindermann makes the point that if the group who ingested calcium antagonists tended to fatigue earlier than when ingesting placebo then one would have seen differences in the ratings of perceived exertion and this was not the case.

Selvey et al (1994) determined the effects of the calcium channel antagonist isradipine, 2.5 mg twice daily for four weeks, on maximal and prolonged submaximal exercise performance. They found that submaximal cycling time at 75% of VO_{2max} was significantly reduced after the ingestion of isradipine. The rating of perceived exertion was also increased after isradipine ingestion during submaximal exercise. This occured despite no change in submaximal oxygen consumption, ventilation, muscle power output or blood concentrations of free fatty acids, lactate and glucose when comparing isradipine to placebo. Selvey suggested that the effects of certain antihypertensive medications may only become apparent during prolonged submaximal exercise testing (61).

Further studies need to be undertaken to address the issue of calcium antagonists and the physiological response and performance during prolonged submaximal exercise as this is firstly the form of exercise that is prescribed for hypertensive patients, and secondly the type of exercise that they are most likely to take part in, not maximal exercise (16). Therefore there is a need to know the effects of these newer, commonly used agents, on this type of exercise.

Haemodynamics :

The effect that a calcium antagonist will have on the haemodynamic profile is determined to a large extent by the type of agent and whether it is an acute or chronic dose.

i) Heart rate

Nifedipine 20 mg as a single oral dose increases the resting heart rate by up to 9 beats per minute and after a single dose a diltiazem 90 mg it is reduced by four beats per minute. With long term treatment these changes are attenuated (36). There are studies which demonstrate no significant change in resting heart rate. Derman et al (1992), found resting heart rate to be unchanged after a single dose of nifedipine 20 mg (17). Studies looking at the chronic effects of felodipine and amlodipine failed to show any differences in resting heart rate (42, 43).

Maximal heart rate as determined during incremental graded exercise appears to be unchanged after nifedipine ingestion (17, 26, 36, 58). However, studies using diltiazem and verapamil demonstrate a fall in the maximum heart rate (36, 58, 71). Luurila et al (1987) demonstrated no change in maximal heart rate on diltiazem (44).

Heart rate during submaximal exercise is significantly increased on nifedipine when compared to placebo (26, 36, 58). There are also studies suggesting that there is no change in submaximal heart rate after the ingestion of nifedipine 20 mg (17). Trials using diltiazem and verapamil have demonstrated a decrease in the submaximal heart rate with both acute and long term administration (36, 44). The long acting dihydropyridines,

felodipine and amlodipine, do not appear to affect submaximal exercise heart rate (42, 43, 54).

The heart rate response at rest and during exercise is predictable considering the mechanisms of action of the different groups of calcium channel antagonists. Nifedipine, having a predominantly vasodilatory effect, results in an increased sympathetic drive. This can be seen in the significant rise in noradrenaline after nifedipine ingestion (49, 58). However, after long term administration there appears to be an attenuation in the response of noradrenaline to the peripheral vasodilatation. Verapamil and diltiazem lower blood pressure by a combination of a reduction in cardiac output and a decrease in the total peripheral resistance. This is accomplished by the dual action on arteriolar smooth muscle and the sinoatrial node. The compensatory tachycardia, seen with the vasodilatation, is inhibited by the inhibition on the sinoatrial node by these drugs. It should be noted that with the newer dihydropyridines, such as amlodipine, one does not see a change in heart rate at rest or during exercise when compared to placebo (42). This is possible as a result of the slower onset of action, negligible effect on the sino atrial node and longer plasma half-life, thereby ensuring a gradual vasodilation which may inhibit the rise in noradrenaline seen with a drug such as nifedipine.

ii) Blood pressure, Cardiac output and Total peripheral resistance:

There is little doubt concerning the efficacy of the calcium antagonists in lowering resting blood pressure (42, 43, 53, 54). Of more interest however, is the question as to how effective they are in lowering blood pressure in hypertensive individuals during maximal and submaximal exercise. It is fairly well established that the greater the pre treatment blood pressure is, the greater will be the antihypertensive effect with calcium influx inhibition (31).

In light of the above it is therefore not surprising to see that some of the studies done on normotensive subjects failed to show a significant reduction in blood pressure during either maximal or sub maximal exercise (17, 58). The total peripheral resistance is reduced to varying degrees with all calcium antagonists in hypertensive subjects at rest and during exercise. This occurs with very little change in cardiac output. However, in normotensive subjects the total peripheral resistance is changed very little and the effect on blood pressure is, therefore, relatively small (36).

Lund Johansen (1984) determined the effects of verapamil 120-240 mg daily in essential hypertensives during exercise. He found the reduction in systolic blood pressure to be significant at rest and low workloads but not significantly reduced at the higher workloads. The mean arterial pressure, however, was significantly reduced in all cases. The heart rate was reduced at rest and during exercise whilst the stroke index was increased thereby maintaining the cardiac output (41). Yamakado et al (1983) found diltiazem 180 mg daily sufficient to lower blood pressure in hypertensive patients during submaximal and maximal exercise. The heart rate was also reduced (71). Unpublished data from the same author suggests that cardiac output is unchanged with more strenuous work, thereby implying, as for verapamil, that the stroke index must have increased. However, there is also work suggesting that blood pressure is unaltered by diltiazem. Luurita et al (1987) compared the effects of diltiazem, mean dose 216 mg/day, and atenolol, mean dose 80 mg/day, versus placebo in hypertensive subjects. Whilst atenolol demonstrated significant reductions in blood pressure during maximal and submaximal exercise diltiazem was ineffective in lowering blood pressure during exercise (44).

Lund Johansen (1990) studied the effects of the phenylalkylamine, tiapamil, and the dihydropyridine calcium antagonists, amlodipine and felodipine, in essential

hypertensives during rest and exercise. He found all three drugs were successful in lowering blood pressure during submaximal exercise. However, the lowering of blood pressure after felodipine and amlodipine was entirely due to a reduction in total peripheral resistance whilst cardiac output was maintained. Tiapamil did not cause a significant drop in the total peripheral resistance and the mechanism whereby it produced a reduction in blood pressure was due to a combination of a reduction in total peripheral resistance as well as a reduction in cardiac output due to a decrease in heart rate (43).

The primary pathophysiological feature of essential hypertension is an increase in the total peripheral resistance. In the early stages of hypertension there is a slightly elevated cardiac output but ultimately, with left ventricular hypertrophy and a decrease in left ventricular compliance, cardiac output is reduced. This relative reduction in cardiac output is accentuated by exercise when compared to normotensive controls (40). When prescribing an antihypertenisive agent it would be preferable to correct the pathophysiology i.e. reduce the total peripheral resistance whilst at least maintaining or increasing the relative cardiac output. In Omvik and Lund Johansen's review (1993) of the haemodynamics after long term antihypertensive treatment the only drugs that demonstrated such a favourable haemodynamic profile at rest and during exercise were the dihydropyridine calcium antagonists, amlodipine and felodipine, and the alpha one receptor blocker, doxazosin (54).

Metabolic response :

Many of the hormones produced by the endocrine pancreas, anterior pituitary and adrenal medulla have a calcium dependent mechanism of release (36). Therefore it is possible that the calcium antagonists could affect the release of these hormones and thereby alter the metabolic response to exercise. Raffestin et al (1985) demonstrated significantly

higher concentrations of growth hormone during submaximal exercise. This was thought to be due to the increased sympathetic drive as demonstrated by the significantly higher concentrations of noradrenaline. It should be emphasised that this was an acute dose study where the catecholamine response is known to be greater. However to date, many of the trials undertaken during exercise, after long term treatment, have not demonstrated a change in serum insulin, growth hormone or cortisol (36, 58).

i) Catecholamines:

Nifedipine invokes an increase in plasma noradrenaline concentration both at rest and during exercise, but plasma adrenaline concentrations are unaffected (15, 39, 49, 58, 60). After long term administration, however, the rise in plasma noradrenaline concentration is attenuated. Plasma adrenaline and noradrenaline concentrations are unaffected by diltiazem or verapimil both at rest and during exercise, when compared to placebo (14, 49, 60). It is likely that the greater vasodilatory effect of nifedipine results in a reflex activation of the sympathetic nervous system, particularly after acute dosing, whereas this is not seen with verapamil or diltiazem which have predominant cardiac effects. An increased plasma renin concentration was found in subjects at rest after nifedipine ingestion which would correlate with an increased sympathetic activity (39). However, after long term administration of nifedipine one sees far less of a change in noradrenaline and renin activity. It would appear that the long term administration of nifedipine attenuates the compensatory mechanisms that occur after acute ingestion (36). There appears to be no effect of diltiazem or verapamil on serum noradrenaline or renin activity during steady state exercise.

ii) Carbohydrate metabolism :

During both steady state and maximal exercise there are no significant differences in blood lactate or glucose concentrations after long term administration of nifedipine and verapamil (36, 57). Raffestin et al (1985) demonstrated significantly higher blood glucose and lactate concentrations after nifedipine compared to placebo during submaximal exercise. He reasoned that this was due to the increased sympathetic drive which would account for an increased gluconeogenic and glycolytic flux and hence explain the higher lactate and glucose concentrations. However, Kindermann (1987) reported higher blood lactate concentrations after diltiazem and nifedipine when compared to placebo during prolonged submaximal exercise. The blood lactate concentration was slightly higher after diltiazem than after nifedipine, but not significantly so. Neither were the blood lactate concentrations significantly different to placebo. Kindermann makes the point that diltiazem brought about no reflex increase in sympathetic activity and therefore the greater concentrations of blood glucose and lactate demonstrated in Raffestin's trial cannot be explained by an increase in beta adrenergic stimulation of glycolysis and gluconeogenesis. However two points need to be highlighted in order to clarify these contradictory findings. Firstly, in Kindermann's study the actual differences in the lactate concentrations after calcium antagonist and placebo ingestion were very small (0.2 mmol/L after nifedipine and 0.7 mmol/L after diltiazem). In Raffestin's study there were much greater and significant differences in lactate concentration after nifedipine compared to placebo (58). It is possible that Kindermann's findings were simply due to random variation and there was no real difference in his results. Secondly, Raffestin used an acute dose in his trial which would induce a greater catecholamine response than long term administration, such as in Kindermann (1987) and Petri's (1986) trial.

In summary, it would appear that only those trials using acute doses of nifedipine demonstrated any real difference in carbohydrate metabolism and it is likely to be explained by the greater catecholamine response induced by this agent.

iii) Lipid Metabolism :

Free fatty acid and glycerol levels during exercise are unaffected by the long term administration of nifedipine or diltiazem. The respiratory exchange ratio is also unaltered when compared with placebo (36). Again it is Raffestin, using an acute dose of nifedipine, who demonsrated a difference in free fatty acids during the recovery phase after steady state exercise. It is possible that this may also be explained by increased lipolysis during exercise due to the increase in circulating noradrenaline. This would correlate well with the fall in the respiratory exchange ratio (RER) values which Raffestin found towards the end of the steady state exercise when on nifedipine (58).

Summary :

Much of the data reviewed thus far would suggest that neither submaximal or maximal exercise performance is adversely affected by the calcium channel antagonists after long term administration. In those studies that do reveal a reduction in performance, it is minimal. Cardiac pump function is maintained during exercise. There is, however, some doubt as to whether the calcium antagonists are effective in lowering blood pressure during exercise. In Omvik's review (1993) he suggests that the vast majority of drugs except epanolol were unsuccessful in decreasing the relative rise in blood pressure during exercise, but perhaps it is not the relative but the absolute rise that needs to be reduced for the acute and chronic end organ protection.

The hormonal and metabolic responses to exercise when a calcium antagonists is used in the long term is unchanged. This is not the case when Beta blockers are used (70). Therefore the calcium antagonists are attractive options when chosing a drug for the athletic or physically active hypertensive. The new dihydropyridine, amlodipine, is a once daily dose, long acting antihypertensive. It is effective in ensuring 24 hour blood pressure control with very few side effects (30). The type of exercise prescribed for hypertensive patients is of the prolonged submaximal type, however there is a paucity of data on performance and the physiological response to such exercise. Therefore the aim of this study is to determine the physiological response to maximal and prolonged steady state exercise after amlodipine ingestion.

THE EFFECTS OF AMLODIPINE ON EXERCISE PERFORMANCE IN MILD TO MODERATE ESSENTIAL HYPERTENSIVES

INTRODUCTION

It is well documented that regular aerobic exercise is beneficial in the prevention and treatment of hypertension (1, 2, 4, 5, 6, 10, 16, 20, 25, 29, 47, 50, 59, 63, 64). Therefore physical exercise is an important component in the comprehensive management of patients with hypertension. The fifth report of the joint national committee on detection, evaluation and treatment of high blood pressure (JNC V), suggests that exercise performed daily at an intensity of 40% to 60% of an individual's maximum oxygen consumption effectively lowers blood pressure in hypertensive subjects (50, 63). Since an increasing number of hypertensive patients will become involved in exercise programmes, it is essential that the medications used to treat hypertension do not interfere with the patients capacity to perform prolonged submaximal exercise.

Many of the traditionally prescribed antihypertensives, particularly the beta-blockers, impair exercise tolerance (55, 62, 65, 68). The calcium antagonists would appear to be one of the preferred agents for use in physically active patients (17, 36, 42, 43, 58). However, available data suggest that these agents are not devoid of an effect on exercise performance (17, 27, 61). Most research has concentrated on the effects of calcium antagonists on maximal exercise performance and very few involve the newer, long acting, dihydropyridine calcium channel antagonists. Furthermore, prolonged submaximal exercise is the optimum exercise mode for patients with hypertension. Hence, there is the need to establish whether the dihydropyridine calcium channel antagonists impair prolonged exercise performance.

Previous studies suggest that the dihydropyridine calcium antagonists effectively lower total peripheral resistance while maintain cardiac output at rest and during seven to eight minutes of submaximal exercise (42, 43). However, there are few data on cardiac output

and performance during more **prolonged** exercise, which is the type of exercise hypertensive patients take part in. Furthermore, the physiological response to maximal and submaximal exercise after the ingestion of amlodipine, a new dihydropyridine calcium channel antagonist, is unknown.

Therefore the aim of this study is to determine the effects of amlodipine on the physiological response to, and performance during, maximal and prolonged submaximal exercise. In order to determine if amlodipine influences the contractile properties of skeletal muscle, muscle function testing was also performed prior to and immediately after submaximal exercise.

MATERIALS AND METHODS

Medication and Study Design:

The effects of 5mg amlodipine ingested once daily on physiological measures and performance during maximal and prolonged submaximal exercise were compared in a double blind, randomised, crossover study. A two week placebo run in period was employed. This was followed by two, two week treatment periods seperated by a fourteen day washout period (fig. 1).

Subjects and testing methods :

The study was approved by the American Food and Drug Administration and the Ethics and Research Committee of the Faculty of Medicine at the University of Cape Town. All subjects provided written informed consent and were given a full medical examination and resting electrocardiogram prior to the start of the study. Subjects for the study were

10 male, hypertensive, recreational athletes. To be included in the study mean supine diastolic blood pressure had to be between 95 and 115 mmHg, determined as the mean of three recordings at the end of the placebo run in period; and the subjects had to be free of any other cardiovascular, respiratory, or musculoskeletal disorders.

Subjects were asked to maintain their usual training programme throughout the trial in order that a constant level of fitness be maintained. Strenuous physical exercise was to be avoided for the 24 hours preceeding each laboratory test. No caffeine containing foods or drinks were to be consumed on the day of testing. All tests were performed at the same time of day, approximately three hours after the ingestion of the last dose of medication.

Subjects reported to the laboratory at the end of the placebo run in period (end of week 2), to perform a familiarization maximal cycle test (fig 1). The maximum oxygen consumption (VO_{2max}) measured in this test was used to determine the workload used in the prolonged submaximal exercise test.

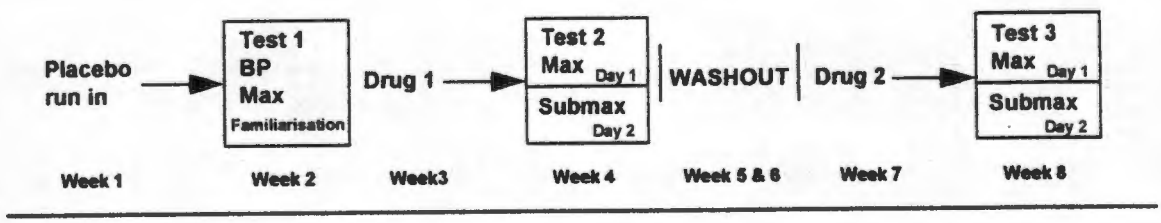

Fig 1. Trial protocol. Abbreviations: BP, blood pressure. Max, incremental graded test to exhaustion. Submax, prolonged submaximal test at 75% of maximum oxygen consumption.

Systolic and diastolic blood pressure and heart rate were measured whilst supine and after 5 minutes of standing (average of three readings, one minute apart), at the end of each week. All blood pressure readings were taken by the same investigator throughout the trial using a mercury sphygmomanometer (Standby, W.A. Baum Co. Inc, New York, USA) recording Korotkoff phase I and IV.

Subjects then ingested either placebo or amlodipine for two weeks followed by a two week washout period, whereafter they ingested either amlodipine or placebo (cross over) for a further two weeks. At the end of weeks 4 and 8, subjects performed a maximum cycle test to exhaustion for determination of $V0_{2max}$ and blood pressure measurements. Heart rate, rating of perceived exertion and blood lactate concentrations were also measured. The following day subjects performed a prolonged submaximal test at 75% $V0_{2max}$ for determination of cardiac output, time to fatigue; heart rate, blood pressure, and blood concentrations of lactate, glucose and free fatty acids.

Incremental Graded exercise testing to exhaustion:

For measurement of $V0_{2max}$ and physiological changes during maximal exercise, subjects performed maximal progressive exercise to exhaustion on an electro-mechanically braked cycle ergometer (Siemens, Johannesburg, South Africa).

A self paced warm up was allowed. Subjects started pedalling at a workload of 700 kiloponds. The workload was increased by 100 kiloponds every minute until the subject voluntarily terminated the test.

Blood was sampled every minute through an indwelling intravenous catheter (Jelco Teflon, Halfway House, South Africa) for determination of plasma lactate concentration

(Lactate Pap, Bio Merieux, Lyon, France). Blood samples were centrifuged, seperated and then frozen for later analysis. Blood pressure was measured every minute by means of audible sphygmomanometry using a calibrated mercury column sphygmomanometer, with the appropriate sized cuff, as previously detailed (Standby, W.A. Baum Co. Inc, New York, USA). Korotkoff phase I & IV were used. Heart rate was determined each minute using an electrocardiogram monitor (Lohmerier, Munich, Germany) with self adhering electrodes in the CM 5 position.

During exercise inspired and expired air was analysed for oxygen and carbon dioxide content as well as inspiratory volume using the Cardiopulmonary Exercise System (Medical Graphics Corporation, CPX / D Series 2 Model No 762018-101, St Paul, Minnesotta, USA). Both analysers were calibrated before each test using gases of known composition.

The VO_{2max} was taken as the highest rate of oxygen consumption measured during any 60 second period (Noakes et al 1988). Rates of oxygen consumption (VO_2), carbon dioxide production (VCO_2), respiratory exchange ratio (RER) and ventilation (V_i) were recorded for every breath cycle. Every 30 seconds the average value of the preceding 9 breaths was recorded and stored for later printing.

Peak workload was taken as the highest workload (kiloponds) maintained for a complete minute during the test. When a subject was unable to complete the full minute at a particular workload, the workload of the immediately preceding, completed workload was recorded as the peak workload. Exercise time to exhaustion was taken to the nearest 30 seconds.

Subjects were asked to report their level of perceived exertion from the appropriate scale during each minute of the exercise test (Borg 1982).

Prolonged submaximal exercise testing:

Prolonged submaximal exercise testing was performed the day following the incremental maximum test. Subjects cycled at a workload corresponding to 75% of their predetermined VO_{2max}. They were to maintain a cadence between 60 and 70 rpm for one hour or until they could no longer maintain a cadence in excess of 60 rpm.

Blood was sampled through an intravenous catheter at rest, 20 min, 40 min, 60 min and 10 minutes after the termination of exercise. Plama lactate concentrations were determined as previously described. Plasma glucose concentrations were determined using the Beckman Glucose analyser 2 (Brea, California, USA). Serum free fatty acid concentrations were determined with a standard enzymatic kit method (Free Fatty Acids, Half-Micro test, Boehringer Mannheim Biochemica, Germany).

Blood pressure, heart rate and rating of perceived exertion were recorded every 15 minutes as previously described.

The rate of oxygen consumption (VO_2), carbon dioxide production (VCO_2), respiratory exchange ratio (RER) and ventilation (V_i) were recorded every 15 minutes using the same cardiopulmonary exercise system (Medical Graphics Corporation, CPX / D Series 2, Model No 762018-101, St Paul, Minnesotta, USA).

Determination of cardiac output was based on the Fick principle. Cardiac output was measured every 15 minutes using the indirect, Defares rebreathing method (32). All of

the calculations required were performed by the computerised cardiopulmonary exercise system.

The total peripheral resistance was calculated by dividing the cardiac output by the mean arterial pressure (MAP). MAP was calculated by adding 1/3 of the pulse pressure to the diastolic blood pressure (3).

Tests of skeletal muscle function:

Tests of skeletal muscle function were performed prior to and directly after the submaximal exercise test. The maximal voluntary isometric torque produced by the right quadriceps muscle was measured on a custom made, leg stabilising chair according to methods previously described (12). Each subject first performed 4-5 maximum voluntary contractions (MVC). After a recovery period, subjects performed repetitive maximum voluntary isometric contractions for 6 seconds followed by a 4 second rest period. Maximum contractions were repeated until the subject was unable to maintain a torque greater than or equal to 70% of the initial MVC for at least 3 seconds of the 6 second contraction. The duration of activity to this point was recorded as the time to fatigue. The value is considered to be a measure of the resistance of the skeletal muscle to fatigue (Coetzer et al 1993).

Statistical analysis

The significance of differences between the variables over time and between trials when on amlodipine or placebo were analysed using a one way analysis of variance. The Student's t - test using two tailed p values corrected for unequal variances was used when comparing the mean values of data at the various time intervals. Significance was

established at the 0.05 confidence level. All data are presented as the means ± standard deviations of the mean. When comparing sample means of groups with $n < 10$, Levene's test for homogeneity was used. If the variances were found to be unequal then the Mann Whitney U test for unpaired data was applied.

RESULTS

Subject characteristics

Subjects for the study were 10 male recreational athletes of mean age 45 ± 8 yrs (range 28 - 53 yrs), mean height 176 ± 9 cm (range 156 - 189 cm), mean mass 80 ± 10 kg (range 65 - 96 kg), and mean VO_{2max} 34 ± 7 ml.O_2.kg^{-1}.min^{-1} (range 24 - 43 ml.O_2.kg^{-1}.min^{-1}).

Resting cardiovascular measurements

The mean standing systolic blood pressure at rest after the two week placebo run in period was 147 ± 18 mm Hg whilst the mean diastolic blood pressure was 103 ± 6 mm Hg. Systolic pressure after two weeks of placebo was 142 ± 13 mm Hg and diastolic pressure was 100 ± 9 mm Hg. Systolic blood pressure decreased to 133 ± 12 mm Hg ($p<0.05$) and diastolic blood pressure tended to be lower at 95 ± 8 mm Hg after the ingestion of amlodipine (fig 2). Heart rate at rest was unchanged (74 ± 12 beats per minute vs 73 ± 12 beats per minute, amlodipine vs placebo) (fig 3).

Exercise performance and cardiorespiratory measurements during maximal exercise:

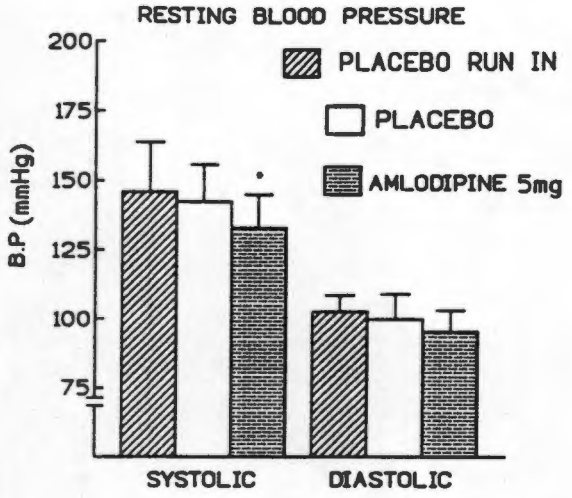

Fig 2. Resting blood pressure measurements in the standing position. * = P<0.05 vs placebo values. All values are means ± SD.

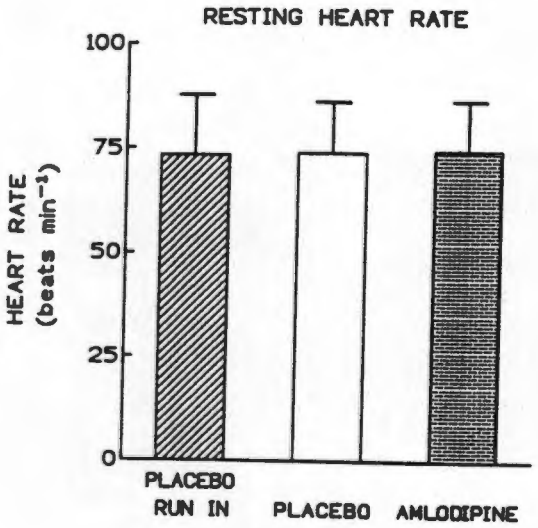

Fig 3. Resting heart rate in the standing position.

	PLACEBO		AMLODIPINE	
Resting heart rate (beats.min^{-1})	73	± 12	74	± 12
Peak heart rate (beats.min^{-1})	165	± 16	168	± 13
Resting systolic blood pressure (mmHg)	142	± 13	133	± 12
Peak systolic blood pressure (mmHg)	170	± 16	181	± 21
$V0_2$ max (ml.O_2.kg^{-1}.min^{-1})	33.1	± 4.9	30.5	± 4.8
Peak RER	1.17	± 0.01	1.26	± 0.1
Ventilation (Litres.min^{-1})	110.4	± 20.9	106.2	± 22.2
Time to fatigue (minutes)	8.3	± 1.7	8.15	± 1.8
Maximum workload (kpm.min^{-1})	1435	± 176	1415	± 179

Table 3 : Physiological measurements at rest and during maximal exercise. Data are presented as means and standard deviations. Abbreviations ($V0_2$ max) maximum oxygen consumption. RER, respiratory exchange ratio.

Data from the maximum tests at peak exercise are documented in Table 3. Although the mean VO_{2max}, time to fatigue and maximum work load tended to be lower with amlodipine, the differences were not significant. Heart rate and ventilation were unaffected by amlodipine. Peak systolic blood pressure tended to be higher after amlodipine.

Measurements of systolic blood pressure, heart rate, plasma lactate concentration, oxygen consumption ($V0_2$), ventilation (V_i) and respiratory exchange ratio were not different during exercise with either amlodipine or placebo. The rating of perceived exertion was higher after the fifth minute of exercise following amlodipine ingestion whereas blood lactate concentrations were not different (figs 4-10).

Exercise performance and cardiorespiratory measurements during submaximal exercise :

Mean time to fatigue was 41 ± 19 min after the ingestion of amlodipine compared with 44 ± 19 min after placebo (fig 11). Ratings of perceived exertion, minute ventilation and submaximal $V0_2$ were not statistically different between the trials. However, submaximal (VO_2) tended to be lower following amlodipine ingestion (figs 12-14).

Haemodynamic measurements:

Heart rate, cardiac output, systolic blood pressure and total peripheral resistance were not different after amlodipine ingestion compared to placebo (figs 15-18).

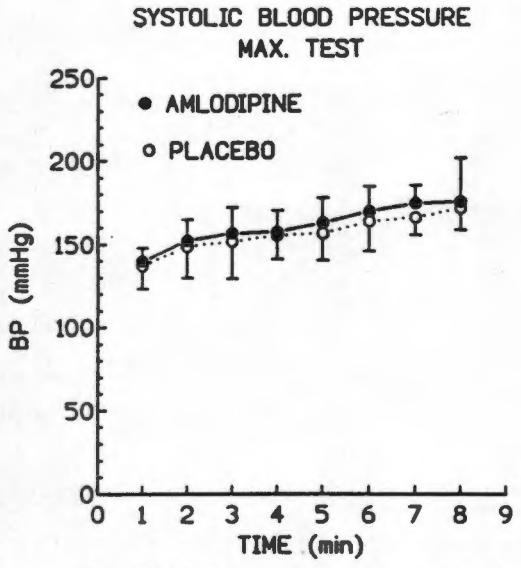

Fig 4. Systolic blood pressure during max. cycle test. Paired data are presented up to min 8 whereafter > 50% of the group had terminated exercise.

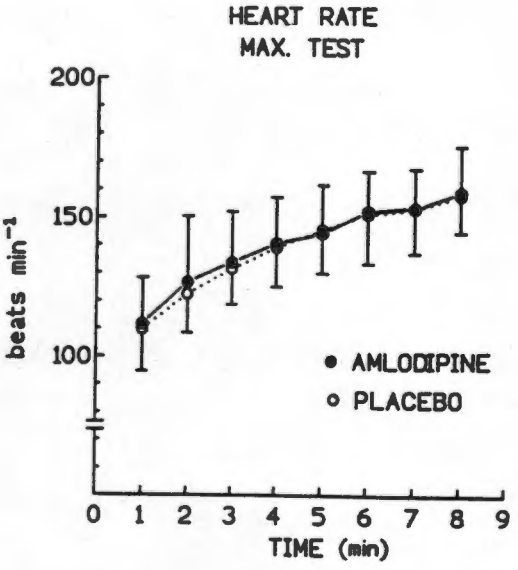

Fig 5. Heart rate during max. test. Paired data are shown up to minute 8 whereafter > 50% of the subjects had terminated exercise.

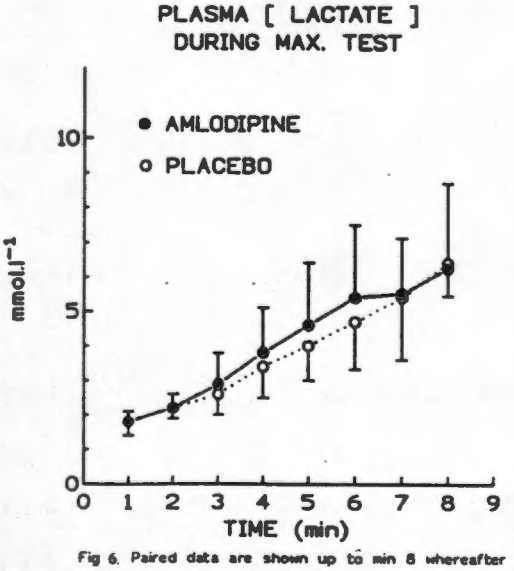

Fig 6. Paired data are shown up to min 8 whereafter > 50% of the subjects had terminated exercise.

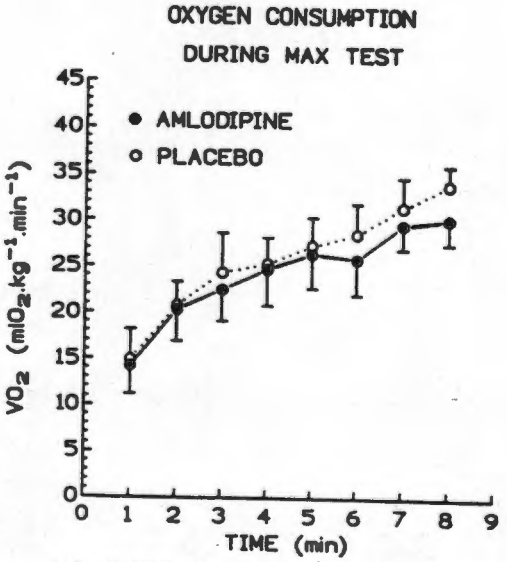

Fig 7. Paired data are shown up to min 8 whereafter > 50% of the subjects had terminated exercise.

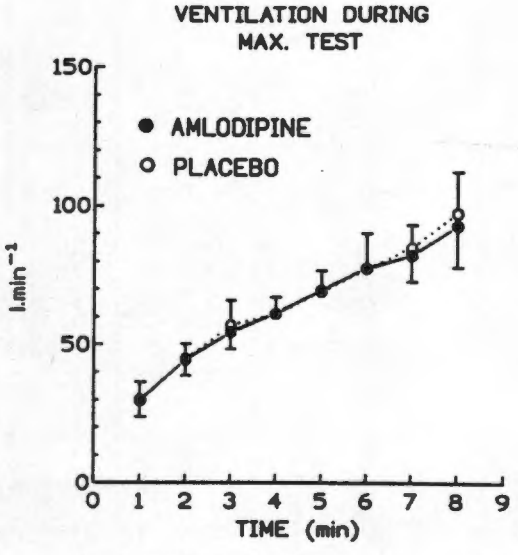

Fig 8. Paired data are shown up to min 8 whereafter > 50% of the subjects hed terminated exercise.

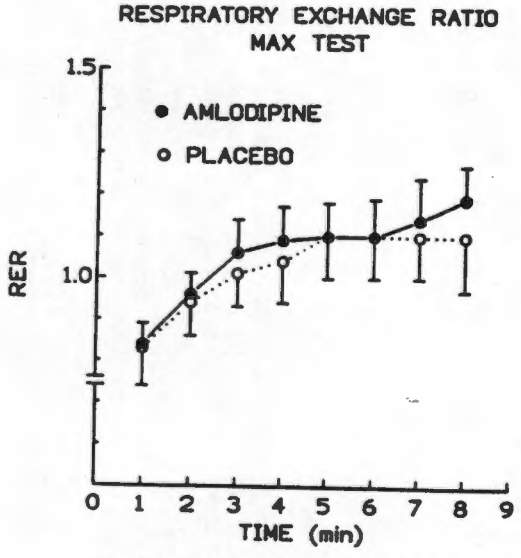

Fig 9. Paired data are shown up to min 8 whereafter > 50% of the subjects had terminated exercise.

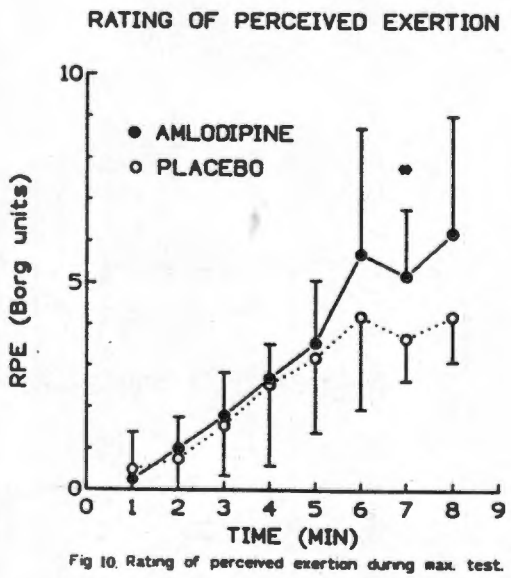

Fig 10. Rating of perceived exertion during max. test. Paired data are shown up to min 8 whereafter > 50% of the subjects had terminated exercise. * $p<0.05$

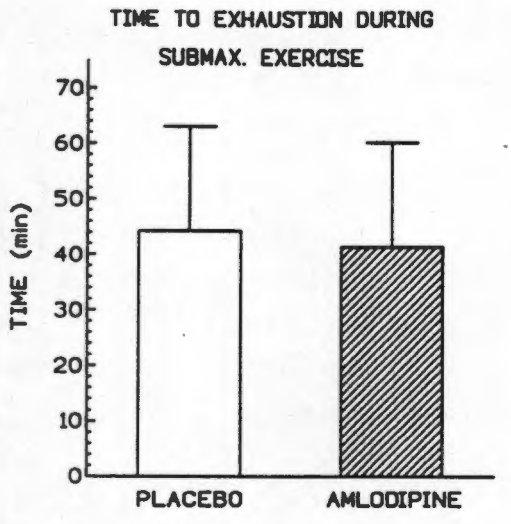

Fig 11. Time to exhaustion during submax. exercise.

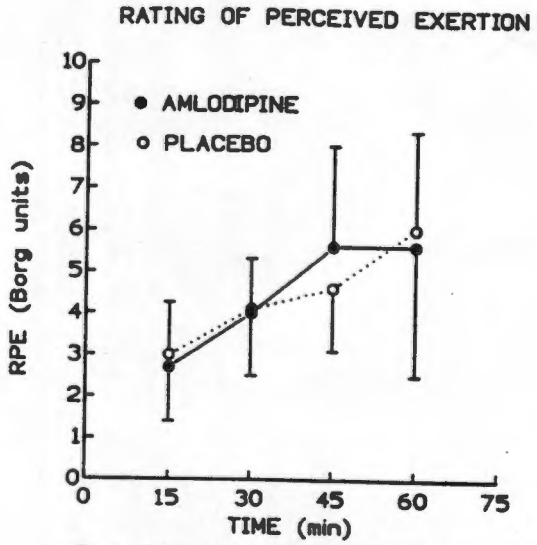

Fig 12. Rating of perceived exertion using the modified Borg scale. Only paired data are shown. At 15 min n=10, 30 min n=7, 45 min n=5, 60 min n=3.

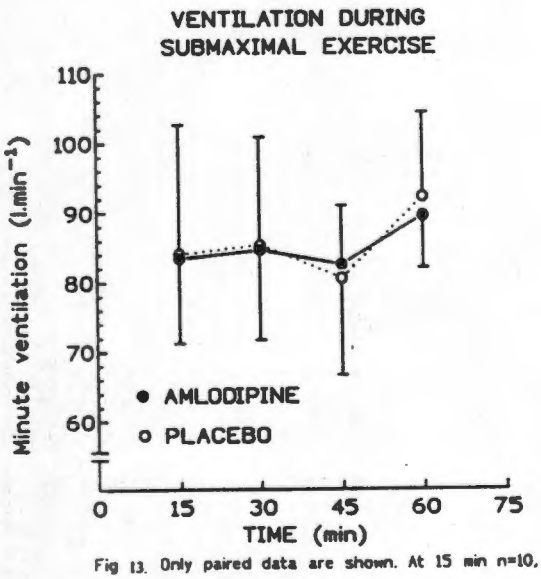

Fig 13. Only paired data are shown. At 15 min n=10, 30 min n=7, 45 min n=5, 60 min n=3.

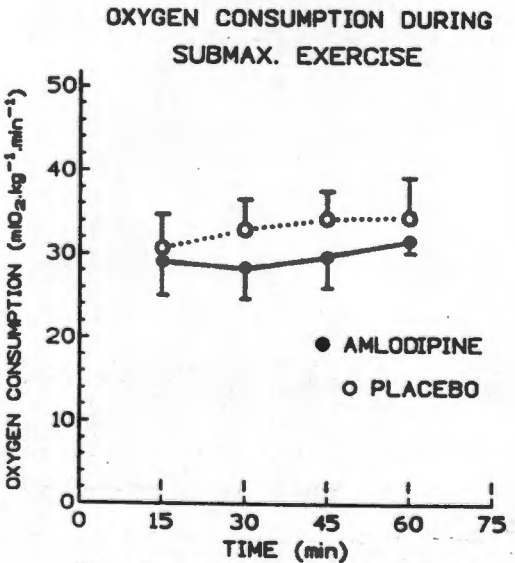

Fig 14. Only paired data are shown. At min 15 n=10, 30 min n=7, 45 min n=5, 60 min n=3.

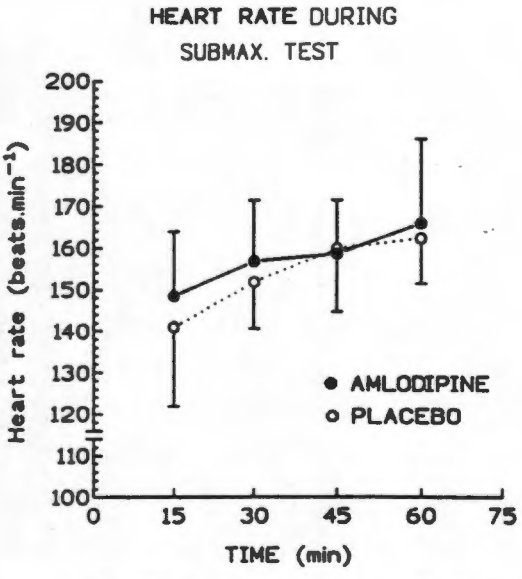

Fig 15. Only paired data are shown. At 15 min n=10, 30 min n=7, 45 min n=5, 60 min n=3.

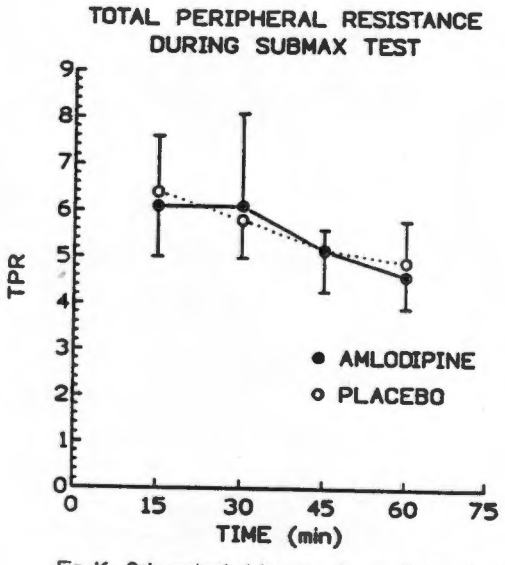

Fig 16. Only paired data are shown. At min 15 n=10, 30 min n=7, 45 min n=5, 60 min n=3.

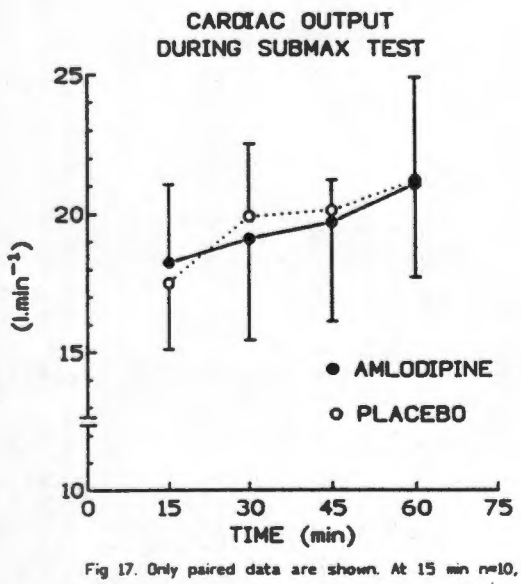

Fig 17. Only paired data are shown. At 15 min n=10, 30 min n=7, 45 min n=5, 60 min n=3.

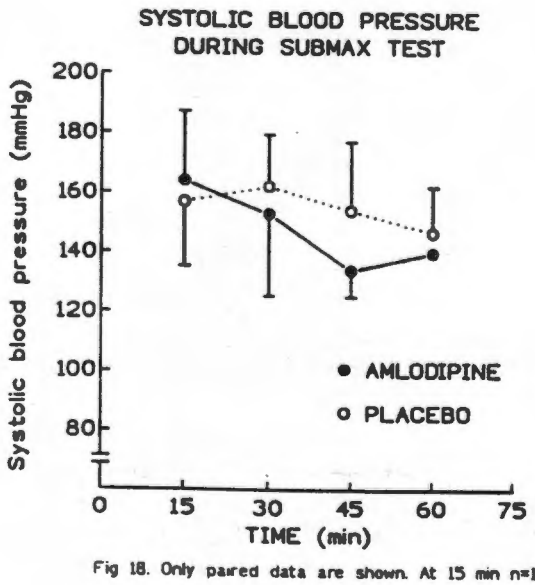

Fig 18. Only paired data are shown. At 15 min n=10, 30 min n=7, 45 min n=5, 60 min n=3.

Skeletal muscle function:

Muscle function was not different between trials when comparing values prior to and after exercise (fig19). Mean maximum voluntary contraction prior to and post exercise was not different when comparing amlodipine with placebo. The time to fatigue prior to and post exercise was not different when comparing amlodipine with placebo.

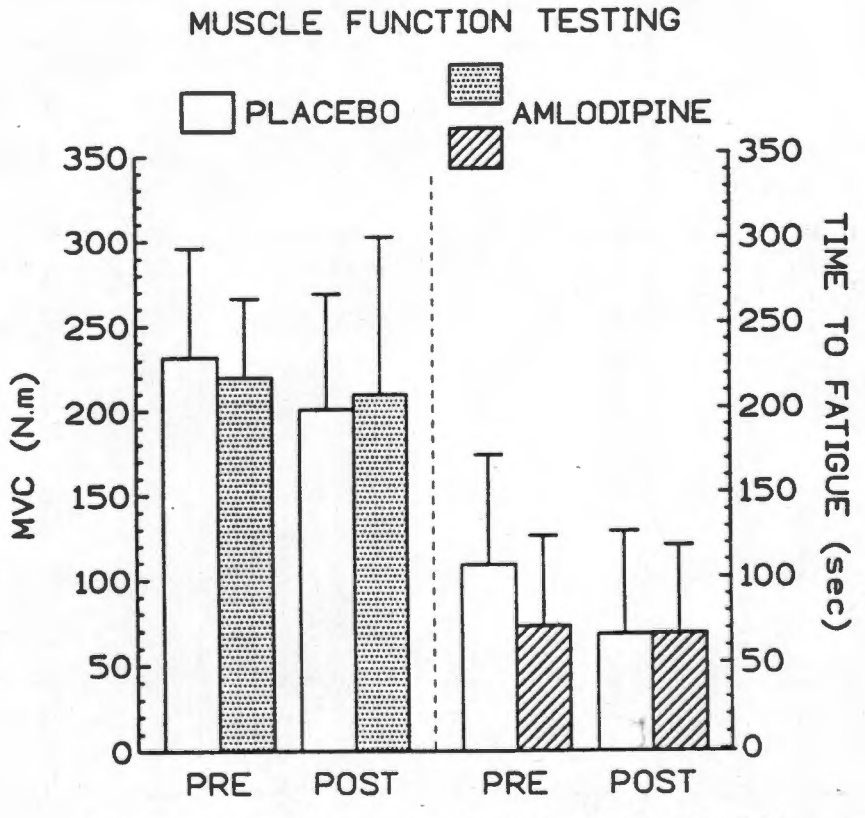

Fig 19. Muscle function testing.MVC = maximum voluntary contraction in Newton metres (N.m).Testing was done pre & post submax exercise.

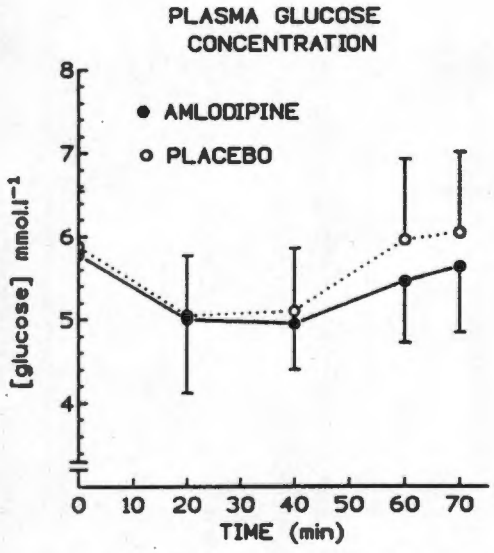

Fig 20. Plasma glucose concentrations at rest 20, 40, 60 and 10 min post termination of exercise. Only paired data are shown. At 20 min n=10, 40 min n=7, 60 min n=3.

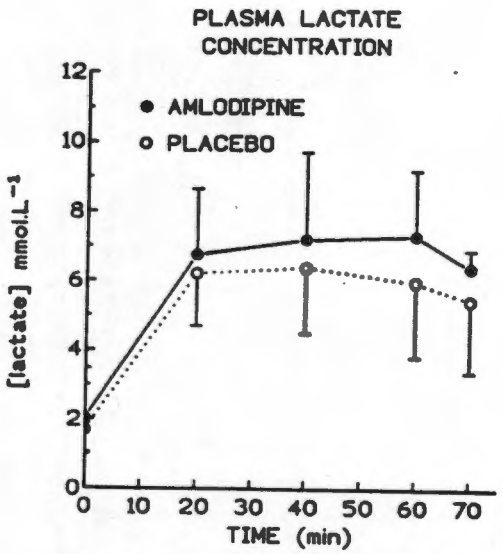

Fig 21. Plasma lactate concentration at rest, 20, 40, 60 and 10 min post termination of exercise. Only paired data are shown. At 20 min n=10, 40 min n=7, 60 min n=3.

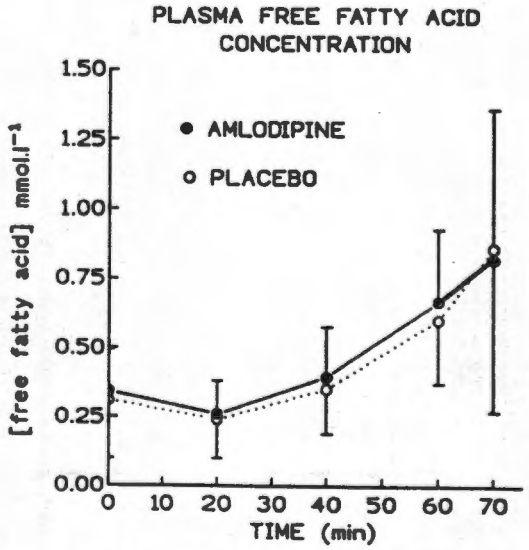

Fig 22. Plasma free fatty acid concentration at rest 20, 40, 60 and 10 min post termination of exercise. Only paired data are shown. At 20 min n=10, 40 min n=7, 60 min n=3.

Plasma glucose, lactate and free fatty acid concentrations:

Plasma glucose, lactate and free fatty acid concentrations were not different between trials (figs 20-22).

Discussion

Essential hypertension is an extremely common disorder. The widespread availability of large numbers of athletic hypertensive patients, willing to undergo invasive exercise testing, is not common. As a result incorporating large numbers of subjects into such studies is difficult. Therefore studies such as the current one, with small numbers of subjects, are prone to type II error. Therefore the power to detect significant differences is greatly reduced. However, accepting this proviso, the current study does demonstrates a number of important findings. First, 5 mg of amlodipine ingested once daily over a two week period, effectively lowered systolic blood pressure at rest in physically active, hypertensive individuals. Resting heart rate was unaffected by ingestion of amlodipine. This is in agreement with other studies (42, 54).

Second, maximal exercise performance measured as peak achieved work load was unaffected by the ingestion of amlodipine. This would concur with the findings of other studies after the long term administration of calcium antagonists (36, 44, 57, 71). There are studies which demonstrate a reduction in performance after the acute ingestion of nifedipine; the aetiology of this effect is not immediately apparent (17, 26). However, there is evidence to suggest that the physiological response after the acute ingestion of antihypertensive agents is different to the physiological response after the long term administration (53, 54). Therefore, it is possible that the altered physiology may explain the reduction in performance.

To date, as far as we are aware, there is only one study demonstrating a reduction in prolonged submaximal exercise performance in hypertensive subjects after the ingestion of a dihydropyridine. Selvey et al (1994) demonstrated a significant reduction in prolonged submaximal exercise performance as well as higher ratings of perceived exertion after the ingestion of isradipine. They concluded that the reduction in performance after the ingestion of isradipine occurred despite unchanged cardiovascular and physiological measurements, as well as no change in measurements of muscle power when compared to placebo. Therefore, the reason for the decrease in performance was not immediately apparent. Selvey et al suggested that the effects of certain antihypertensives may only become apparent during prolonged submaximal exercise (61).

However, the third important finding in the present study was that prolonged submaximal exercise performance was not affected by the ingestion of amlodipine in keeping with previous studies (36, 58). A criticism of these studies is that the exercise was not continued until volitional exhaustion but was discontinued after pre-set times of 45 minutes (58) and 50 minutes (36). All subjects in these studies completed the required exercise time. In the latter it was argued that if there was to be a difference in performance beyond 50 minutes then this would have been reflected in the preceding ratings of perceived exertion when compared to placebo, however these were not different.

The fourth finding of the study was that systolic blood pressure and heart rate were not altered during incremental graded exercise after the ingestion of amlodipine when compared to placebo. The effects on heart rate are in keeping with the findings of Lund Johansen et al (42, 43). However, they found that submaximal systolic blood pressure

was significantly lower at all work loads, predominantly due to a fall in total peripheral resistance, after the ingestion of amlodipine.

Cardiac output, systolic blood pressure, heart rate and total peripheral resistance were not affected during prolonged submaximal exercise after the ingestion of amlodipine in the present study. As previously indicated, these findings contrast with those of Lund Johansen et al (1990) who found that systolic blood pressure was significantly decreased at submaximal work loads after the long term ingestion of amlodipine (42) and felodipine (43). Cardiac output was either unchanged (felodipine) or increased (amlodipine). The reduction in blood pressure was entirely due to a decrease in the total peripheral resistance. Therefore, it is surprising that no difference in blood pressure was detected during exercise after the ingestion of amlodipine in the current study.

The lack of a measurable change in exercising blood pressure in our subjects might be explained by a number of possibilities or a combination thereof. Firstly, amlodipine may have had no effect on exercising blood pressure due to the subjects' physically trained state. Secondly, the exercising blood pressure may have been reduced but the actual reduction might have been too small to be detected due to an inadequate washout period, inherent difficulties with indirect blood pressure measurement or the dosage of amlodipine used. These points will be discussed in detail below.

i) The subjects in the current study were a hypertensive population with a mean systolic blood pressure after the placebo run in of 147 ± 18 mm Hg and diastolic blood pressure of 103 ± 6 mm Hg. However, the systolic blood pressure of these subjects, during both prolonged submaximal and maximal exercise, was not characteristic of a true hypertensive response to exercise. The American College of Sports Medicine describe a hypertensive response to exercise as one in which the peak exercising systolic blood

pressure is greater than 225 mm Hg (2). However, the subjects in the present study had a mean peak systolic blood pressure of 170 ± 16 mm Hg during the incremental maximum test after placebo ingestion. In both of Lund Johansen et al's trials (42, 43) the subjects had a mean systolic blood pressure of > 200 mm Hg at 100 watts of submaximal exercise after the ingestion of placebo. A work load of 100 Watts corresponds to approximately 700 kiloponds which is equivalent to the work load at which our subjects began cycling during the maximum test. Mean systolic blood pressure at this work load after the ingestion of placebo was 137 ± 14 mm Hg. Therefore, although the subjects in the present study are truly hypertensive as reflected by their resting blood pressure measurements whilst on placebo, the increase in blood pressure during exercise is not of the magnitude one would expect with untrained hypertensive subjects. It is known that the higher the blood pressure, the greater the effect of calcium channel antagonists in reducing it (31). It is therefore possible that, due to their state of physical training resulting in a lower exercising blood pressure response compared to untrained hypertensive subjects, calcium antagonists might not have had as great an effect on systolic blood pressure during exercise.

The second possibility was that there may have been a reduction in blood pressure but this was too small to be detected.

ii) The washout period period used in the current study was ten days. Amlodopine is recomended as a once daily dosage due to the long plasma half-life. It is therefore possible that the two week washout period may not have been adequate for subjects to clear the drug effectively. Therefore, the subjects who ingested placebo second may not have been completely clear of amlodopine. As a result, exercising blood pressure measured during that part of the trial may have been reduced due to the residual effects

of amlodipine and thereby resulting in a falsely reduced mean exercising systolic blood pressure in the placebo group.

iii) The percent change in systolic blood pressure at rest was only 6% after the ingestion of amlodipine. Using intra-arterial blood pressure monitoring, it has been shown that the percent reduction in systolic blood pressure at rest is greater than the percent reduction during exercise after long term administration of calcium channel antagonists (54). It is therefore possible that, due to the difficulty in accurately measuring blood pressure during exercise using the indirect technique, we may not have been able to detect small (< 6%) changes in systolic blood pressure during submaximal exercise (21, 28, 69).

iv) Finally, in Lund Johansen's trials higher mean doses of dihydropyridines were used, 9 mg of amlodipine and 15 mg of felodipine daily compared to the 5 mg of amlodipine used in our study (42, 43). Therefore 5 mg of amlodipine may not have been sufficient to significantly lower exercising blood pressure in our subjects.

During the incremental graded exercise test the rating of perceived exertion (RPE) tended to be higher beyond the fifth minute after the ingestion of amlodipine, and at minute seven it was significantly higher. However the other physiological variables such as oxygen consumption (VO_2), respiratory exchange ratio (RER), plasma lactate concentration and minute ventilation were not different during prolonged submaximal exercise following the ingestion of amlodipine. Derman et al (1992) also found a higher RPE after the ingestion of calcium antagonists and they speculated that it might be due to an effect on the central nervous system or impaired muscle contractile function (17). Muscle function testing before and after the prolonged submaximal test, revealed no differences between drug and placebo in our trial thereby excluding increased skeletal muscle fatigue as a cause of the increased perception of effort. Furthermore there was no

change in performance suggesting that the contractile properties of skeletal muscle during the maximal test were maintained. Therefore the reason for the increased rating of perceived exertion in the latter stages of the incremental test is not directly apparent but was not related to changes in oxygen consumption, respiratory exchange ratio, minute ventilation, plasma lactate concentrations or skeletal muscle function.

During prolonged submaximal exercise, oxygen consumption, rating of perceived exertion, minute ventilation, plasma glucose and lactate concentrations and blood free fatty acid concentrations, were not altered by amlodipine ingestion which is in keeping with other studies (36). However, the potential problems with the long haif life of amlodipine as described earlier, may have affected these variables as well.

Conclusion

This study has extended previous work on the effects of ingestion of long acting calcium antagonists, in particular the dihydropyridines, on exercise performance. We conclude that the daily administration of 5 mg of amlodipine over two weeks is effective in lowering resting systolic pressure but the haemodynamic response during exercise, in athleticly trained hypertensive individuals, was not significantly different when compared to placebo. Maximal, prolonged submaximal exercise performance and skeletal muscle function are unaltered following the ingestion of amlodipine in these patients. The sample size in the current study is small and therefore the findings are limited by the possibility of a type II error. However, amlodipine would appear to be a physiologically appropriate and effective drug for the use in physically active hypertensive patients. Further studies with greater subject numbers are needed.

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