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Comparative effects of calcium channel antagonism and beta-1 selective blockade on exercise performance in physically active hypertensive patients.

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Declaration

I, *Christine Enid Selvey*, hereby declare that the work on which this thesis is based is my original work and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

This thesis is presented in fulfilment of the requirements for the degree of Master of Science in Medicine.

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Publications and presentations

The research described in this thesis has been published in abstract form: Selvey, CE, Derman EW, Noakes TD. Calcium antagonists impair prolonged submaximal exercise performance without altering VO_2max or anaerobic power. Med Sci Sports Exerc 1994;26(5):Suppl. 1033.

A journal article reporting on the studies presented in this thesis is in the late stages of preparation to be submitted to *Clinical Drug Investigations*.

The research was presented by myself at the annual conference of the Australian Sports Medicine Federation in November 1993 in Melbourne: Selvey CE, Derman EW, Noakes TD. Comparative effects of calcium channel antagonism and β_1-selective blockade on exercise performance in active hypertensive patients.
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Abstract

The current recommendations by the American Heart Association for health promotion are that all persons should partake in regular physical activity in order to reduce the risk of cardiovascular disease. Regular physical exercise reduces blood pressure and is an important component of the management of hypertension. It is therefore important that patients with hypertension participate in habitual physical exercise. Many hypertensive patients who exercise will require anti-hypertensive medication. However, some anti-hypertensive agents cause fatigue during exercise. In order for patients to gain the full benefits of an active lifestyle, it is important that the prescribed anti-hypertensive agent does not prevent them performing and enjoying sustained exercise.

It has been well documented that ß-blockers cause premature fatigue during physical exercise. The effects on exercise performance of other first line anti-hypertensive medications, such as calcium channel antagonists have not been extensively investigated. In particular, the effects of these agents on prolonged submaximal exercise endurance have not been well studied.

The object of this thesis was to compare the effects of isradipine, a dihydropyridine calcium channel antagonist, to those of atenolol, a β_1-selective antagonist, on maximal and submaximal exercise performance and on short duration high-intensity exercise in physically active hypertensive patients.

The study design was a crossover trial where drug treatments were double blinded and randomised. Physically active volunteers with mild to moderate hypertension were recruited. 11 subjects performed i) progressive exercise to exhaustion for determination of maximal oxygen consumption (VO_2max), maximal work load and cardiorespiratory responses to maximal exercise, ii) prolonged submaximal exercise for determination of exercise endurance, cardiorespiratory responses and ratings of perceived exertion (RPE), and iii) short duration, high intensity exercise consisting of a 30 second maximal

exercise test (Wingate test) to determine skeletal muscle power output, following 4 weeks ingestion of isradipine (2.5mg bd), atenolol (50mg bd) or placebo.

Diastolic blood pressure at rest was reduced by both atenolol and isradipine, but was lowered to a greater extent by atenolol (83.3 vs 89.0 vs 96.1 mmHg, atenolol vs isradipine vs placebo, $p<.0005$). Systolic blood pressure at rest tended to be similarly reduced by both agents, but was significantly reduced during maximal and submaximal exercise by atenolol only ($p<.001$,atenolol vs isradipine, placebo). Heart rate at rest and during maximal and submaximal exercise was decreased by atenolol only ($p<.0005$, atenolol vs isradipine, placebo).

Maximal exercise performance was reduced after atenolol ingestion compared to placebo but not after isradipine ingestion. Peak workload achieved during the maximal exercise test was decreased after atenolol but unchanged after isradipine ingestion(214 vs 243 W, atenolol vs placebo, $p<.01$). Similarly, VO_2max was reduced after atenolol compared to placebo but was unchanged after isradipine ingestion (33.6 vs 36.4, 33.6 vs 36.1 mlO_2/kg/min, atenolol vs placebo, atenolol vs isradipine, $p<.05$).

Both atenolol and isradipine ingestion reduced submaximal endurance time compared to placebo (27.8 vs 46.4, 34.4 vs 46.4 min, atenolol vs placebo, isradipine vs placebo, $p<.005$), and increased rating of perceived exertion (RPE) after 30 min of submaximal exercise ($p<.05$). Submaximal oxygen consumption (VO_2), ventilation, respiratory exchange ratio (RER) and blood lactate, glucose and free fatty acid concentrations were not altered after the ingestion of either agent.

Neither agent influenced peak skeletal muscle power, total work done, or rate of fatigue during the Wingate test compared to placebo.

The results of these studies indicate that impaired performance and increased RPE during submaximal exercise after ingestion of either atenolol or isradipine is not due to alterations of ventilation, VO_2, RER, or blood lactate, glucose and free fatty acid concentrations during prolonged submaximal exercise. Similarly, reduced submaximal exercise performance after atenolol or isradipine ingestion is not due to factors which would also limit the ability of skeletal muscle to perform short duration, high intensity exercise before a bout of prolonged exercise.

This study demonstrates that prolonged submaximal exercise testing can reveal an impairment in exercise performance after ingestion of anti-hypertensive medication which is not evident during maximal exercise testing. This finding is important as prolonged submaximal exercise is the form of exercise which most hypertensive patients actually perform.

Further research is required on the effects of anti-hypertensive medications on submaximal exercise performance before firm recommendations can be made regarding medications most suitable for the physically active hypertensive patient.

The results of these and other studies indicate that it is not yet possible to make claims that the calcium channel antagonist agents are without effect on physical exercise performance in physically active hypertensive patients.

Contents

Chapter 1. Introduction.

Regular physical activity has been shown to reduce all-cause mortality (Paffenbarger et al. 1986). In particular, regular physical activity has beneficial effects in reducing the risk of cardiovascular disease (Powell et al. 1987) and of sudden death (Siskovick et al. 1982, 1984). Habitual exercise reduces blood pressure (Arroll & Beaglehole 1992; Kelley & McClellan 1994), and reduces the risk of cardiovascular disease independently of its effect on blood pressure (Paffenbarger et al. 1984). In addition, regular physical activity helps control obesity and favourably influences blood lipid abnormalities (Findlay et al. 1987; Stamford et al. 1984). There is thus ample reason for the American Heart Association (1992) to advocate participation in regular physical exercise for persons of all ages to promote health and prevent disease.

More specifically, regular physical activity is recognised as an important component of the management of essential hypertension. The introduction of a physical exercise program can be sufficient to control mild hypertension (Houston 1992; Kaplan 1985). However, as non-pharmacological methods of blood pressure control exert only modest reductions in blood pressure (Arroll & Beaglehole 1992; Grobbee & Hofman 1986), most patients with moderate or severe hypertension who participate in regular physical activity will require anti-hypertensive medication for adequate blood pressure control. These patients therefore require medication which would allow them to perform and enjoy regular, sustained physical activity so that the health benefits of exercise can be attained.

Beta-blockers are commonly used in the management of hypertension yet they impair both maximal and sub-maximal exercise performance (Gordon & Duncan 1991; Gullestad et al. 1989a; Van Bortel & Van Baak 1992). Patients treated with these agents frequently complain of fatigue during exercise (Van Bortel & Van Baak 1992). Furthermore, ratings of perceived exertion during submaximal exercise are increased after β-blockade (Derman et al. 1992).

Thus, patients treated with β-blockers are less able to perform and enjoy physical activity than those not ingesting these agents.

The prescription of anti-hypertensive agents, such as β-blockers, which impair exercise performance to patients who participate in regular physical activity may therefore lead to non-compliance. Medication may be ingested intermittently or not at all to allow for "medication free" competition or participation in exercise. Therefore, when prescribing anti-hypertensive agents for individuals with hypertension who participate in competitive exercise, it is important to know the effects of these medications on exercise capacity.

The effects of β-receptor blockade on exercise performance have been well studied (Gordon & Duncan 1991; Kaiser 1984; Tesch 1985; Van Baak 1988). However, the effects of other first line anti-hypertensive agents, such as calcium channel antagonists and ACE inhibitors, on exercise performance have not been equally well investigated.

Calcium channel antagonists are now established as important drugs in the first line treatment of hypertension (Halperin & Cubeddu 1986). These agents are safe, effective, well tolerated and cause few metabolic disturbances (Kaplan 1989; Man in't Veld 1989; Messerli et al. 1988). Calcium channel antagonists inhibit cardiac and smooth muscle contraction by reducing calcium influx into the muscle cell. This leads to peripheral vasodilatation and a fall in arterial blood pressure (Messerli et al. 1988). Calcium channel antagonists can be classified into two groups on the basis of tissue specificity; verapamil-like drugs which have negative inotropic and chronotropic effects with mild peripheral vascular effects, and dihydropyridine derivatives, including nifedipine, which have lesser cardiac and more marked peripheral vasodilatory effects (Kaplan 1989; Man in't Veld 1989).

The influence of dihydropyridine calcium channel antagonists on physical exercise capacity has not been thoroughly investigated. Nifedipine, a dihydropyridine calcium channel blocker, decreases maximal exercise capacity

in normotensive subjects (Andersen & Vik-mo 1984; Chick et al. 1986; Derman et al. 1992; Duffey et al. 1984; Gordon et al. 1986, 1987), but no reduction in maximal exercise performance occurs in hypertensive subjects (Ashmore et al. 1990; Gosse et al. 1992; Halperin et al. 1993). Whether these differences are due to hypertension per se or due to other factors including the physical activity status of the subjects or methodological problems is unclear.

Previous investigations from our laboratory have demonstrated that the dihydropyridine derivative, isradipine, reduced submaximal exercise tolerance in normotensive subjects (Selvey 1991). However, the dihydropyridine derivative, amlodipine, had no effect on submaximal exercise performance when administered to physically active hypertensive patients (Gillies et al. 1996). There are no other reported studies of the effect of dihydropyridine calcium channel blockade on submaximal exercise capacity in either normotensive or hypertensive subjects.

Maximal exercise testing is the most common measure of exercise performance which is described in the literature on drug effects on exercise. However, as prolonged submaximal exercise is the most common form of exercise performed by hypertensive patients, it is particularly important to investigate the effects of anti-hypertensive agents during this form of exercise. Furthermore, submaximal exercise testing may reveal differences between agents which are not revealed by maximal exercise testing (McLenachan et al. 1991).

The emphasis on maximal oxygen consumption (VO_2max) as a measure of exercise performance stems from a belief that it is either oxygen delivery to, or oxygen uptake and use by, the exercising muscles which is the limiting factor in exercise performance (Noakes 1988). Noakes (1988) has challenged this belief, and suggests that it is failure of muscle contractility which determines the onset of fatigue. Anti-hypertensive medications which reduce exercise tolerance may perhaps be acting on skeletal muscle to cause premature fatigue. The effects of calcium channel antagonism on skeletal muscle function

have not previously been determined. Some indication of skeletal muscle function may be given by the performance of short duration, high intensity exercise, as measured by the Wingate test, as this test correlates well with skeletal muscle composition (Bar-Or 1987).

Accordingly, this thesis investigates the effects of the dihydropyridine calcium channel antagonist, isradipine, on submaximal and maximal exercise performance, and on short duration, high intensity exercise. The effects of this agent are compared to the effects of the β_1-selective blocker, atenolol, and to the effects of placebo.

A major haemodynamic abnormality in essential hypertension is peripheral vasoconstriction; this is reversed by calcium channel antagonism resulting in blood pressure reduction (Cody 1987; Katzman et al. 1987; Omvik et al. 1988). Calcium antagonists do not reduce blood pressure in normotensive individuals who do not have peripheral vasoconstriction (Derman et al. 1993; Omvik & Lund-Johansen 1988; Raffestin et al. 1985; Vanhees et al. 1988). Because of this difference in haemodynamic effects of calcium channel blockade between normotensive and hypertensive subjects, it is possible that the effects of these agents on exercise performance in hypertensive subjects may differ to those in normotensive subjects. Accordingly, this thesis investigates the effects of isradipine in hypertensive subjects.

Beta-blockade causes a greater reduction in exercise tolerance in trained individuals compared to untrained individuals (Joyner et al. 1986). It is possible that a similar effect may occur in any reduction in exercise capacity seen with other anti-hypertensive agents. Therefore it is important to investigate the effects of calcium channel antagonists on exercise performance in physically active subjects. This study examines the effects of isradipine on exercise performance in patients with hypertension who participate in regular physical exercise.

Aim of this thesis

The aim of this thesis is therefore, to examine the effects of the dihydropyridine calcium channel antagonist, isradipine, on maximal, prolonged submaximal and short duration, high intensity exercise performance in physically active subjects with hypertension, and to compare these effects to the effects of the β_1-antagonist, atenolol.

Chapter 2. Literature review - The effects of calcium channel antagonists on exercise performance and the physiological response to exercise in normotensive and hypertensive individuals.

2.1 Introduction

Calcium channel antagonists are important drugs for the management of hypertension. They are safe, effective, well tolerated and cause few metabolic alterations (Kaplan 1989; Man in't Veld 1989; Messerli et al. 1988). This review summarizes the available literature on the effect of calcium channel antagonists on exercise performance and on the physiological response to exercise.

Calcium channel antagonists act by reducing calcium flux through voltage sensitive calcium channels and thereby reduce the entry of extracellular calcium into cells during depolarisation. As these cells are dependent on the influx of calcium for contraction, the effect of calcium channel antagonists is to inhibit cardiac and smooth muscle contraction. A rise in intracellular calcium concentration is also necessary for conduction through the sinoatrial and atrioventricular nodes in the heart. Thus, calcium channel antagonists have a negative chronotropic and inotropic effect and cause peripheral vasodilatation. The vasodilatation causes a reduction in mean blood pressure (Kaplan 1989; Man in't Veld 1989).

Voltage sensitive calcium channels are also found in skeletal muscle cell membranes and while their exact role is unknown they are thought to be involved in excitation-contraction coupling. The coupling occurs without calcium entry into the cell (Caswell & Brandt 1989; Romey et al. 1988). Verapamil has been shown to reduce muscle twitch amplitude in the skeletal muscle of anaesthetised cats (Kraynack et al. 1983) and dogs (Lawson et al. 1983)

suggesting that it possesses a neuromuscular blocking action. Clinically significant neuromuscular blocking action by verapamil has not been reported. However the neuromuscular junction remains a site where calcium antagonists could potentially impair skeletal muscle function.

Calcium blockers can be classified into two groups on the basis of tissue specificity; firstly, verapamil and diltiazem like drugs which have marked cardiac effects and mild peripheral vascular effects, and secondly, the dihydropyridine derivatives (including nifedipine), which have lesser cardiac and more marked peripheral vasodilatory effects (Kaplan 1989; Man in't Veld 1989). Because of the difference between these two classes of agents the effects of each on exercise parameters will be discussed separately.

Most studies of the effects of the calcium antagonists involving exercise have examined the effects of these agents on the cardiovascular system. Exercise is used to stress the cardiovascular system in order that any latent effects of the drug on the cardiovascular system can be measured. The performance of exercise per se has not been considered important and indeed, is frequently not measured (Cody 1987; D'Agostino et al. 1983; Jones et al. 1983; Katzman et al. 1987; Omvik et al. 1988). Even fewer studies examine other variables which may potentially affect exercise performance (including glucose metabolism and thermoregulation). To date, no studies have measured the effect of these agents on skeletal muscle strength.

The exercise protocols used and the parameters measured vary greatly between the reported studies. Although the studies report the effects of calcium channel antagonists, different drugs with varying efficacies and doses are used for different periods of time and via different methods of administration. All these factors make direct comparisons of the results of these studies difficult (Ashmore et al. 1990; Chick et al. 1986; D'Agostino et al. 1983; Derman et al. 1992; Gordon et al. 1987; Halperin et al. 1993; Jones et al. 1983; Katzman et al. 1987; Myburgh et al. 1987; Raffestin et al. 1985).

The primary haemodynamic abnormality in essential hypertension is raised systemic vascular resistance (Cody 1987; Katzman et al. 1987; Lund-Johansen 1985). This results in a raised mean arterial pressure. During exercise, hypertensive subjects have a fall in total peripheral resistance (TPR), but it remains higher than normal, resulting in raised TPR and mean arterial pressure during exercise. Hypertensive subjects have a lower cardiac index (CI) and stroke volume index (SVI) at rest and during exercise than subject without hypertension (Cody 1987; Lund-Johansen 1987). Calcium channel blockers cause vasodilatation and therefore have the potential to reverse these haemodynamic effects.

In normotensive subjects however, where TPR is not raised, neither systolic nor diastolic blood pressure (BP) is reduced by calcium channel antagonists (D'Agostino et al. 1983; Derman et al. 1992; Petri et al. 1986; Raffestin et al. 1985; Vanhees et al. 1988). Because of the different effects of calcium channel blockers on BP in normotensive and hypertensive individuals, and because alterations in BP could possibly influence exercise capacity, the effects of these agents on exercise performance in normotensive and hypertensive subjects will be discussed separately.

2.2 Verapamil and Diltiazem

2.2.1 Verapamil and diltiazem in normotensive subjects

2.2.1.1 Exercise performance in normotensive subjects

In normotensive subjects, progressive exercise tests to exhaustion have failed to show any effect of verapamil or diltiazem on maximum oxygen uptake (VO_2max), maximal workload (WLmax), exercise duration or ratings of perceived exertion (RPE) (Derman et al. 1991b; Gordon et al. 1986; Petri et al. 1986; Vanhees et al. 1988).

Submaximal exercise performance in normotensive individuals is not effected by the administration of verapamil or diltiazem (Derman et al. 1991b; Herbertsson & Fagher 1990; Vanhees et al. 1988).

Derman et al. (1993) examined the effects of diltiazem (30mg tds) given for one week on isokinetic skeletal muscle function. Diltiazem had no effect on peak power, average power and work done at a variety of contraction velocities during 10 second tests, or on total work done and rate of work decline during a 30 second test.

Hence, studies to date indicate that neither verapamil nor diltiazem administered to normotensive subjects alters maximal or submaximal exercise performance, and diltiazem does not alter isokinetic exercise performance.

2.2.1.2 Cardiovascular, respiratory, metabolic and hormonal parameters following verapamil or diltiazem administration in normotensive subjects

The influence of verapamil and diltiazem administration in normotensive subjects on cardiovascular parameters at rest and during exercise is shown in Table 2.1. Verapamil and diltiazem in moderate doses do not alter systolic or diastolic BP or heart rate (HR) at rest or during maximal, submaximal dynamic or isometric exercise in normotensive subjects (D'Agostino et al. 1983; Derman et al. 1991b, 1993; Gordon et al. 1986; Petri et al. 1986; Stein et al. 1984;

Table 2.1 Influence of verapamil and diltiazem in normotensive subjects on cardiovascular parameters at rest and during exercise.

	BP_{rest}	HR_{rest}	$BP_{mx\ ex}$	$HR_{mx\ ex}$	BP_{submx}	HR_{submx}	BP_{iso}	HR_{iso}
Verapamil	↔7,8,9 ↓6*	↔6,7,8,9	↔7,9	↔5,9 ↓7,8	↔1,5,9 ↓6#	↔1,5,9 ↓6^	↔8	↔8
Diltiazem	↔3,4	↔3,4		↔3,5	↔2,3,5			

*Diastolic BP at high dose (320mg daily) only, #Systolic BP at high dose only, ^High dose only
1-D'Agostino et al. 1983, 2-Derman et al. 1992, 3-Derman et al. 1991b, 4-Derman et al. 1993, 5-Gordon et al. 1986, 6-Herbertsson & Fagher 1990, 7-Petri et al. 1986, 8-Stein et al. 1984, 9-Vanhees et al. 1988.
Abbreviations: BP_{rest}= systolic and diastolic blood pressure at rest, HR_{rest}= heart rate at rest, $BP_{mx\ ex}$= systolic blood pressure at maximal exercise, $HR_{mx\ ex}$= maximal heart rate, BP_{submx}= systolic and diastolic blood pressure during submaximal exercise, HR_{submx}= heart rate during submaximal exercise, BP_{iso}= systolic and diastolic blood pressure during isometric exercise, HR_{iso}= heart rate during isometric exercise.

Vanhees et al. 1988). High doses only of verapamil (320mg daily) may reduce HR and mean BP during submaximal exercise in healthy individuals (Herbertsson & Fagher 1990).

Minute ventilation (V_i), respiratory exchange ratio (RER), carbon dioxide production (VCO_2) and blood lactate concentrations during maximal and submaximal exercise were unchanged after verapamil or diltiazem administration compared to placebo in normotensive subjects (Derman et al. 1991b; Gordon et al. 1986; Petri et al. 1986; Stein et al. 1984; Vanhees et al. 1988). Blood glucose, glycerol, free fatty acids (Petri et al. 1986), potassium, and noradrenaline (Stein et al. 1984) concentrations during maximal exercise testing are similarly unaltered following verapamil administration. Similarly, serum concentrations of potassium, glucose, free fatty acids, triglycerides and growth hormone during submaximal exercise were unchanged by diltiazem administration (Derman et al. 1992).

Thus, in normotensive subjects, it appears that verapamil and diltiazem to not alter exercise performance. There may be a reduction of around 15 bpm in maximal HR with verapamil but this is not a consistent finding. High doses of verapamil may reduce HR and systolic BP during submaximal exercise. Plasma concentrations of hormones and carbohydrate and fat metabolites during exercise are not altered by these two agents. The study by Herbertsson & Fagher (1990), where ingestion of verapamil resulted in decreased HR and mean BP but no reduction in submaximal exercise performance, is evidence against the argument that alterations in central haemodynamics cause the decreased exercise capability seen after β-blockade.

2.2.2 Verapamil and diltiazem in hypertensive subjects

2.2.2.1 Exercise performance in hypertensive subjects

Administration of oral verapamil to hypertensive patients has no effect on VO_2max, maximal exercise duration or maximal workload (Ashmore et al.

1990; Cody et al. 1986, Halperin et al. 1993). Diltiazem had no effect on VO_2max, maximal exercise test duration or RPE during a maximal test when administered to hypertensive patients over periods ranging from 2 to 16 weeks (Kelemen et al. 1989; Luurila et al. 1987; Myburgh & Gordon 1987; Szlachcic et al. 1987; Yamakado et al. 1983). The study by Myburgh & Gordon (1987) involved physically active subjects with a mean age of 33 years. Gosse et al. (1992) and Pool et al. (1985) reported that exercise duration during a maximal exercise test was increased in hypertensive patients after oral verapamil and diltiazem respectively. However, in both these studies, there was no difference in maximal exercise test duration between the treatment and control groups. There were also methodological weaknesses in these studies in that the physical exercise practices of the subjects were not controlled and there was the possibility of habituation to the test as the subjects were initially sedentary.

Mooy et al. (1987) found that 4 weeks of verapamil treatment in hypertensive patients had no effect on time to exhaustion during submaximal exercise. No other studies have reported on submaximal exercise performance in hypertensive subjects ingesting verapamil or diltiazem.

2.2.2.2 Cardiovascular, respiratory, metabolic and hormonal parameters following verapamil or diltiazem administration in hypertensive subjects

The influence of verapamil and diltiazem on cardiovascular parameters at rest and during exercise in hypertensive subjects is shown in Table 2.2. Systolic and diastolic BP at rest and during exercise is reduced after the ingestion of verapamil and diltiazem by hypertensive subjects (Ashmore et al. 1990; Gosse et al. 1992; Gould et al. 1982; Halperin et al 1993; Lund-Johansen 1985), although the hypotensive effect of these agents may be lost at high exercise intensities (Yamakado et al. 1983). Resting heart rate when supine is unchanged after verapamil or diltiazem administration in hypertensive subjects (Halperin et al. 1993; Lund-Johansen 1985; Mooy et al. 1987; Pool et al. 1985). However, heart rate while standing at rest, and during exercise, is reduced in hypertensive subjects after verapamil or diltiazem administration (Gosse et al.

Table 2.2 Influence of verapamil and diltiazem in hypertensive subjects on cardiovascular parameters at rest and during exercise.

	BP_{rest}	HR_{supine}	HR_{stand}	$BP_{mx\ ex}$	$HR_{mx\ ex}$	BP_{submax}	HR_{submax}
Verapamil	↓6	↔1,5,8,10	↓8,10	↓1,3,5 ↔2*	↓1,5 ↔2*	↓1,4,5,8 ↓10#	↓1,5,8,10,15 ↔2*
Diltiazem	↓6	↔7,13,14,16 ↓11,12	↓13,16	↓9#,13 ↔16	↓11,13,16 ↔14	↓11,12,13,14,16 ↓7#,9#	↓7,11,12,13,16 ↔14

*Short term study, #Diastolic BP only.
1-Ashmore et al. 1990, 2-Cody et al. 1986, 3-Gosse et al. 1992, 4-Gould et al. 1982, 5-Halperin et al 1993, 6-Kaplan 1989, 7-Klein et al. 1983, 8-Lund-Johansen 1985, 9-Luurila et al. 1987, 10-Mooy et al. 1987, 11-Myburgh & Gordon 1987, 12-Omvik & Lund-Johansen 1988, 13-Pool et al. 1985, 14-Szlachcic et al. 1987, 15-Van Baak et al. 1987b, 16-Yamakado et al. 1983.
Abbreviations: BP_{rest}= systolic and diastolic blood pressure at rest, HR_{supine}= heart rate while supine, HR_{stand}= heart rate while standing, $BP_{mx\ ex}$= systolic blood pressure at maximal exercise, $HR_{mx\ ex}$= maximal heart rate, BP_{submx}= systolic and diastolic blood pressure during submaximal exercise, HR_{submx}= heart rate during submaximal exercise.

1992; Gould et al. 1982; Halperin et al. 1993; Kaplan 1989; Klein et al. 1983; Lund-Johansen 1985; Mooy et al. 1987; Myburgh & Gordon 1987; Omvik & Lund-Johansen 1988; Pool et al. 1985; Yamakado et al. 1983).

The results of invasive haemodynamic investigations in hypertensive patients at rest and during submaximal exercise after the administration of calcium channel antagonists are shown in Table 2.3. Diltiazem treatment administered to hypertensive patients results in reduced mean arterial pressure during exercise due to reduced TPR during exercise, while cardiac output is maintained (Omvik & Lund-Johansen 1988) or even increased (Klein et al.

Table 2.3. Influence of calcium channel antagonists in hypertensive subjects on cardiovascular parameters at rest and during submaximal exercise.

	TPR_{rest}	SVI_{rest}	CI_{rest}	TPR_{submx}	SVI_{submx}	CI_{submx}
Verapamil	↓2	↑2	↔2	↔2*	↔2*	↔2*
Diltiazem	↓1,5			↓1,5	↑1,5	↑1 ↔5
Nifedipine	↓1,3	↔1,3	↔1,3	↓1,3	↔3 ↑1	↑1 ↔3
Nisoldipine	↓6	↔6	↔6	↔6	↔6	↓6
Amlodipine	↓4	↑4	↔4	↓4	↔4	↑4

*Small sample size, isotonic exercise.
1-Klein et al. 1983, 2-Lund-Johansen 1985, 3-Lund-Johansen & Omvik 1983, 4-Lund-Johansen et al. 1992, 5-Omvik & Lund-Johansen 1988, 6-Omvik et al. 1988.
Abbreviations: TPR_{rest}=total peripheral resistance at rest, SVI_{rest}=stroke volume index at rest, CI_{rest}=cardiac index at rest, TPR_{submx}=total peripheral resistance during submaximal exercise, SVI_{submx}=stroke volume index during submaximal exercise, CI_{sbmx}=cardiac index during submaximal exercise.

1983). A reduction in TPR during exercise has not been reported after verapamil administration (Lund-Johansen 1985). This may be to the relatively small dose of verapamil used (240mg daily), which resulted in only a modest reduction in resting mean arterial pressure, and to the small sample size so that the trends were not statistically significant.

Van Baak et al. (1987b) found that verapamil therapy given to hypertensive subjects was not associated with any changes in plasma glucose, lactate, free fatty acid or glycerol concentrations compared to placebo during submaximal exercise. This finding implies that hormone secretion is not altered by verapamil ingestion. VO_2 and V_i during submaximal exercise were also unaltered following verapamil administration compared to placebo (Van Baak et al. 1987b).

Thus, reports on the effects of verapamil and diltiazem in hypertensive subjects, have failed to show any impairment of maximal or submaximal exercise performance. This is despite the fact that most studies have shown that systolic and diastolic BP during submaximal exercise are reduced by these agents when administered to hypertensive subjects. In addition, most studies have indicated that, in hypertensive subjects, HR is reduced during submaximal and maximal exercise, after verapamil and diltiazem ingestion. Hence, reduced BP and HR during exercise are not necessarily associated with an impairment in exercise capacity.

2.3 Dihydropyridine derivatives

2.3.1 Dihydropyridine derivatives in normotensive subjects

Nifedipine is the only dihydropyridine derivative of which the effects during exercise have been investigated in normotensive subjects.

2.3.1.1 Exercise performance in normotensive subjects

2.3.1.1a Maximal exercise performance

In most studies using normotensive subjects, VO_2max was unaltered following nifedipine ingestion compared to placebo (Chick et al. 1986; Derman et al. 1992; Duffey et al. 1984; Gordon et al. 1987; Kindermann 1987; Raffestin et al. 1985). However, Gordon et al. (1986) found a small but significant reduction in VO_2max after a single oral dose of 10mg of nifedipine. The significance of this result is unclear, as the former studies either used higher doses of nifedipine and/or longer periods of administration.

Although VO_2max at peak exercise is unchanged following ingestion of nifedipine, most studies have shown a reduction in exercise test duration and/or WLmax. Chick et al. (1986) found that, following nifedipine administration, WLmax was decreased by 4%, with a corresponding decrease in exercise time, despite no change of VO_2max (exercise was "less efficient"). Derman et al. (1992) also reported a reduction in peak workload achieved and a decrease in time to exhaustion, without any significant change in VO_2max. Furthermore, in four other studies exercise duration was decreased (Andersen & Vik-mo 1984; Duffey et al. 1984; Gordon et al. 1986, 1987). Thus, it appears that maximal exercise capacity is impaired after nifedipine administration in normotensive subjects.

2.3.1.1b Submaximal exercise performance

Few studies have investigated the effect of nifedipine on prolonged submaximal exercise endurance in healthy subjects. In the studies involving submaximal exercise, the subjects do not exercise to exhaustion; instead a set workload is used for a specified duration which is achieved by all subjects. Derman et al. (1992) reported that RPE during submaximal exercise was unaltered by a single dose of 20mg of nifedipine, but was increased by atenolol and cilazapril. Similarly, Kindermann et al. (1987) reported that all subjects were able to exercise at 75% VO_2max for 50 minutes after ingestion of both nifedipine and placebo, but in a similar trial, were unable to do so following β-

blocker administration. These findings suggest that any alteration of submaximal exercise tolerance following ingestion of nifedipine is less than that experienced following β-blockade.

2.3.1.2 Cardiovascular, respiratory, metabolic and hormonal parameters following dihydropyridine derivative administration in normotensive subjects

The influence of nifedipine in normotensive subjects on cardiovascular parameters at rest and during exercise is shown in Table 2.4. The effects of other dihydropyridine derivatives on these parameters have not been reported in normotensive subjects.

Most studies report that systolic and diastolic BP and HR at rest are unchanged after nifedipine ingestion in normotensive subjects (Derman et al. 1992; Kindermann et al. 1987; Raffestin et al. 1985; Stein et al. 1984). However, the reports of the effect of nifedipine on BP and HR during exercise in normotensive subjects are conflicting. Mean BP during maximal and submaximal exercise has been reported to be reduced after nifedipine administration (Andersen & Vik-mo 1984; Chick et al. 1986), although other authors report no change in systolic or diastolic BP during exercise after nifedipine ingestion (Derman et al. 1992;. Raffestin et al. 1985). During submaximal exercise at a mild to moderate intensity, nifedipine ingestion by

Table 2.4. Influence of nifedipine on cardiovascular parameters at rest and during exercise in normotensive subjects.

	BP_{rest}	HR_{rest}	$BP_{mx\ ex}$	$HR_{mx\ ex}$	BP_{submx}	HR_{submx}
Nifedipine	↔3,4,8	↔3,7,8,9 ↑4	↓1,2 ↔3	↔1,2,3,4,5,6,7,8 ↓9*	↔3,8 ↓1	↑1,2,5,6,8 ↔1,2,3,7#

*High dose only (20mg tds), #High intensity exercise.
1-Andersen & Vik-mo 1984, 2-Chick et al. 1986, 3-Derman et al. 1992, 4-Duffey et al. 1984, 5-Gordon et al. 1986, 6-Gordon et al. 1987, 7-Kindermann et al. 1987, 8-Raffestin et al. 1985, 9-Stein et al. 1984.
Abbreviations: BP_{rest}=systolic and diastolic blood pressure at rest, HR_{rest}=heart rate at rest, $BP_{mx\ ex}$=systolic blood pressure at maximal exercise, $HR_{mx\ ex}$=maximal heart rate, BP_{submx}= systolic and diastolic blood pressure during submaximal exercise, HR_{submx}=heart rate during submaximal exercise.

normotensive subjects results in an increased HR at a given workload (Andersen & Vik-mo 1984; Chick et al. 1986; Gordon et al. 1986, 1987; Raffestin et al. 1985), but during high intensity exercise, no difference in HR has been documented (Andersen & Vik-mo 1984; Chick et al. 1986; Derman et al. 1992; Kindermann 1987). Similarly, maximal HR is reported as unchanged following nifedipine administration in healthy subjects (Andersen & Vik-mo 1984; Chick et al. 1986; Derman et al. 1992; Duffey et al. 1984; Gordon et al. 1986, 1987; Kindermann 1987; Raffestin et al. 1985).

Andersen & Vik-mo (1984) used echocardiography to assess changes in sub-maximal exercise haemodynamics in normotensive subjects with a single sub-lingual dose of nifedipine compared to placebo. They found that at submaximal workloads, although HR was increased, the rate-pressure product was decreased because of a fall in systolic and diastolic BP. At high submaximal and maximal workloads, stroke volume was increased after administration of nifedipine. The authors felt that this may be explained by reduced impedance to systolic cardiac emptying, as a result of vasodilatation. The rise in stroke volume at higher workloads, combined with a rise in HR at lower workloads, would result in a increase in cardiac output (Andersen & Vik-mo 1984).

Stein et al. (1984) measured haemodynamic parameters during isometric handgrip exercise. Heart rate and systolic and diastolic BP during isometric exercise were unaltered after 4 days of nifedipine ingestion in normotensive patients.

V_i or RER at maximal exercise are unchanged after nifedipine ingestion in normotensive individuals (Chick et al. 1986; Derman et al. 1992; Gordon et al. 1986, 1987; Raffestin et al. 1985). Similarly, VO_2, V_i and RER at a given submaximal workload are unaltered following nifedipine administration in healthy subjects (Derman et al. 1992; Gordon et al. 1986, 1987; Kindermann 1987; Raffestin et al. 1985).

As dihydropyridine calcium channels are located on secretory cells and calcium channel antagonists are known to inhibit calcium dependent hormone release in vitro (Raffestin et al. 1985), it is possible that hormone release during exercise may be reduced by calcium channel blockers and that this may affect exercise performance. However, serum noradrenaline, growth hormone, and glucagon concentrations are all increased, and serum adrenaline and insulin concentrations are unaltered, during submaximal exercise after nifedipine administration (Kindermann 1987; Raffestin et al. 1985). Furthermore, serum noradrenaline concentration was found to be unchanged at maximum exercise after nifedipine ingestion, despite a higher resting concentration (Stein et al. 1984). Thus, there is no evidence that, in normotensive subjects, hormone concentrations during exercise are reduced by dihydropyridine calcium channel antagonists. The increase in HR, noradrenaline and other blood hormone concentrations during exercise is thought to be due to reflex sympathetic stimulation, secondary to vasodilatation caused by nifedipine ingestion (Raffestin et al. 1985).

Raffestin et al. (1985) also report an increase in serum glucose, ketones, lactate and free fatty acid concentrations during submaximal exercise following nifedipine administration in normotensive subjects. This was surmised by the authors to be due to an increased rate of glycogenolysis and lipolysis as a result of increased sympathetic stimulation (Raffestin et al. 1985). Chick et al. (1986) also found increased blood lactate concentrations during submaximal exercise following ingestion of nifedipine. However, other authors have failed to document this effect on blood lactate concentrations (Derman et al. 1992; Kindermann 1987).

Thus, it appears that nifedipine does impair maximal exercise capacity in normotensive subjects. The cause of this small decrement in performance is unclear. Most studies show that HR at rest and at maximal exercise is unchanged after nifedipine ingestion. Mean BP at maximal exercise is probably reduced, but this is compensated by an increase in stroke volume resulting in an increased cardiac output at maximal exercise (Andersen & Vik-mo 1984).

This would act to maintain blood flow to active muscle despite vasodilatation. The concentration of serum noradrenaline, growth hormone, and glucagon during exercise following nifedipine ingestion in normotensive subjects is increased. Submaximal exercise performance after the administration of nifedipine to healthy individuals has, however, not been adequately investigated.

2.3.2 Dihydropyridine derivatives in hypertensive subjects

2.3.2.1 Exercise performance in hypertensive subjects

Previous studies have found that nifedipine, lacidipine or amlodipine administered to patients with mild to moderate hypertension does not alter VO_2max, maximal exercise test duration or the WLmax achieved (Ashmore et al. 1990; Fariello et al. 1991; Gillies et al. 1996; Gosse et al. 1992; Halperin et al. 1993). The subjects in these studies were sedentary except in the study by Gillies et al. (1996), where subjects were physically active.

Prolonged submaximal exercise performance has been found to be unaltered following 2 weeks of amlodipine ingestion by physically active hypertensive patients (Gillies et al. 1996).

Gillies et al. (1996) examined the effects of amlodipine ingestion on skeletal muscle function. These authors reported that the torque produced by maximal voluntary isometric contraction of the quadriceps muscle in physically active hypertensive patients is unaltered following amlodipine ingestion.

2.3.2.2 Cardiovascular, respiratory and hormonal parameters following dihydropyridine derivative administration in hypertensive subjects

The influence of nifedipine, nicardipine, nisoldipine, isradipine, amlodipine and lacidipine in hypertensive subjects on cardiovascular parameters at rest and during exercise is shown in Table 2.5.

Table 2.5. Influence of dihydropyridine derivatives on cardiovascular parameters at rest and during exercise in hypertensive subjects.

	BP_{rest}	HRrest	BPmx ex	HRmx ex	BPsubmx	HRsubmx
Nifedipine	↓6,9,10,12,13	↔1,6,8,9,10,12,13	↓1,8 ↔10	↔10 ↓1	↓1,6,9,13 ↓10*,12*	↔1,6,10,12,13
Isradipine	↓2,3,15	↔2 ↑3	↓2	↔2	↓2 ↓15*	
Nicardipine	↓4,11,17	↔4,11 ↑17			↓4,11,17	↔4,11,17
Lacidipine	↓5		↓5	↔5		
Nisoldipine	↓16	↔16			↓16	↔16
Amlodipine	↓14 ↓7#	↔7,14		↔7	↓14 ↔7	↔7,14
Nitrendipine	↓6	↔6			↓6	↔6

*Diastolic BP only, #Systolic BP only.
1-Ashmore et al. 1990, 2-Cantor & Cristal 1990, 3-Dvorak et al. 1991, 4-Fariello et al. 1989, 5-Fariello et al. 1991, 6-Franz & Wiewel 1984, 7-Gillies et al. 1996, 8-Gosse et al. 1992, 9-Gould et al. 1982, 10-Halperin et al. 1993, 11-Jones et al. 1983, 12-Klein et al. 1983, 13-Lund-Johansen & Omvik 1983, 14-Lund-Johansen et al. 1992, 15-Mayer et al. 1991, 16-Omvik et al. 1988, 17-Taylor et al. 1982.
Abbreviations: BP_{rest}=systolic and diastolic blood pressure at rest, HR_{rest}=heart rate at rest, $BP_{mx\ ex}$= systolic blood pressure at maximal exercise, $HR_{mx\ ex}$=maximal heart rate, BP_{submx}= systolic and diastolic blood pressure during submaximal exercise, HR_{submx}=heart rate during submaximal exercise.

Administration of dihydropyridine derivatives results in a reduction in systolic and diastolic BP at rest and during submaximal and maximal exercise in individuals with hypertension (Ashmore et al. 1990; Cantor & Cristal 1990; Fariello et al. 1989; Franz & Wiewel 1984; Gould et al. 1982; Jones et al. 1983; Lund-Johansen & Omvik 1983; Lund-Johansen et al. 1992; Omvik et al. 1988; Taylor et al. 1982). However, some authors have reported a decrease in diastolic BP but not in systolic BP during submaximal exercise following nifedipine and isradipine administration despite normalisation of resting diastolic and systolic BP (Halperin et al. 1993; Klein et al. 1983; Mayer et al. 1991). In hypertensive subjects, HR at rest and during exercise is unchanged following ingestion of dihydropyridine derivatives (Cantor & Cristal 1990; Fariello et al. 1989; Franz & Wiewel 1984; Gillies et al. 1996; Gould et al. 1982; Halperin et al. 1993; Jones et al. 1983; Klein et al. 1983; Lund-Johansen & Omvik 1983; Lund-Johansen et al. 1992; Omvik et al. 1988; Taylor et al. 1982).

The haemodynamic response to isometric hand grip exercise has been examined in hypertensive subjects following ingestion of nicardipine and

isradipine. Most studies have found that the effect of these agents on systolic and diastolic BP during isometric exercise is similar to that found for isotonic exercise. The exercise associated increase in systolic and diastolic BP during the isometric contraction was unaltered following drug administration, but BP during isometric exercise was lower due to lower resting BP (Dvorak et al. 1991; Fariello et al. 1989; Taylor et al. 1982). Cantor & Cristal (1990) reported no change in systolic BP with isometric handgrip exercise, although diastolic BP was reduced resulting in reduced mean arterial pressure. HR during isometric handgrip exercise was unaltered by isradipine treatment (Cantor & Cristal 1990).

The results of invasive haemodynamic investigations in hypertensive patients at rest and during submaximal exercise after administration of dihydropyridine derivatives are shown in Table 2.3. These agents reduce TPR at rest and during exercise (Klein et al. 1983; Lund-Johansen & Omvik 1983; Lund-Johansen et al. 1992). In contrast, Gillies et al. (1996), using indirect techniques, found that TPR was unaltered following amlodipine administration. Most studies demonstrate that SVI and CI at rest are unaltered by dihydropyridine derivatives in hypertensive subjects (Klein et al. 1983; Lund-Johansen & Omvik 1983; Omvik et al. 1988). Reports of the effects on SVI and CI during submaximal exercise are conflicting.

Submaximal oxygen consumption at any given workload is unchanged following nifedipine, amlodipine or nisoldipine administration to hypertensive patients (Gillies et al. 1996; Lund-Johansen & Omvik 1983; Omvik et al. 1988). Similarly, V_i and RER during submaximal and maximal exercise are unaltered following amlodipine ingestion in hypertensive subjects (Gillies et al. 1996).

Klein et al. (1983) reported that plasma noradrenaline concentration at rest was increased after 8 weeks of nifedipine therapy administered to hypertensive patients, but concentrations during exercise were unchanged. In contrast, Halperin et al. (1993) reported that long term nifedipine ingestion resulted in increased noradrenaline concentrations at maximal exercise but not at rest.

Both authors concluded that raised noradrenaline concentration was evidence for reflex action of the sympathetic nervous system resulting from nifedipine therapy, despite lack of increase in HR.

Gillies et al. (1996) reported that plasma glucose, lactate and free fatty acid concentrations during submaximal exercise and blood lactate concentrations at maximal exercise were unaltered following ingestion of amlodipine by hypertensive patients.

Thus, it appears that the dihydropyridine derivatives do not affect maximal exercise performance in sedentary or physically active patients with hypertension (Ashmore et al. 1990; Fariello et al. 1991; Gillies et al. 1996; Gosse et al. 1992; Halperin et al. 1993). Similarly, submaximal exercise performance is unaltered following amlodipine administration in physically active patients with hypertension (Gillies et al. 1996). Most reports have found that dihydropyridine derivatives ingested by hypertensive subjects lead to a reduction in systolic and diastolic BP during exercise, although in some studies only diastolic BP is reduced and not systolic BP. The majority of studies have indicated that, in hypertensive subjects, HR at rest and during exercise is unaltered following administration of these agents. Most studies have found that TPR at rest and during submaximal exercise is reduced after ingestion of dihydropyridine derivatives in hypertensive individuals; however the effects on CI and SVI are conflicting.

2.4 Summary and Discussion

The available evidence indicates that ingestion of verapamil and diltiazem have no effect on maximal or submaximal exercise performance in normotensive or in hypertensive subjects (Ashmore et al. 1990; Cody et al. 1986; Derman et al. 1991b; Gordon et al. 1986; Halperin et al 1993; Herbertsson & Fagher 1990; Kelemen et al. 1989; Mooy et al. 1987; Myburgh & Gordon 1987; Petri et al. 1986; Pool et al. 1985; Szlachcic et al. 1987; Vanhees et al. 1988; Yamakado

et al. 1983). However, the number of investigations examining the effect of these agents on submaximal exercise performance in hypertensive patients is small.

Nifedipine however, has been consistently shown to reduce maximal exercise performance in normotensive subjects (Andersen & Vik-mo 1984; Chick et al. 1986; Derman et al. 1992; Duffey et al. 1984; Gordon et al. 1986, 1987). In contrast, studies on hypertensive subjects have failed to demonstrate any effect of nifedipine or other dihydropyridine derivative on maximal exercise performance (Ashmore et al. 1990; Fariello et al. 1991; Gillies et al. 1996; Gosse et al. 1992, Halperin et al. 1993). The studies conducted on normotensive subjects differ to those conducted on hypertensive subjects in that studies using normotensive subjects involved a younger population who had higher values of VO_2max than studies of hypertensive subjects (VO_2max range from 40 to 55 mlO_2/kg/min for normotensive subjects and from 24 to 34 mlO_2/kg/min, where stated, for hypertensive subjects).The study by Gillies et al. (1996) involved recreational athletes; however these subjects had a mean VO_2max of only 34 mlO_2/kg/min which is lower than the mean VO_2max for any of the studies with normotensive subjects. The fatiguing effect of β-blockers has been shown to be greater in individuals with high values of VO_2max than those with low values of VO_2max (Joyner et al. 1986; Van Baak et al. 1988). If dihydropyridine derivatives also have a fatiguing effect which is greatest in individuals with high values of VO_2max, then it is possible that the difference in VO_2max between the studies on normotensive and hypertensive subjects explains the difference in the observed effect on maximal exercise performance. Further investigation on the effects of dihydropyridine treatment on exercise performance in hypertensive subjects with higher VO_2max values are required.

Alternatively, it is possible that dihydropyridine derivatives effect a reduction in exercise capacity in normotensive but not hypertensive individuals. Calcium channel antagonists reverse an increase in peripheral vasoconstriction in hypertensive subjects (Cody 1987; Omvik & Lund-Johansen 1988), but cause

vasodilatation in normotensive subjects. A feasible explanation is that, in normotensive subjects ingesting dihydropyridine derivatives, vasodilatation results in impaired maximal exercise capacity; whereas, in hypertensive patients ingesting these agents, there is no vasodilatation and therefore no impairment in maximal exercise capacity.

The finding that verapamil and diltiazem administration does not affect maximal exercise capacity (Derman et al. 1991b; Gordon et al. 1986; Petri et al. 1986; Vanhees et al. 1988), but that nifedipine does cause some attenuation of maximal exercise performance in normotensive subjects is a consistent conclusion (Andersen & Vik-mo 1984; Chick et al. 1986; Derman et al. 1992; Duffey et al. 1984; Gordon et al. 1986, 1987). This observed difference between the effects of verapamil/diltiazem and nifedipine is not likely to be due to differences in study design as it was also found in one study where verapamil was compared to nifedipine (Gordon et al. 1986). The authors of the relevant studies speculate that the decline in exercise performance after nifedipine ingestion in normotensive subjects is due to peripheral vasodilatation. This could lead to changes in blood flow distribution with a fall in blood flow to the exercising muscles. This could potentially result in decreased oxygen supply to the active muscle or in an impairment of the removal of skeletal muscle metabolites. Reduced blood flow and oxygen delivery to the active muscle is likely to lead to an increase in blood lactate concentration during exercise. Some authors have reported that nifedipine administration in normotensive subjects results in increased blood lactate concentration during exercise (Chick et al. 1986; Raffestin et al. 1985); however others have reported that there is no alteration in blood lactate concentration (Derman et al. 1992; Kindermann 1987). However, blood lactate concentration during exercise is not altered after verapamil or diltiazem administration in either normotensive or hypertensive subjects (Derman et al. 1992; 1991b; Gordon et al. 1986; Petri et al. 1986; Stein et al. 1984; Vanhees et al. 1988; Van Baak et al. 1987b). These findings of different effects on blood lactate concentration during exercise between verapamil/diltiazem and nifedipine support the hypothesis that nifedipine impairs maximal exercise performance in normotensive subjects

by reducing blood flow to the active skeletal muscle and thereby increasing blood lactate concentration. As verapamil and diltiazem have lesser effect on the vasculature than nifedipine (Man in't Veld 1989), this postulate is consistent with the observed greater effect of nifedipine than verapamil or diltiazem on maximal exercise performance.

As nifedipine is known to have fewer negative inotropic and chronotropic effects than verapamil (Kaplan 1989; Man in't Veld 1989), the fact that maximal exercise performance in normotensive subjects is reduced by nifedipine and not verapamil, implies that it is not central cardiovascular effects which cause the reduction in maximal exercise capacity following nifedipine administration. Verapamil does not impair maximal exercise capacity; therefore, any reduction in cardiac function due to the negative effects of verapamil is not sufficient to limit exercise capacity. In addition, Ashmore et al. (1990) reported that verapamil (but not nifedipine) ingestion for a 3 week period by hypertensive patients impaired left ventricular peak emptying and filling rates during a maximal exercise test. However, maximal exercise capacity was unchanged. This is further evidence against the hypothesis that changes in central cardiovascular function due to anti-hypertensive agents result in reduction of exercise capacity.

Nifedipine causes greater peripheral vascular dilatation than verapamil, resulting in, at least in the short term, greater reflex sympathetic stimulation (Agabiti-Rosei et al. 1986; Kaplan 1989; Man in't Veld 1989). There is some speculation that long term administration of calcium channel blockers results in a blunting of the physiological response to sympathetic stimulation (Yamakado et al. 1983). This would explain why the reflex tachycardia seen with the dihydropyridine derivatives usually subsides over time despite high serum concentrations of noradrenaline (Klein et al. 1983). As exercise is a state of high sympathetic flux, an attenuated physiological response to sympathetic stimulation could possibly explain the observed impairment of exercise performance following nifedipine ingestion. Alternatively, nifedipine could be

acting peripherally at the level of the skeletal muscle to impair contractility. These areas warrant further investigation.

There is no evidence that hormone secretion, at rest or during exercise, is inhibited by calcium channel antagonism (Kindermann 1987; Raffestin et al. 1985; Stein et al. 1984); therefore the impairment of maximal exercise performance following nifedipine ingestion in healthy subjects is not due to reduced hormone secretion during exercise.

Few studies have investigated the effects of dihydropyridine derivatives on submaximal exercise performance. Gillies et al. (1996) found no effect of amlodipine on submaximal exercise endurance in physically active hypertensive patients. Although the subjects in this study were all recreational athletes, their mean VO_2max was relatively low at 34 mlO_2/kg/min. Further research into the effects of dihydropyridine derivatives on submaximal exercise performance in physically active subjects with hypertension is needed. This is important, as it is precisely submaximal exercise which physically active patients taking anti-hypertensive medication perform. Further, differences between medications that are not evident during maximal exercise testing may become apparent with submaximal exercise testing (McLenachan et al. 1991).

Furthermore, it is not known if calcium channel antagonism alters the physiological adaptations (including a beneficial effect on hypertension) to exercise training in hypertensive patients. Further investigation is needed in order to clarify these issues so that accurate advice can be given to active hypertensive patients regarding their anti-hypertensive medication.

Chapter 3. Literature review - The effects of beta-receptor antagonists on exercise performance and comparison with the effects of calcium channel antagonists.

3.1 Introduction

The effects of β-receptor antagonists on exercise performance and the physiological response to exercise have been fully reviewed recently by several authors (Gordon & Duncan 1991; Kaiser 1984; Tesch 1985; Van Baak 1988). This review will not attempt to re-evaluate all the results in the literature. It will merely present the key findings which are of specific relevance to this thesis and compare these to the effects of calcium channel antagonists outlined in the previous chapter.

3.2 Exercise performance

3.2.1 Maximal exercise performance

Most studies on normotensive subjects have indicated that measures of maximum exercise capacity including VO_2max, WLmax and exercise test duration are reduced by administration of β-antagonists (Ades et al. 1984; Gullestad et al. 1989a, 1991; Kullmer et al. 1987; Van Baak 1988; Van Bortel & Van Baak 1992). This finding is in contrast to the reports on verapamil and diltiazem in normotensive subjects where there is no effect on maximal exercise capacity following ingestion of these agents (Derman et al. 1991b; Gordon et al. 1986; Petri et al. 1986; Vanhees et al. 1988). Some attenuation of maximal exercise capacity is reported after nifedipine ingestion in normotensive subjects. However, in studies where nifedipine is compared to a β-blocker, the reduction in maximal exercise capacity seen with nifedipine is

not as great as that reported with the β-blocker (Derman et al. 1992; Gordon et al. 1986).

Some studies report a similar reduction in maximal exercise capacity following β-blockade in hypertensive subjects to that seen in normotensive subjects (Gordon et al. 1988, Kaiser et al. 1985, Thompson et al. 1989). However, in other studies no impairment in maximal exercise performance is reported (Leenen et al. 1980; Luurila et al. 1987; Reybrouck et al. 1977). This discrepancy might be explained by differences in physical activity status of the subjects. Most studies which have examined the effect of β-blockade on trained subjects (whether hypertensive or normotensive), have found that β-blockers clearly decrease maximal exercise performance (Anderson et al. 1985; Derman et al. 1992; Thompson et al. 1989). However, many studies using sedentary subjects have reported that maximal exercise performance is not altered following β-blocker ingestion (Franciosa et al. 1980; Reybrouck et al. 1977; Violante et al. 1984). Van Baak et al. (1988) investigated the effects of β-antagonists on maximal exercise performance in hypertensive patients and normotensive controls matched for VO_2max, and found a similar reduction in VO_2max and WLmax in both groups. These findings indicate that it is the physical activity status of the subjects, and not the presence of hypertension, which determines the effect of β-blockade on their maximal exercise capability. In concurrence with this finding, Joyner et al. (1986) found that β-blockers reduce maximal exercise capacity to a greater extent in trained men compared with untrained men.

Studies investigating the effect of calcium channel antagonists on maximal exercise performance in hypertensive subjects have failed to demonstrate any impairment. However, these studies investigated subjects with low values of VO_2max and hence, it is possible that, as for β-blockers, a reduction in maximal exercise capacity may be evident only in trained subjects with high values of VO_2max.

3.2.2 Submaximal exercise performance

The time to exhaustion during prolonged submaximal exercise is reduced by up to 50% following the ingestion of β-blocking agents (Lundborg et al. 1981; Van Baak 1988; Van Bortel et al. 1991; Vanhees et al. 1988). The impairment in prolonged exercise endurance occurs in both normotensive and hypertensive subjects. It occurs to a greater extent with non-selective β-blockade than with β_1-selective blockers (Anderson et al. 1985).

Whilst the effect of β-blockade on submaximal exercise capacity has been extensively investigated, the same studies have not been performed using calcium channel antagonists. The available studies report that there is no impairment in submaximal exercise endurance after verapamil or diltiazem ingestion in normotensive or hypertensive subjects (Derman et al. 1991b; Herbertsson & Fagher 1990; Mooy et al. 1987; Vanhees et al. 1988). However, the number of studies is small. In normotensive subjects, any impairment in submaximal exercise capacity after the ingestion of dihydropyridine derivatives is less than that seen with β-blockade (Derman et al. 1992; Kindermann 1987). Submaximal exercise performance in hypertensive subjects after dihydropyridine administration has not been studied.

3.3 Physiological effects of exercise

3.3.1 Central haemodynamics

Beta-blockers reduce HR and systolic and diastolic BP at rest and during exercise. The reduction in HR is partially compensated for by an increase in stroke volume both at rest and during exercise (Frisk-Holmberg et al. 1985; Scruggs et al. 1991), so that the reduction in cardiac output is less pronounced than the HR reduction (Van Baak 1988). Most studies have demonstrated a reduction in cardiac output during β-blockade at rest and during maximal and submaximal exercise of 5-15% (Bonelli et al. 1977; Freund et al. 1987; Van Baak 1988).

submaximal exercise of 5-15% (Bonelli et al. 1977; Freund et al. 1987; Van Baak 1988).

In contrast to β-blockers, calcium channel antagonists do not reduce cardiac output at rest (Klein et al. 1983; Lund-Johansen et al. 1992, Omvik et al. 1988). Also, most studies show that, in hypertensive subjects, cardiac output during exercise is either unchanged or increased after calcium channel antagonist administration (Gillies et al. 1996; Klein et al. 1983; Lund-Johansen et al. 1992; Omvik & Lund-Johansen 1988).

The reduction in cardiac output after administration of β-blockers has been the traditional explanation for the reduction in exercise performance found following ingestion of these agents. However, there are several findings which do not concur with this hypothesis. Firstly, β-blockers with intrinsic sympathomimetic activity do not decrease cardiac output as much as other β-blockers (Ades et al. 1989), but result in the same degree of premature fatigue (Duncan et al. 1990; Kullmer et al. 1987). Secondly, agents which result in the same degree of reduction in resting and exercising heart rate produce different degrees of impairment of maximal exercise performance (Lundborg et al. 1981). Thirdly, other anti-hypertensive agents reduce resting and exercise BP without affecting exercise performance (Myburgh & Gordon 1987; Petri et al. 1986). Thus, there is considerable evidence to indicate that it is not the changes in central haemodynamics produced by β-blockade that result in impairment of exercise performance.

3.3.2 Peripheral haemodynamics

Beta-adrenergic receptors are found in skeletal muscle vasculature and hence β-blockade would be expected to lead to vasoconstriction of these vessels and consequently reduction of skeletal muscle blood flow. Several studies have shown this to occur (Freund et al. 1987; McSorley & Warren 1978). However, other studies have measured leg oxygen uptake and found that while blood

flow to the leg was reduced by 10% during submaximal exercise, the arterio-venous oxygen difference was increased so that leg oxygen uptake was unchanged (Frisk-Holmberg et al. 1985; Trapp-Jensen et al. 1976). Thus, it appears that any interference with blood flow to the working muscle caused by β-blockade does not result in a diminished oxygen uptake by the muscle. However, it may result in a decreased rate of removal of muscle metabolites.

3.3.3 Ventilation and gaseous exchange

There have been some reports of changes in ventilatory parameters during exercise after ingestion of β-blockers (Joyner et al. 1987; McLeod et al. 1985). However, these changes in ventilation are small (Pearson et al. 1987) and are unlikely to cause the decreased exercise performance produced by these agents.

Most studies have not demonstrated any effect of calcium channel antagonism on ventilatory parameters during maximal or submaximal exercise in hypertensive or normotensive subjects (Chick et al. 1986; Derman et al. 1991b, 1992; Gordon et al. 1986, 1987; Kindermann 1987; Petri et al. 1986; Raffestin et al. 1985; Stein et al. 1984; Van Baak et al. 1987b).

3.3.4 Carbohydrate metabolism

Skeletal muscle and blood lactate concentrations during exercise are the result of a complex interaction between release of lactate into the blood stream by exercising and non-exercising muscle, the hepatic uptake of lactate for conversion to blood glucose, the use of lactate as a fuel source by exercising muscle and the lactate distribution volume (Stanley et al. 1985). Muscle lactate concentrations have been reported to be unchanged (Broberg et al. 1988; Frisk-Holmberg et al. 1979; Lausitiola et al. 1983) or decreased (Lundborg et al. 1981) during exercise with β-blockade. Similarly, reports of blood lactate concentrations during submaximal and high intensity exercise after β-blockade are inconsistent (Van Baak 1988). These discrepancies suggest that any effect

of β-blockers on lactate kinetics is probably small, and is unlikely to explain the reduction in exercise performance seen with β-blockade.

Some studies have shown a reduction in blood glucose concentrations with β-blockade during high intensity exercise (Van Baak 1988) or prolonged submaximal exercise (Lundborg et al. 1981, Wijnen et al. 1993). However, other studies have not found lower blood glucose concentrations during either maximal or submaximal exercise after β-blockade, even though exercise performance was impaired (Gullestad et al. 1989b, 1991; Lausitiola et al. 1983; Van Baak et al. 1993). These findings demonstrate that hypoglycaemia is probably not a cause of the premature fatigue during exercise experienced after β-blockade in these studies.

3.3.5 Fat metabolism

Beta-adrenoreceptors are found in adipose tissue and their stimulation results in lipolysis. β-blockers reduce the plasma concentration of free fatty acids during exercise (Frisk-Holmberg et al. 1985; Lausitiola et al. 1983; Lundborg et al. 1981; Van Baak et al. 1987a; Verstappen & Van Baak 1987), although some authors report that β-blockade decreases plasma free fatty acid concentration only after exercise (Cosenzi et al. 1995; Wijnen et al. 1993). As the uptake of free fatty acids by skeletal muscle depends on the plasma concentration (Ahlborg et al. 1974), the exercising muscle will take up less fatty acid than normal after β-blockade. This is likely to cause a shift from fat to carbohydrate oxidation by the active skeletal muscle (Wijnen et al. 1993) and there is some evidence that liver glycogenolysis (and not muscle glycogenolysis) is accelerated during exercise after β-blockade (Ahlborg & Juhlin-Dannfelt 1994). This is a possible cause of premature fatigue during prolonged exercise. However, Van Baak et al. (1993) infused triglycerides during submaximal exercise in subjects ingesting either β-blockers or placebo. Premature fatigue occurred after β-blockade despite raised plasma free fatty

acid concentrations. Thus inhibition of adipose lipolysis is an improbable cause of the reduced endurance seen during β-blockade.

The plasma concentration of free fatty acids, glycerol and triglycerides during exercise are unchanged by verapamil or diltiazem in hypertensive or normotensive subjects (Derman 1993; Petri et al. 1986) suggesting that lipolysis is unaltered by these agents. However, nifedipine increases the concentration of free fatty acids and ketones in the plasma during exercise in normotensive subjects (Raffestin et al. 1985). Together with the increase in blood glucose and lactate concentrations reported in this study, this is evidence that there is an increased rate of glycogenolysis and lipolysis as a result of increased sympathetic stimulation in normotensive subjects. This may subside with time. Gillies et al. (1996) found no alteration in plasma glucose, lactate or free fatty acid concentrations during submaximal exercise following amlodipine ingestion for 2 weeks by hypertensive patients.

3.3.6 Serum potassium concentrations

The stimulation of β-receptors associated with the membrane Na^+K^+-ATPase in muscle cells promotes the uptake of potassium into the cell (Van Baak 1988). β-blockers increase serum potassium during both maximal and submaximal exercise and during recovery (Gullestad et al. 1989b; Leenen et al. 1980; Lundborg et al. 1981; Schneider et al. 1994; Van Baak et al. 1987a). As very high serum potassium concentrations (above 5-6 mmol/l) are known to impair skeletal muscle contraction (Jones 1981), the raised potassium levels seen with β-blockade are a plausible cause of reduced exercise performance. Further, non-selective β-blockade results in a higher potassium concentration during exercise than β_1-selective blockade (Gullestad et al. 1989b, 1991), and exercise performance is reduced to greater degree following non-selective than selective β-blockade (Anderson et al. 1985).

However, there is evidence to suggest that the reduced exercise capacity seen with β-blockade is not attributable to increased serum potassium concentration. Gullestad et al. (1991) reported that the non-selective β- blocker, propranolol, reduced maximal exercise capacity and increased serum potassium concentration during exercise; however, selective antagonism of β_2-receptors reduced maximal exercise performance but did not alter serum potassium concentration during exercise. Derman (1993) found that serum potassium concentration was not different in those subjects who experienced premature fatigue during prolonged submaximal exercise from those subjects who did not fatigue prematurely. McKelvie & Jones (1991) reported that while serum potassium was raised to the same concentration by both high and low dose β-blockade, maximal exercise capacity was reduced only by the high dose β-blockade. These findings demonstrate a dissociation between raised serum potassium concentration and impaired exercise performance and indicate that the reduction in exercise performance following β-blockade is not a result of an increase in serum potassium concentration.

Serum potassium concentration during exercise in normotensive subjects are not altered after the administration of verapamil or diltiazem (Derman 1993; Stein et al. 1984). The effects of verapamil or diltiazem on serum potassium concentration in hypertensive subjects, or the effects of dihydropyridine derivatives have not been reported.

3.3.7 Hormone concentrations

Beta-blockers have no effect on the concentration of most hormones at rest but hormonal levels during exercise are markedly altered (Gullestad et al. 1989a). The normal increase in plasma adrenaline concentrations seen with exercise is substantially accentuated by β-blockade (Cleroux et al. 1987; Gullestad et al. 1989a). The normal increase in plasma noradrenaline concentration is unaltered during submaximal exercise (Cleroux et al. 1987; Lundborg et al. 1981) or is slightly increased (Gullestad et al. 1989a). Plasma concentrations

of growth hormone, prolactin and cortisol during submaximal exercise are increased after β-blockade, while plasma dopamine concentration is unchanged (Gullestad et al. 1989a). The physiological increase in plasma renin concentration during exercise is attenuated (Bonelli et al. 1977; Gullestad et al. 1989a) following β-blockade. Gullestad et al. (1989a) reported that there was no correlation between the perception of fatigue and plasma adrenaline, noradrenaline, growth hormone, prolactin, cortisol or renin concentrations. Ratings of perceived exertion during submaximal exercise were higher after non-selective than β_1-selective blockade, but there were no differences in hormone concentrations between non-selective and β_1-selective blockade. This finding suggests that the increased perception of fatigue seen with β-blockers is not associated with altered plasma hormone concentrations during exercise.

3.3.8 Skeletal muscle contractile dysfunction

Most studies which have examined the effect of β-blockers on skeletal muscle power output during high intensity exercise of short duration report no effect of β-blockade on the ability to generate power (Derman et al. 1993; Rusko et al. 1980; Yoroko et al. 1990), although others have found that β-blockade reduces power output (Kaiser 1984).

Cupido et al. (1994) reported that the torque achieved by a maximum voluntary contraction of the quadriceps muscle and electromyographic activity of the muscle after a 4 minute fatigue protocol, consisting of intermittent voluntary isometric contractions of the quadriceps, were unaltered following β-blockade. However, two authors have reported that when short term, high intensity exercise was tested immediately following the completion of prolonged submaximal exercise, β-blockade resulted in a decrease in mean muscle power output in subjects who fatigued prematurely during the prolonged exercise (Derman et al. 1991a; Karlsson et al. 1983). The reduction in muscle power output did not occur before the bout of prolonged submaximal exercise had commenced. This suggests that β-blockade induces fatigue of skeletal

muscle during exercise. Further, Derman et al. (1991a) found that in those subjects who fatigued prematurely during prolonged submaximal exercise after β-blockade, integrated electromyographic activity was increased during the preceding 10 minutes prior to exhaustion, suggesting increased recruitment of muscle fibres perhaps in response to impaired skeletal muscle function. Hence, it is possible that β-receptor antagonists reduce exercise performance by inducing early fatigue of the active skeletal muscle. This is consistent with the hypothesis that it is skeletal muscle contractility and not cardiovascular function which determines the quality of exercise performance (Noakes 1988).

Recent evidence suggests that protein oxidation is increased following β-blockade both at rest (Lamont 1995) and during exercise (Lamont et al. 1995). In addition, Powers et al. (1995) reported that β-blockers administered to rats during an exercise training program reduced the training induced increase in skeletal muscle oxidative capacity compared to rats undergoing an exercise training program without β-blockade. It is possible that these effects of β-blockade on muscle protein and oxidative capacity may influence skeletal muscle contractility or cause premature fatigue.

In contrast to the above findings on the effects of β-blockade on skeletal muscle function, Gillies et al. (1996) reported that ingestion of the dihydropyridine derivative, amlodipine, did not alter skeletal muscle function either before or after prolonged submaximal exercise in hypertensive patients. Skeletal muscle function was tested by measuring the torque achieved by maximum voluntary isometric contractions of the quadriceps muscle, and recording the time taken before the subject was unable to maintain a torque equal to 70% of the initial torque during repeated maximum contractions. This finding suggests that skeletal muscle function is unaltered by dihydropyridine derivative ingestion. Prolonged submaximal exercise endurance was also unaltered by amlodipine ingestion in this study, which contrasts with the effect of β-blockade in the studies where impaired skeletal muscle function was found after prolonged submaximal exercise (Derman et al. 1991a; Karlsson et al.

1983). Thus, after amlodipine ingestion by hypertensive patients, there is no impairment of submaximal exercise endurance and no impairment of skeletal muscle function after prolonged submaximal exercise, suggesting that there is no premature skeletal muscle fatigue. This is consistent with the hypothesis that premature skeletal muscle fatigue may be the basis of impaired exercise performance when it occurs following anti-hypertensive medication administration.

3.4 Conclusions

The influence of β-blockade and calcium channel antagonism on exercise performance and the physiological response to exercise are summarised in Tables 3.1 and 3.2.

While β-blockers and calcium channel antagonists both act to reduce systolic and diastolic BP during rest and exercise in individuals with hypertension, these agents act via different pathways. Consequently, they have different effects on the physiological response to exercise and this may lead to different effects on exercise performance.

Beta-blockade has been consistently shown to reduce maximal and submaximal exercise performance in both normotensive and hypertensive

Table 3.1 Influence of β-blockade and calcium channel antagonism on exercise performance and the physiological response to exercise.

	Maximal ex. performance	Submax. ex. performance	BP during exercise	HR during exercise	Cardiac output	Minute ventilation
β-blockers	↓^	↓	↓	↓	↓	↓, ↔
Verapamil Diltiazem	↔	↔	↓#, ↔*	↓#	↔, ↑#	↔
Nifedipine	↓*, ↔#	?	↓#, ↔*	↔#	↔, ↑#	↔

^Physically active subjects, *Normotensive subjects, #Hypertensive subjects
Abbreviations: ↓=decreased, ↑=increased, ↔=unaltered, ?=unknown, ex.=exercise, submx.=submaximal, BP=systolic and diastolic blood pressure, HR=heart rate.

Table 3.2 Influence of β-blockade and calcium channel antagonism on serum metabolite concentrations and skeletal muscle fatigue.

Concentrations during exercise	Blood lactate	Blood glucose	Serum free fatty acids	Serum potassium	Serum hormones	Skeletal muscle fatigue
β-blockers	↔, ↓, ↑	↓, ↔	↓	↑	Many ↑ Some ↔	↑
Verapamil Diltiazem	↔	↔	↔	↔*, ?#	↔	?
Nifedipine	↑*, ?#	↑*, ↔*, ?#	↑*, ?#	?	Many ↑ Some ↔	?

^Physically active subjects, *Normotensive subjects, #Hypertensive subjects.
Abbreviations: ↓=decreased, ↑=increased, ↔=unaltered, ?=unknown.

subjects (Van Baak 1988). Calcium channel antagonism has been shown to, at most, have lesser effects on exercise performance than β-blockade, although the effects of calcium channel antagonists have not been extensively investigated.

Beta-blockers reduce cardiac output during rest and exercise whilst calcium channel antagonists maintain cardiac output. However, there is evidence to show that it is not the reduction in cardiac output seen with β-blockers results in the reduction in exercise performance. Blood flow to active skeletal muscle may be reduced during exercise with either β-blockade or calcium channel antagonism: with β-blockade this does not reduce the oxygen supply to the working muscle but may interfere with the removal of muscle metabolites.

Beta-blockade results in small changes to ventilatory parameters during exercise but these are unlikely to lead to a reduction in exercise performance. Calcium channel antagonism does not alter ventilation during exercise.

Both β-blocker and calcium channel antagonist ingestion results in small changes in blood lactate concentrations during exercise but these findings are inconsistent and so are unlikely to lead to significant changes in exercise performance. A reduction in blood glucose during exercise is sometimes reported after β-blockade, but this is not always seen even in the presence of

an impairment of exercise performance. Nifedipine, but not verapamil or diltiazem, results in increased blood glucose concentrations during exercise in normotensive subjects and this has been attributed to an increase in sympathetic stimulation secondary to vasodilatation.

The concentration of serum free fatty acids during and after exercise is reduced after β-blockade, but there is evidence that this does not cause the impairment in exercise performance seen after β-blockade. Nifedipine, but not verapamil or diltiazem, results in an increase in serum free fatty acid concentration during exercise. This is thought to be due to increased lipolysis as a result of increased sympathetic stimulation.

Beta-blockade results in increased serum potassium concentration due to decreased uptake of potassium into muscle cells; however there is evidence that the reduction in exercise performance following β-blockade is not due to the increased serum potassium concentration.

Beta-blockade results in increases in the concentrations of many hormones during exercise but this does not correlate with the reduction in exercise performance. Verapamil and diltiazem do not alter noradrenaline or growth hormone concentrations during exercise but nifedipine increases these in normotensive subjects. The increase in hormone concentration seen with nifedipine is different from that seen with the β-blockers, in that nifedipine raises noradrenaline concentration and not adrenaline concentration, while the reverse is true with β-blockade. The increase in hormone concentrations seen after nifedipine administration is thought to be due to increased sympathetic stimulation. It is not known whether the increased sympathetic stimulation is sustained over long periods of administration of nifedipine.

It is possible that β-blockade results in premature fatigue of skeletal muscle fibres either via an increase in skeletal muscle protein oxidation, a reduction in skeletal muscle oxidative capacity, a direct influence on the skeletal muscle

fibre or a combination of several of the effects on exercise physiology discussed above. It appears that amlodipine does not alter skeletal muscle function in hypertensive subjects (Gillies et al. 1996). The effects of other calcium channel antagonists on skeletal muscle function have not been reported.

The evidence for increased sympathetic stimulation after nifedipine ingestion by normotensive subjects has been reported as documented above. This does not occur after verapamil or diltiazem ingestion in either normotensive or hypertensive subjects. Bearing in mind the lack of comprehensive research into the effects of calcium channel antagonists on exercise performance, the only evidence of impairment of exercise performance seen after calcium channel antagonist administration is seen after nifedipine ingestion by normotensive subjects. However, it is not known whether the increase in sympathetic stimulation is causally related to the impairment in maximal exercise performance. This differs from the situation seen with β-blockade where the sympathetic system is blocked from exerting its complete action.

Chapter 4. General methodology.

The general methodology common to the different studies in Chapters 5-8 is described in this chapter. Methodology specific to any particular chapter is outlined in that chapter.

All studies described in this thesis were approved by the South African Medicines Control Council and the Ethics and Research Committee of the Faculty of Medicine at the University of Cape Town.

4.1 Anti-hypertensive drugs

Isradipine is a calcium channel blocker of the 1,4-dihydropyridine group. It acts primarily as a vasodilator with minimal negative inotropic effects (Chellingsworth et al. 1988). Several multicentre clinical trials have shown that isradipine has greater efficacy in reducing blood pressure than propranolol, hydrochlorothiazide, prazosin and diltiazem (Dahlöf 1989; Vermeulen et al. 1988). It has a dose dependent effect for the reduction of blood pressure (up to 5 to 7.5 mg twice daily) and for the presence of side effects (Dahlöf 1989). At a dose of 2.5 mg twice daily, isradipine results in blood pressure reduction of approximately 80% of the maximum and an incidence of side effects which is not different to that of placebo (Kirch et al. 1990; Simonsen & Sundstedt 1989). The most common side effects are headache, palpitations, dizziness, flushing and oedema. These side effects often disappear if therapy is continued for several weeks (Dahlöf 1989). It does not have adverse metabolic effects, there is no associated tachycardia, fluid retention or orthostatic hypotension and renal function is preserved (Dahlöf 1989). Isradipine has a long duration of action with twice daily doses producing a sustained reduction in blood pressure over 12 hours (The Italian-Belgian isradipine study group 1989).

Atenolol is a β_1-selective adrenergic receptor antagonist which is widely used in the treatment of hypertension, angina pectoris, cardiac arrhythmias and myocardial infarction. It has only very weak action at β_2-receptors and hence

results in little bronchoconstriction and vasoconstriction. It has no partial agonist activity. Atenolol has low lipid solubility and so concentrations in brain tissue are low; this may be the reason for the low incidence of central nervous system side effects compared to lipophilic β-blockers such as propranolol. Atenolol is well tolerated, although in 2-3% of patients therapy must be withdrawn due to adverse effects. The most common side effects are cold extremities and fatigue (Dollery 1991).

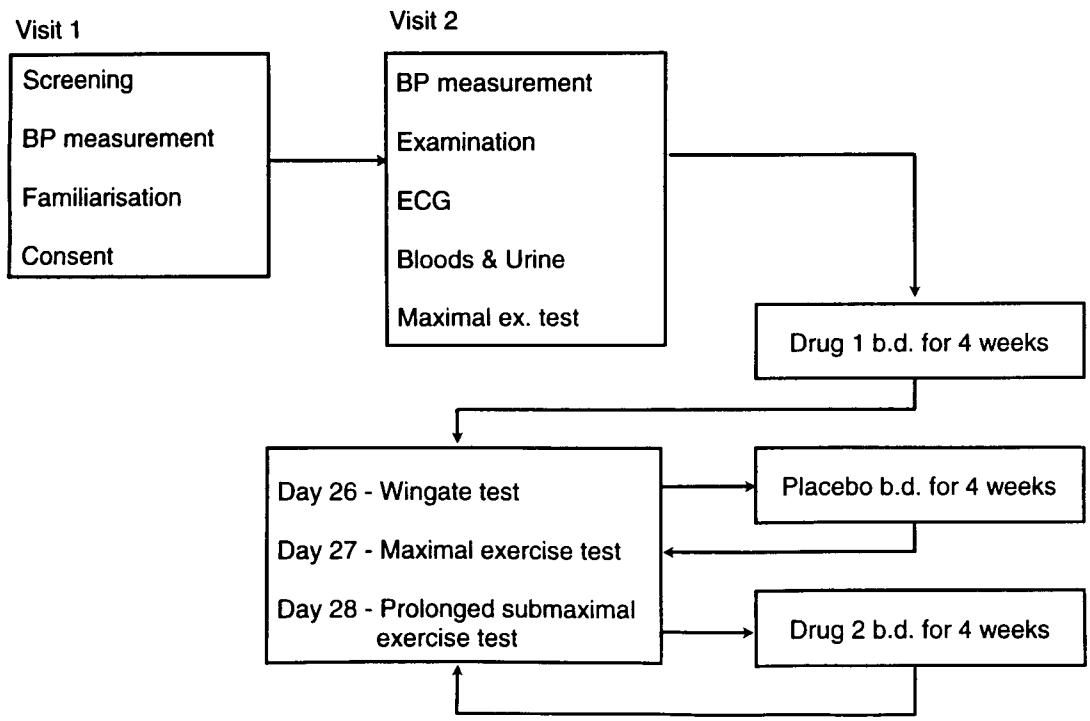
4.2 Study Overview

The effects of two different anti-hypertensive agents, isradipine, a dihydropyridine calcium channel antagonist and atenolol, a β_1-selective adrenergic antagonist, on different aspects of exercise performance were compared in physically active subjects with mild to moderate essential hypertension. A placebo controlled, crossover study design where active drug treatments were randomised and double blinded, was used. Maximal, submaximal and short duration, high intensity exercise performance was assessed.

Twelve subjects with resting diastolic blood pressure greater than 90 mmHg who performed vigorous recreational exercise on at least 4 occasions a week were recruited to participate in these studies. All subjects gave their written informed consent for these studies. Their descriptive characteristics were: 10 males and 2 females, mean age 45 yrs (range 26-61 yrs), mean systolic blood pressure 155 mmHg (range 140-175 mmHg), mean diastolic blood pressure 100 mmHg (range 90-108 mmHg), mean heart rate at rest 61 bpm (range 38-73 bpm), mean VO_2max 37.8 mlO_2/min/kg (range 31.8-46.7 mlO_2/min/kg), mean weight 76 kg (range 41-90 kg), mean height 173 cm (range 140-190 cm). All subjects were free of any serious medical disorders other than hypertension, were non-smokers and not on any concurrent medication. Subjects were instructed to maintain a constant level of activity throughout the duration of the trial and to avoid any strenuous physical exercise for 36 hours preceding each laboratory visit.

An overview of the study design is given in Figure 4.1. After a minimum period of 2 weeks without medication, subjects visited the laboratory on at least two occasions for determination of blood pressure, physical examination, ECG blood and urine analysis, familiarisation with the testing equipment and an initial incremental exercise test to exhaustion for determination of baseline VO_2max. Subjects then began the first active drug treatment period during which time they ingested either isradipine 2.5 mg twice daily, or atenolol 50 mg twice daily for 4 weeks. These dosages of isradipine and atenolol were chosen as they have been shown to be the standard doses used in the management of hypertension and to have equipotent blood pressure lowering effects (Isradipine in Hypertension Study Group 1989). During the fourth week of the drug treatment period the subjects underwent exercise testing on three consecutive days. On the first day of testing, a Wingate test was performed to measure their ability to perform short duration, high intensity exercise. On the second day of testing, subjects performed an incremental exercise test to exhaustion to assess maximal exercise capacity. On the third day, the subjects underwent a prolonged submaximal exercise test to measure time to

Figure 4.1 Overview of study design.



exhaustion, and cardiorespiratory and metabolic parameters during prolonged exercise. A placebo was then ingested twice daily for a period of four weeks with identical exercise protocol testing performed during the fourth week. This was followed by the second drug treatment period where the alternate drug was ingested. The exercise testing protocol was repeated in the fourth week.

Drug treatments were randomised and double blind; however the placebo treatment was single blind. This was done to avoid the need for washout periods between drug treatments, which would have increased the length of time during which these hypertensive patients were without active medication. Blood pressure and side effects were monitored regularly throughout the study.

Subjects attended the laboratory at the same time of day on each day of exercise testing. They were asked to eat a standardised meal 2 to 4 hours before testing and to ingest their medication 3 hours prior to testing. Before testing started, subjects were seated in a quiet environment for a period of 15 minutes. Resting blood pressure (seated and standing) was then measured and recorded twice using a calibrated mercury sphygmomanometer (Korotkoff phase I and IV), and the mean blood pressure in each of the seated and standing positions was calculated. Heart rate at rest (seated and standing) was measured by palpation of the radial artery. Body mass was measured on a Seca electronic scale.

4.3 Exercise tests

4.3.1 Maximal and submaximal exercise tests

Before exercise commenced, a forearm vein was cannulated with an 18 gauge Jelco flexible catheter (Criticon, Tampa, Florida, USA). A 3 way stopcock (Discofix-3, Belgium) was attached to enable multiple blood samples to be taken during the tests. Blood was drawn at regular intervals throughout the maximal and submaximal tests and 1.0 ml added to test tubes containing 2 ml of 70% perchloric acid and stored in ice for blood lactate analysis. During the

prolonged submaximal exercise test the catheter and stopcock were flushed with 2.0 ml of normal saline after drawing blood to maintain patency. During both the maximal and submaximal tests, immediately prior to sampling, 0.5 ml of blood was drawn and discarded to empty the catheter of any blood or saline.

The maximal and submaximal exercise tests were administered on a electromechanically braked cycle ergometer (Godart, Bilthoven, Holland). During these tests the subjects cycled with a model no. 2766 counterbalanced head support holding a model no. 2700 Rudolph valve (both by Hans Rudolph Inc., Kansas City, KS, USA). A clip prevented nasal breathing. Expired air was measured for oxygen (Ametec O_2 Analyzer Model 3A, Theridox, Pittsburgh, PA, USA) and carbon dioxide content (Ametec Carbon Dioxide Analyzer Model CD-3A, Theridox, Pittsburgh, PA, USA). Both analysers were calibrated prior to testing using gases of known composition. Inspiratory volume was measured with a Mijnhardt dry gas meter that had been calibrated against a Collins chain-compressed gasometer (Collins Inc., Braintree, MA, USA). Total inspiratory ventilation (V_i), oxygen uptake (VO_2), carbon dioxide production (VCO_2) and respiratory exchange ratio (RER) were calculated every 3 sec by an on-line microcomputer (Sperry), using software based on conventional equations as previously described from this laboratory (Noakes et al. 1990). The average value of each parameter for each minute was stored for later printing.

Blood pressure during the maximal and submaximal exercise tests was measured by means of audible sphygmomanometry using the same calibrated mercury sphygmomanometer (Standby, WA Baum Co. Inc., New York, USA). Korotkoff phase I and IV were used. The systolic blood pressure was recorded during exercise at intensities less than approximately 80% of the subjects VO_2max. During exercise above this intensity, upper body and arm movements become too great to allow accurate blood pressure measurements. Heart rate during both the maximal and submaximal exercise tests was recorded using an electrocardiogram monitor (Loheimer M607, Munich, West Germany) with self-adhering electrodes placed in the modified CM_5 position.

The subjects indicated their Borg rating of perceived exertion (RPE) on a ten point scale during the maximal and submaximal tests (Borg 1982).

On completion of each exercise test, the collected blood samples were centrifuged at 2000 rpm for 15 min in a Sigma 302-K centrifuge (Munich, Germany). The tubes containing 2.0 ml of 70% perchloric acid had been weighed on a Sartorius 1412MP*-1 scale (Gottingen, West Germany) before the test began and stored in a refrigerator. After centrifuging, the samples were again weighed to calculate the actual volume of blood collected. The supernatant was then decanted and frozen for later analysis. An assay adapted from Gutman and Wahlfeld (1974) was used to determine the lactate concentration of the samples.

4.3.1.1 Maximal exercise test

The maximal exercise test was a progressive exercise test to exhaustion. Male subjects began cycling at a workload of 120W and female subjects at a workload of 90W. The workload was increased every minute by 15W until the subject was unable to continue pedalling. Every minute throughout the test, heart rate and RPE were recorded and 1.0 ml of blood drawn for lactate estimation. Blood pressure was recorded every second minute. Further samples of blood were drawn every minute for 5 min after exercise terminated.

The VO_2max and the peak V_i were taken as the highest VO_2 and highest V_i respectively recorded during any one minute period (Noakes 1988). Peak workload was taken as the highest workload (W) maintained for a complete minute during the test. Exercise time to exhaustion was calculated as the total time for which the subject continued cycling including the fraction of any uncompleted minute.

After each maximal exercise test, 75% of the VO_2max was calculated. Blood pressure and blood lactate concentration at 75% of VO_2max were determined as that blood pressure and blood lactate concentration recorded during the

period in which the VO_2 was closest to 75% of VO_2max. The first period in which the lactate concentration was greater than 4.5 mmol/l was determined.

Ninety percent of the VO_2max obtained at the preliminary maximal exercise test was calculated. The approximate workload at which the VO_2 was equal to 90% of the VO_2max during the preliminary maximal exercise test was recorded. For each subsequent maximal test the RPE at this particular workload was designated as the RPE at 90% of VO_2max. For each maximal exercise test the workload at which the RPE = 4 was the first workload in which a RPE of four or greater was recorded.

4.3.1.2 Submaximal exercise test

The submaximal exercise test consisted of prolonged exercise at 75% of the subject's initial VO_2max. After 3 min warm up at 50% of VO_2max, the workload was increased to 75% of VO_2max and subjects were instructed to pedal for 1 hour or until a cadence of 70 rpm could no longer be maintained.

Heart rate, blood pressure, and RPE were recorded every 15 minutes, as described above. VO_2, VCO_2, V_i and RER were recorded for the last 5 minutes in every 15 minute interval by on-line microcomputer as described. The duration of exercise was taken as the number of completed minutes performed at 75% of VO_2max.

Eleven ml of blood were collected from the cannula prior to the commencement of exercise and every 15 minutes during exercise for later analysis of blood lactate, serum glucose and serum free fatty acid concentration. Six ml of the sample were immediately injected into a vacutainer (SST Gel and clot activator, L42911) for analysis of serum free fatty acid concentration. Four ml were injected into a Vac-U-Test (potassium oxalate/sodium fluoride) glass test tube for measurement of serum glucose concentration, and the remaining 1 ml was added to a tube containing 2.0 ml of

70% perchloric acid for blood lactate analysis. The tubes were inverted to mix the contents and were stored on ice until the completion of the test.

On completion of each submaximal exercise test, the collected blood samples were centrifuged at 2000 rpm for 15 min in a Sigma 302-K centrifuge (Munich, Germany). After centrifuging, the plasma was removed from the samples for glucose and free fatty acid analysis and frozen for subsequent analysis. The tubes containing the samples for determination of blood lactate concentration were weighed and the supernatant frozen for later analysis as previously described.

Serum free fatty acid concentrations were determined using a standard enzymatic kit method (Free Fatty Acids, Half-Micro test, Boehringer Mannheim Biochemica, Mannheim, Germany).

Serum glucose assays were performed on a Technicon RA-XT (Technicon, Ireland) automated glucose analyser which operates using the glucose oxidase method. The accuracy of the machine was checked by running a standard after every 10 samples.

4.3.2 Short duration, high intensity exercise test

Short duration, high intensity exercise performance was tested using a standardised Wingate test as described by Bar-Or (1987). This test lasts 30 seconds and requires maximal effort against a supramaximal workload. The test was performed on a Monark mechanical cycle ergometer. Before beginning the test subjects completed a 2 min warm up. To begin the test, the subjects increased the cadence to over 110 revolutions/min against minimal resistance. The resistance was suddenly increased to approximately 0.08 kiloponds per kilogram bodyweight while the subjects pedalled at the highest cadence they were able to maintain for 30 seconds. The subjects were motivated verbally by the investigator throughout the test. Pedal revolutions were counted electronically and recorded by an on-line personal computer. The

power output for each 0.5 sec period for the first 5 sec and each 5 sec period from 5 to 30 sec was calculated by the computer. Peak power was the highest power output for a 0.5 sec period. Mean power over the 30 second test period, power to bodyweight ratio, total work done, and average pedal frequency were calculated by the computer, using the cadence for each 5 second period, the resistance and the subjects bodyweight. The rate of fatigue (W/sec) is the difference between the peak power output and the power output over the last 5 sec divided by the time elapsed between the two measurements.

4.4 Statistical Analysis

Data were analysed using analysis of variance (ANOVA) for repeated measures, and Duncan's multiple range test to identify the location of significant differences. Statistical significance was established at the $p<0.05$ confidence level (Ganz 1980).

With respect to variables measured in the submaximal exercise test, only paired data were used: i.e. subjects who were unable to complete 60 min were excluded from the analysis from the time that they dropped out. In the analysis of RPE during submaximal exercise, all subjects were included throughout the test; subjects who did not complete 60 min were given a RPE of 10 for the time points after they had dropped out.

Chapter 5. Cardiovascular measurements at rest and side effects of ingested medications.

This chapter will describe the effects of isradipine and atenolol on blood pressure and heart rate at rest. The side effects reported during the drug treatments will be presented and discussed.

5.1 Cardiovascular measurements at rest

Cardiovascular measurements at rest are listed in Table 5.1. Diastolic blood pressure at rest, while seated and standing, was significantly decreased by both atenolol and isradipine, but was reduced to a greater extent by atenolol than isradipine (83.3 mmHg vs 89.0 mmHg vs 96.1 mmHg while seated, (A vs I vs P, p=.0001). Systolic blood pressure at rest tended to be reduced by both agents, but this trend was not statistically significant. Heart rate while seated at rest was reduced by atenolol compared to both isradipine and placebo (53 bpm

Table 5.1 Influence of isradipine, atenolol and placebo on resting cardiovascular parameters.

	Placebo	Isradipine	Atenolol
DBP - Sitting (mmHg) %change	96.1 ± 2.5	89.0 ± 1.8 -7.4^{**++}	83.3 ± 2.6 -13.3$^{\#\#++}$
SBP - Sitting (mmHg) %change	145.0 ± 4.7	138.5 ± 3.4 -4.5	133.3 ± 5.4 -8.1
HR - Sitting (bpm) %change	63.5 ± 2.9	68.1 ± 4.3 7.2	52.6 ± 4.0 -17.2$^{\#\#++}$
DBP - Standing (mmHg) %change	101.7 ± 2.2	94.1 ± 2.0 -7.5^{**++}	88.5 ± 2.6 -13.0$^{\#\#++}$
SBP - Standing (mmHg) %change	146.9 ± 4.8	140.3 ± 3.5 -4.5	136.9 ± 6.3 -6.8
HR - Standing (mmHg) %change	68.6 ± 3.3	74.4 ± 4.4 8.5^{**++}	55.2 ± 4.5 -19.5$^{\#\#++}$
Body Mass (kg) %change	76.0 ± 4.2	76.2 ± 4.1 0.3	76.4 ± 4.4 0.5

Values are expressed as means ± SE, n=11.
**p<.001 isradipine vs placebo, $^{\#\#}$p<.001 atenolol vs placebo, $^{++}$p<.001 atenolol vs isradipine
Abbreviations: HR=heart rate, SBP=systolic blood pressure, DBP=diastolic blood pressure.

vs 68 bpm, 64 bpm, A vs I,P, p=.0001), and was unchanged by isradipine compared to placebo. Heart rate while standing was reduced by atenolol compared to both isradipine and placebo, but was increased by isradipine compared to placebo and atenolol (55.2 bpm vs 74.4 bpm vs 68.6 bpm, A vs I vs P, p=.0001). Body weight was unchanged throughout the trial.

5.2 Discussion

Whilst ingestion of both atenolol and isradipine lowered blood pressure in this group of mildly hypertensive subjects, atenolol reduced the diastolic blood pressure by 6 mmHg greater than did isradipine. Thus the two agents did not have equipotent blood pressure lowering effects in these subjects at the dosages used in this study.

These subjects demonstrated an increase in heart rate of 6 bpm while standing after ingesting isradipine for 4 weeks. The heart rate while seated tended to be higher following isradipine ingestion, but this was not statistically significant. Most studies investigating the effects of isradipine have reported a mild tachycardia (Kirkendall 1988; Nelson et al. 1986; Rupoli et al. 1989), but this is not a consistent finding (Chellingsworth et al. 1988; Persson et al. 1989), and was found to be transitory in one study (Vermeulen et al. 1988). Tachycardia after the ingestion of calcium channel antagonists is thought to be a reflex phenomenon due to the vasodilatation and reduced blood pressure (Lund-Johansen & Omvik 1983). It is possible that these exercise trained subjects are more susceptible to postural hypotension resulting from greater venous pooling than untrained subjects (Raven & Pawelczyk 1993), and this could explain why the tachycardia was present only while standing.

5.3 Side effects

Five subjects reported headaches occurring at the beginning of the isradipine treatment period. Of these, only 2 subjects required analgesia. No headaches

were reported after 5 days with continuing isradipine treatment. Five subjects reported that the medication was interfering with their usual exercise training whilst ingesting atenolol. Two other subjects reported feeling more tired than usual during training whilst ingesting atenolol but did not attribute their symptoms to their medication. No other side effects were reported.

The exercise tolerance of one subject, JF, was so severely compromised during the atenolol treatment period (which was his first treatment) that he was unable to complete the four weeks on the medication. He described extreme fatigue during activities of daily living such as walking to his car. This may have been partly due to having run a 56 km marathon a week prior to commencing the drug treatment. However, his fatigue rapidly resolved on withdrawal of the medication for a 2 week period, and recurred when the medication was recommenced. This suggests that atenolol ingestion was responsible for his symptoms. He was unable to complete the full duration of atenolol therapy and did not undergo exercise testing while on atenolol. He did complete the placebo and isradipine treatments and did undergo exercise testing during these treatments. Because of the absence of measures of exercise performance during the atenolol treatment this subject's results have been excluded from the analysis. However, the severe impairment of physical activity apparently caused by atenolol in this subject should be noted.

It has been reported in the literature that the fatiguing effects of β-blockers are more marked in some individuals than in others (Kaiser et al. 1981). It appears that this subject, JF, is particularly sensitive to this effect of atenolol. Hence the study population in this thesis should be described as only those physically active hypertensive patients who are able to tolerate both atenolol and isradipine treatments and who are able to participate in regular physical activity while ingesting these medications.

It is noteworthy that whereas 7 subjects reported increased fatigue during exercise whilst ingesting atenolol, no subject described increased fatigue during exercise whilst ingesting isradipine or placebo. It is possible that there

was some bias in the reporting of side effects, as most of these subjects were runners who were well informed on the effects of β-blockade and who were accustomed to measuring their resting pulse rate. Nevertheless, fatigue during physical exercise was an important side effect of the atenolol treatment, as this particular side effect may lead to poor compliance in hypertensive subjects who are physically active. This is consistent with the literature; β-blockers are well known to cause subjective feelings of increased fatigue during physical activity (Van Bortel & Van Baak 1992). Complaints of impaired exercise capacity are rare in patients ingesting calcium channel blockers (Lund-Johansen 1987).

Chapter 6. Comparative effects of isradipine and atenolol on maximal exercise performance in physically active hypertensive patients.

6.1 Introduction

The results of studies on the effects of calcium channel antagonists on maximal exercise performance are conflicting. Verapamil and diltiazem ingestion have been shown to be without effect on maximal exercise capacity in normotensive or hypertensive subjects (Derman et al. 1991b; Keleman et al. 1989; Myburgh and Gordon 1987; Szlachcic et al. 1987; Vanhees et al. 1988). Similarly, nifedipine ingestion is also without effect on VO_2max, WLmax or maximal exercise test duration when administered to hypertensive patients (Ashmore et al. 1990; Gosse et al. 1992; Halperin et al. 1993). Similarly, neither VO_2max nor WLmax was altered following lacidipine or amlodipine administration (Fariello et al. 1991; Gillies et al. 1996). However, it appears that nifedipine ingestion results in a small impairment of maximal exercise capacity in normotensive subjects (Chick et al. 1986; Derman et al. 1992; Gordon et al. 1986, 1987).

The cause of the impairment of maximal exercise performance after nifedipine ingestion in normotensive subjects is not clear. As discussed in Chapter 2, it is possible that the reason for this discrepancy is related to the physical activity status of the subjects. Investigations into the effects of dihydropyridine treatment on exercise performance in hypertensive subjects who are physically active and consequently have a high capacity to perform maximal exercise are required.

Studies which have examined the effects of β-blockers on maximal exercise performance in physically active hypertensive subjects have reported a

reduction in maximal exercise capability following β-blockade (Szlachcic et al. 1987; Van Baak et al. 1988).

Thus, it is important to investigate the effects of anti-hypertensive agents on maximal exercise performance in hypertensive individuals who are physically active. The effects of isradipine on maximal exercise performance are unknown. This chapter compares the effects of isradipine and atenolol on incremental exercise to exhaustion in physically active hypertensive subjects.

6.2 Methods

The effects of isradipine and atenolol on maximal exercise performance in active subjects with mild to moderate essential hypertension were compared in a placebo controlled, crossover study where drug treatments were randomised and double blinded. The study design is described in Chapter 4.

6.3 Results

The influence of isradipine and atenolol on cardiovascular and respiratory parameters and exercise performance during incremental exercise to exhaustion are documented in Table 6.1.

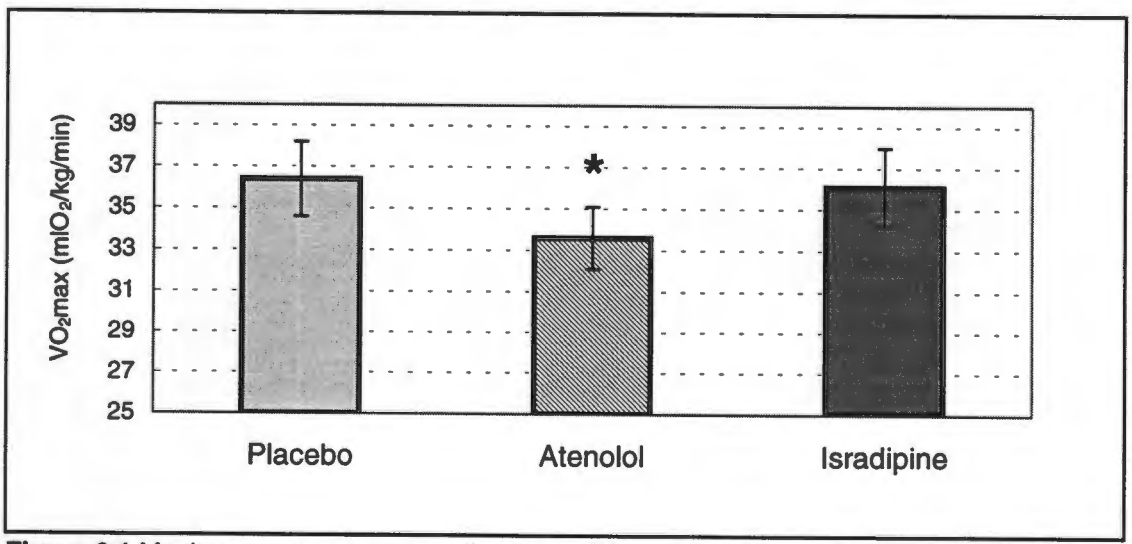


Figure 6.1 Maximum oxygen consumption following ingestion of anti-hypertensive medication. *p<.05 atenolol vs placebo, isradipine. Values +/- SE.

Table 6.1. Influence of isradipine, atenolol and placebo on physiological measurements during incremental exercise to exhaustion in physically active hypertensive patients.

	Placebo	Isradipine	Atenolol
Maximum HR (bpm)	170.7 ± 2.2	171.6 ± 1.9	130.2 ± 6.3$^{\#\#++}$
VO_2max (mlO_2/kg/min) % change	36.4 ± 1.8	36.1 ± 1.9 -0.8	33.6 ± 1.5$^{\#+}$ -7.7
Peak workload (W) %change	243 ± 19	229 ± 18 -5.8	214 ± 15$^{\#\#}$ -11.9
Test duration (min) %change	9.5 ± 1.1	8.6 ± 1.1 -9.5	7.8 ± 0.9$^{\#}$ -17.9
Peak minute ventilation %change (l/min)	91.7 ± 6.5	90.8 ± 7.3 -1.0	82.1 ± 6.4$^{\#+}$ -10.5
RER at maximum exercise	1.13 ± 0.015	1.13 ± 0.018	1.13 ± 0.021
Systolic BP at 75%VO_2max (mmHg)	195.0 ± 9.1	197.0 ± 6.3	170.5 ± 8.7$^{\#\#++}$
Diastolic BP at 75%VO_2max (mmHg)	94.0 ± 2.7	91.0 ± 3.1	88.0 ± 2.9
RPE at 90% of VO_2max	5.7 ± 0.7	6.9 ± 0.6	7.0 ± 0.7
Workload at RPE = 4 (W)	195 ± 11	179 ± 12	181 ± 11

Values are expressed as means ± SE
$^{\#}$ p<.05 atenolol vs placebo, $^{\#\#}$ p<.005 atenolol vs placebo,
$^{+}$p<.05 atenolol vs isradipine, $^{++}$p<.005 atenolol vs isradipine
Abbreviations: VO_2max=maximum oxygen consumption, HR=heart rate, RER=respiratory exchange ratio, BP=blood pressure, RPE=rating of perceived exertion.

Maximum heart rate was decreased following ingestion of atenolol only (130 vs 171 vs 172 bpm, A vs P vs I, p<0.001).

VO_2max was reduced after atenolol but unchanged after isradipine ingestion (33.6 vs 36.4, 33.6 vs 36.1 mlO_2/kg/min, A vs P, A vs I, p<.05) (Figure 6.1). Peak workload (214 vs 243 W, A vs P, p<.01) (Figure 6.2), test duration (7.8 vs 9.5 min, A vs P, p<.05), and peak V_i (82.1 vs 91.7 l/min, A vs P, p<.05) were similarly reduced following atenolol ingestion compared to placebo. There was no significant difference in these parameters following isradipine ingestion, when compared either to placebo or atenolol treatments.

There was no change in RER at maximum exercise with either agent.

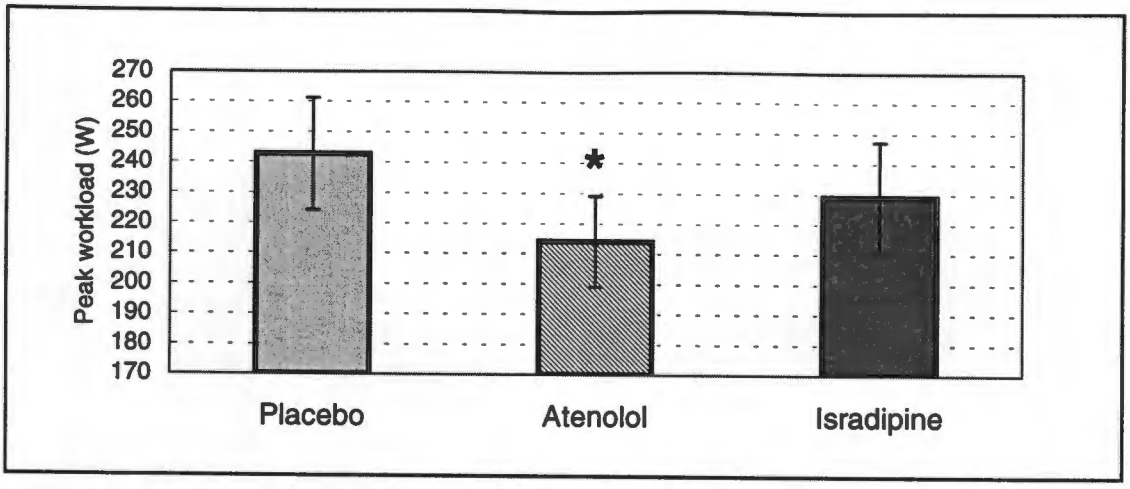


Figure 6.2 Peak workload achieved in incremental exercise to exhaustion following ingestion of anti-hypertensive medication.
*p<.01 atenolol vs placebo. Values +/- SE.

Systolic blood pressure while cycling at 75% of VO_2max was decreased following atenolol only (171 vs 195 vs 197 mmHg, A vs P vs I, p<.001).

RPE at 90% of VO_2max and the workload at which a RPE of 4 was reported, were unaltered following ingestion of either isradipine or atenolol.

Blood lactate concentrations were similarly unaffected following ingestion of either isradipine or atenolol (Table 6.2). Neither the maximum blood lactate concentration, the lactate concentration at 75% of VO_2max nor the time at

Table 6.2. Influence of isradipine, atenolol and placebo on blood lactate concentrations during incremental exercise to exhaustion in physically active hypertensive patients.

	Placebo	Isradipine	Atenolol
Peak lactate conc. (mmol/l)	9.11 ± 0.71	8.42 ± 1.02	8.28 ± 0.97
Time when blood lactate conc. > 4.5 mmol/l (min)	6.7 ± 1.5	6.3 ± 1.4	7.1 ± 1.3
Blood lactate conc. at 75%VO_2max (mmol/l)	3.17 ± 0.49	3.65 ± 0.55	2.87 ± 0.50

Values are expressed as means ± SE
Abbreviations: conc=concentration, 75%VO_2max=75% of maximum oxygen consumption.

which the blood lactate concentration exceeded 4.5 mmol/l were altered by either agent.

6.4 Discussion

The principal finding of this study was that in hypertensive subjects who are able to maintain regular physical activity while ingesting isradipine and atenolol, maximal exercise performance, measured as VO_2max, peak workload and test duration, was reduced after atenolol ingestion compared to placebo, but unaltered following ingestion of isradipine compared to placebo.

VO_2max was reduced by almost 8% after atenolol, which is consistent the extent of exercise intolerance described in previous reports (Van Baak 1988).

That no reduction in maximal exercise capacity was seen following ingestion of isradipine concurs with the finding of authors who studied sedentary hypertensive subjects ingesting the dihydropyridine derivatives, nifedipine, amlodipine and lacidipine (Ashmore et al. 1990; Fariello et al. 1991; Gosse et al. 1992; Halperin et al. 1993). It also concurs with the study by Gillies et al. (1996) who found that maximal exercise performance was unaltered following amlodipine ingestion in hypertensive patients who were physically active.

The mean VO_2max of the hypertensive subjects in this study was 38 mlO_2/kg/min. This is higher than the mean VO_2max of the subjects in the studies on sedentary hypertensive subjects and also higher than the mean VO_2max of subjects in the study on physically active hypertensive patients by Gillies et al. (1996). However it is not as high as the mean VO_2max of subjects in the studies on normotensive subjects which found an impairment of maximal exercise capacity following nifedipine ingestion in normotensive subjects (Chapter 2). Hence, it is still unclear whether it is the physical activity status of subjects, the presence of hypertension, or differences between nifedipine and the other dihydropyridine derivatives, which determines if dihydropyridine ingestion results in impaired maximal exercise performance.

VO_2max was reduced following atenolol ingestion compared to both placebo and isradipine. However, whilst peak workload and test duration following atenolol ingestion were decreased compared to placebo, there was no difference in peak workload and test duration following atenolol ingestion compared to these parameters following isradipine ingestion. Thus, there was a trend for peak workload and test duration to be reduced following isradipine ingestion.

Maximum heart rate was reduced following ingestion of atenolol but not isradipine. This finding is consistent with numerous studies where β-blockade has been found to reduce exercise heart rate (Frisk-Holmberg et al. 1985; Gordon & Duncan 1991; Joyner et al. 1986; Scruggs et al. 1991; Szlachcic et al. 1987; Tesch 1985; Van Baak 1988). The finding that isradipine ingestion did not alter maximum heart rate also concurs with reports that maximum heart rate is unaltered after dihydropyridine derivative administration (Cantor & Cristal 1990; Fariello et al. 1991; Gillies et al. 1996; Halperin et al. 1993).

Systolic blood pressure during the graded exercise test was reduced following ingestion of atenolol but not isradipine. This finding concurs with the results of many studies which have established that β-blockade reduces systolic blood pressure during exercise (Franz & Wiewel 1984; Joyner et al. 1986; Lund-Johansen 1987; Myburgh & Gordon 1987; Van Baak 1988; Yamakado et al. 1983). Most studies report that, in hypertensive subjects, both systolic and diastolic blood pressure are reduced by dihydropyridine derivatives at maximal and submaximal levels of exercise (Ashmore et al. 1990; Cantor & Cristal 1990; Fariello et al. 1989; Franz & Wiewel 1984; Lund-Johansen et al. 1992; Omvik et al. 1988). However, other authors have reported that systolic blood pressure during submaximal exercise is unaltered after nifedipine, amlodipine and isradipine administration (Gillies et al. 1996; Halperin et al. 1993; Klein et al. 1983; Mayer et al. 1991), as was the finding in this study. The reasons for this discrepancy are not directly apparent, but may be due to differences in the exercise protocol used, with those studies finding a reduction in systolic blood pressure during exercise after dihydropyridine treatment tending to use an

exercise protocol of lower exercise intensity than those which did not show a reduction in systolic blood pressure during exercise.

RPE were unaltered by either agent in this study. It is difficult to explain why the RPE were unchanged after atenolol ingestion as there was a reduction in maximal exercise capacity with atenolol. Whilst there was a trend for the RPE to be higher after ingestion of atenolol, this did not achieve statistical significance. It is possible, however, that had the study sample been larger, this trend may have reached statistical significance.

Blood lactate concentrations were unchanged during and after the maximal exercise test following either isradipine or atenolol ingestion compared to placebo. This finding concurs with findings in other studies on dihydropyridine derivatives (Derman et al. 1992; Gillies et al. 1996; Kindermann 1987) although some authors have reported an increase in blood lactate concentration during exercise following dihydropyridine ingestion in normotensive subjects (Chick et al. 1986; Raffestin et al. 1985). Blood lactate concentrations during submaximal and high intensity exercise after β-blockade are reported as being unchanged (Derman et al. 1992; Lundborg et al. 1981; Van Baak et al. 1987b), increased (Broberg et al. 1988) and decreased (Verstappen & Van Baak 1987).

Thus, the results of this study demonstrate that maximal exercise performance is unaltered after isradipine ingestion in physically active hypertensive patients who are able to maintain regular physical activity while ingesting isradipine and atenolol. However, atenolol ingestion by these subjects results in impaired maximal exercise capacity.

Chapter 7. Comparative effects of isradipine and atenolol on prolonged submaximal exercise performance in physically active hypertensive patients.

7.1 Introduction

Whilst graded exercise to exhaustion is frequently used to assess exercise capacity, it is clearly not the type of exercise which humans typically perform. Most recreational and occupational forms of exercise require effort at a submaximal intensity over a far longer duration than that involved in a maximal exercise test. As the physiological mechanisms determining maximal and submaximal exercise capacity differ, it is important to conduct prolonged submaximal exercise testing when investigating the effects of pharmacological agents or other interventions on exercise performance.

McLenachan et al. (1991) reported that there was no difference between the effect of two β-blockers, celiprolol and atenolol, on maximal exercise capacity. However, atenolol, but not celiprolol, increased subjective indices of breathlessness and fatigue during submaximal exercise. This finding indicates that submaximal exercise testing may demonstrate differences between anti-hypertensive agents that are not detected with maximal exercise testing.

Studies which have examined the effects of β-blockade on prolonged submaximal exercise performance report that the time to exhaustion during this form of exercise is reduced by 10-50% following the ingestion of β-blocking agents (Van Baak 1988; Van Bortel et al. 1991; Vanhees et al. 1988). However, most studies report that these agents reduce maximal exercise performance by only 4-10%. This finding further suggests that the effects of anti-hypertensive medications may become most apparent during prolonged submaximal exercise testing.

Submaximal exercise capacity in normotensive or hypertensive subjects is unchanged following ingestion of verapamil or diltiazem (Derman et al. 1991b, Herbertsson & Fagher 1990; Mooy et al. 1987; Vanhees et al. 1988). Similarly, Gillies et al. (1996) found that prolonged submaximal exercise performance was unaltered after ingestion of the dihydropyridine derivative, amlodipine, by physically active hypertensive patients. Further research is required to determine the effects of other dihydropyridine calcium channel blockers on prolonged submaximal exercise performance.

The capacity of the active skeletal muscle to oxidise lipids during prolonged submaximal exercise is decisive in order to spare consumption of glucose and glycogen stores and hence prolong activity. It is possible that this capacity is altered after drug ingestion. Therefore, it is important to demonstrate any alteration of substrate fuel kinetics during exercise and so to measure indices of fuel substrate utilisation when examining the effects of agents on prolonged submaximal exercise.

Accordingly, this chapter investigates the effects of isradipine and atenolol on prolonged submaximal exercise performance and on cardiovascular, respiratory and metabolic parameters during submaximal exercise in physically active hypertensive patients.

7.2 Methods

The effects of isradipine and atenolol on prolonged submaximal exercise performance in physically active subjects with mild to moderate essential hypertension were compared in a placebo controlled, crossover study where drug treatments were randomised and double blinded. The study design is described in Chapter 4.

Briefly, after a 3 min warm up, subjects pedalled at a workload of 75% of their initial VO_2max for one hour, or until a cadence of 70 rpm could no longer be maintained.

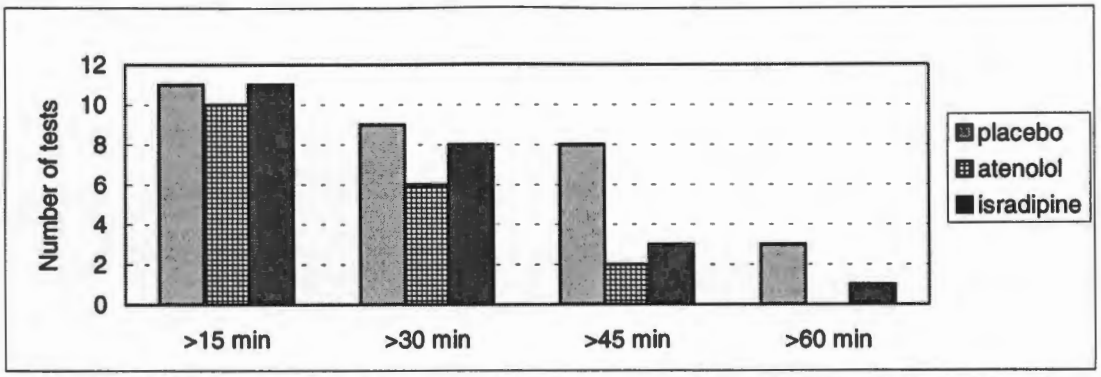


Figure 7.1 Number of tests in which time to exhaustion was greater than each 15 minute interval.

7.3 Results

Figure 7.1 shows the number of tests completed at the end of each 15 min interval. Whilst 8 subjects were able to cycle for over 45 minutes following ingestion of placebo, only 3 subjects completed 45 minutes after ingestion of isradipine and 2 subjects completed 45 minutes after ingestion of atenolol.

The mean time to exhaustion for each treatment is depicted in Figure 7.2. Both atenolol and isradipine ingestion reduced the time to reach exhaustion at 75%VO_2max (27.8, 34.4 vs 46.4 min, A,I vs P, p<.005). The time to exhaustion after isradipine ingestion was not significantly different to that after atenolol ingestion.

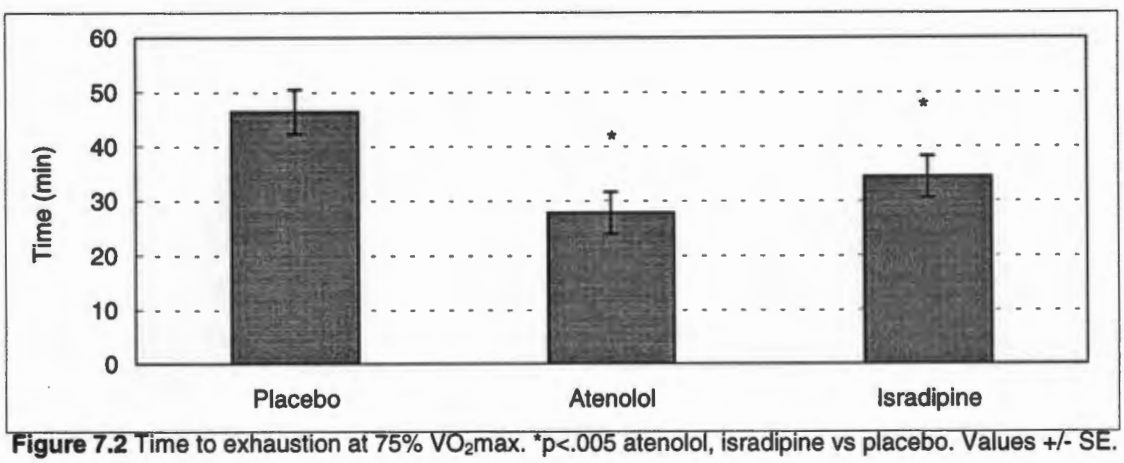


Figure 7.2 Time to exhaustion at 75% VO_2max. *p<.005 atenolol, isradipine vs placebo. Values +/- SE.

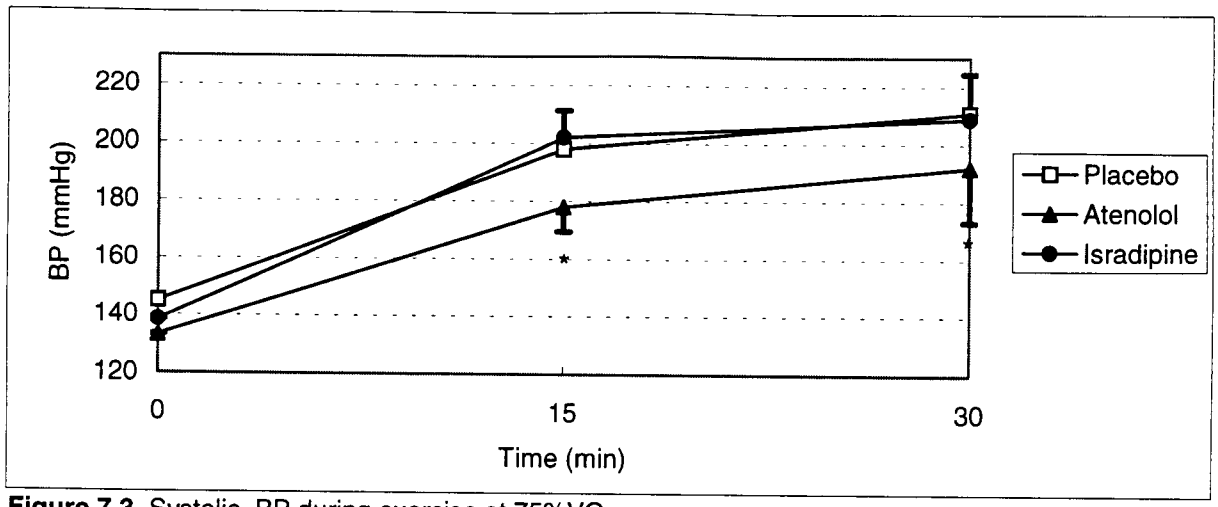


Figure 7.3 Systolic BP during exercise at 75%VO_2max.
*p<.05 atenolol vs placebo, isradipine at 15 and 30 min. Values +/-SE.

Systolic blood pressure during submaximal exercise is shown in Figure 7.3. Systolic blood pressure after placebo ingestion at 30 min of exercise at 75% of VO_2max was 211 mmHg. Systolic blood pressure while cycling at 75% of VO_2max was reduced by atenolol at both 15 min and 30 min (p<.001 A vs P,I). Systolic blood pressure during submaximal exercise was not altered after isradipine ingestion.

Changes in heart rate during the submaximal test are shown in Figure 7.4. Heart rate during exercise was reduced after ingestion of atenolol only (p<.001

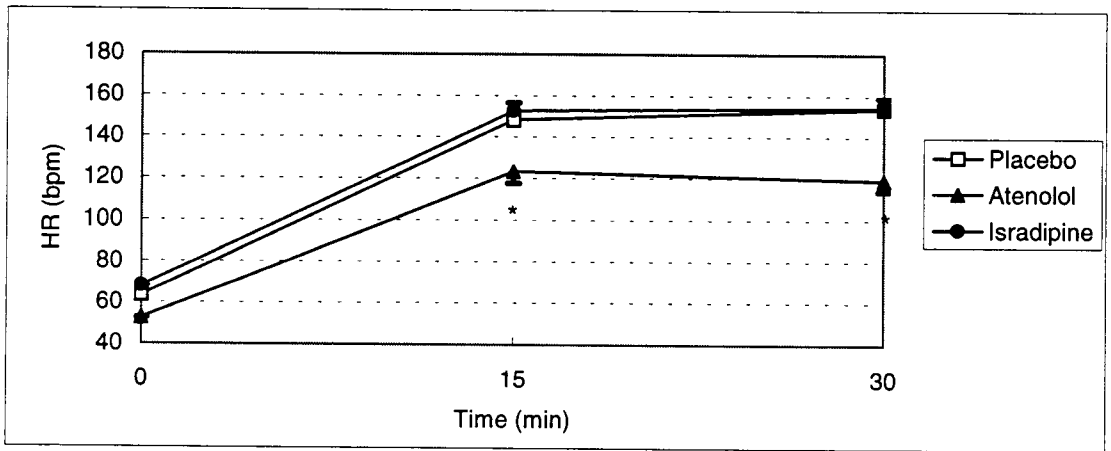


Figure 7.4 Heart rate during exercise at 75%VO_2max.
*p<.001 atenolol vs placebo, isradipine at 15 and 30 min. Values +/-SE.

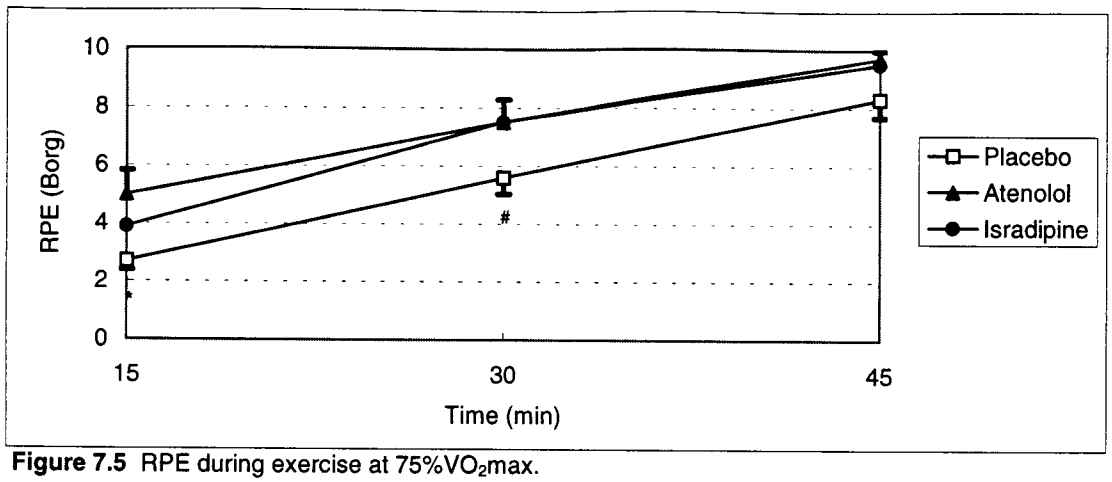


Figure 7.5 RPE during exercise at 75%VO_2max.
*p<.05 atenolol vs placebo at 15 min, #p<.05 atenolol vs placebo, isradipine at 30 min. Values +/-SE.

A vs P,I). Heart rate during submaximal exercise after isradipine ingestion was not different to that after taking placebo.

RPE during submaximal exercise are shown in Figure 7.5. RPE following ingestion of placebo increased during submaximal exercise from 2.6 at 15 min to 8.3 at 45 min. RPE was increased during exercise after atenolol ingestion compared to placebo at 15 min and by both atenolol and isradipine compared to placebo at 30 min. By 45 min, too many subjects had terminated their tests (and so received a RPE of 10), for the differences in RPE between treatments and placebo to be significant.

Maximum oxygen consumption, RER and V_i measured at 15 min and at 30 min of submaximal exercise are shown in Table 7.1. RER decreased during exercise after ingestion of placebo, of isradipine and of atenolol. VO_2, RER and V_i were not significantly different following ingestion of the different agents. Similarly, blood lactate, glucose and free fatty acid concentrations were not altered after the ingestion of either isradipine or atenolol. (Table 7.2).

Table 7.1. Influence of isradipine, atenolol and placebo on oxygen consumption, respiratory exchange ratio and minute ventilation during prolonged submaximal exercise in physically active hypertensive patients.

	15 min n=7	30 min n=5
VO_2 (mlO_2/kg/min)		
Placebo	28.9 ± 1.6	29.9 ± 4.4
Isradipine	29.7 ± 1.5	30.2 ± 3.8
Atenolol	29.3 ± 1.5	28.9 ± 4.3
RER		
Placebo	1.00 ± 0.02	0.98 ± 0.01
Isradipine	0.99 ± 0.01	0.95 ± 0.01
Atenolol	1.01 ± 0.01	0.98 ± 0.02
V_i (l/min)		
Placebo	68.8 ± 6.4	73.0 ± 6.0
Isradipine	69.6 ± 5.4	73.6 ± 3.8
Atenolol	67.5 ± 4.3	69.3 ± 6.3

Values are expressed as means ± SE.
Abbreviations: VO_2=oxygen consumption, RER=respiratory exchange ratio, V_i=minute ventilation.

7.4 Discussion

The first important finding of this study was that submaximal endurance time was substantially reduced by both atenolol and isradipine. Subjects were able to cycle at 75%VO_2max for 46 min after placebo ingestion compared to 28 and 34 minutes following ingestion of atenolol and isradipine respectively. This

Table 7.2. Influence of isradipine, atenolol and placebo on blood lactate, glucose and free fatty acid concentrations during prolonged submaximal exercise in physically active hypertensive patients.

	Rest n=9	15 min n=9	30 min n=4
Lactate (mmol/l)			
Placebo	2.12 ± 1.06	5.95 ± 0.75	5.34 ± 1.44
Isradipine	1.68 ± 0.50	6.28 ± 0.56	7.69 ± 2.42
Atenolol	1.06 ± 0.08	6.59 ± 0.66	6.45 ± 1.39
Glucose (mmol/l)			
Placebo	6.84 ± 0.40	6.26 ± 0.31	7.27 ± 0.97
Isradipine	7.88 ± 0.51	5.79 ± 0.19	5.90 ± 0.40
Atenolol	6.39 ± 0.25	5.84 ± 0.50	6.60 ± 0.40
Free fatty acid (mmol/l)			
Placebo	0.31 ± 0.06	0.20 ± 0.03	0.18 ± 0.05
Isradipine	0.27 ± 0.05	0.15 ± 0.01	0.24 ± 0.03
Atenolol	0.24 ± 0.04	0.15 ± 0.04	0.17 ± 0.04

Values are expressed as means ± SE.

represents a reduction in endurance time of 39% and 26% respectively. The difference between the endurance times for atenolol and isradipine were, however, not significant.

The reduction in submaximal exercise performance following ingestion of atenolol corresponds to that reported in the literature (Lundborg et al. 1981; Van Baak 1988). Only one study has reported on the effect of dihydropyridine calcium channel blockers on prolonged submaximal exercise where the subjects have exercised to exhaustion. Gillies et al. (1996) found that amlodipine administration to physically active hypertensive patients had no effect on prolonged submaximal exercise endurance. The study by Gillies et al. (1996) is similar to this study in that the subjects in both studies had similar initial values of blood pressure (147/103 mmHg vs 155/100 mmHg respectively), VO_2max (34 mlO_2/kg/min vs 38 mlO_2/kg/min) and prolonged submaximal exercise time to exhaustion after placebo ingestion (44 min. vs 46 min). The similarity between this study and the study by Gillies et al. (1996) suggests that the difference between the effect of isradipine ingestion and amlodipine ingestion on submaximal exercise performance is due to a difference between the two agents. In fact, the effect of amlodipine ingestion on resting blood pressure was different to that of isradipine, in that amlodipine did not significantly alter resting blood pressure compared to placebo (Gillies et al. 1996), whereas isradipine reduced diastolic blood pressure at rest compared to placebo. This is further evidence that amlodipine and isradipine at doses used in the 2 studies have different effects on the physiology of the subjects.

The second important finding of this study was that RPE was increased by both agents compared to placebo at 30 min and by atenolol compared to placebo at 15 min.

As blood lactate, glucose and free fatty acid concentrations and VO_2, RER, V_i during submaximal exercise were not different between treatment periods, the increase in RPE and reduction in time to exhaustion seen after isradipine and

atenolol ingestion cannot be attributed to changes in these parameters. Further, as heart rate and blood pressure during submaximal exercise were unaltered after isradipine ingestion, the increase in RPE and reduction in time to exhaustion during submaximal exercise after isradipine ingestion cannot be attributed to changes in heart rate and blood pressure during exercise.

Submaximal oxygen consumption, V_i, and RER were not altered by either atenolol or isradipine. Some authors have reported small reductions in VO_2 and V_i after β-blockade (Frisk-Holmberg et al. 1985; Pearson et al. 1987) but others have reported that these indices are unchanged (Dodd et al. 1988; Van Baak 1988). VO_2, V_i, and RER for a given submaximal workload have been reported to be unchanged after dihydropyridine derivatives in normotensive and hypertensive subjects (Derman et al. 1992; Gillies et al. 1996; Kindermann 1987; Omvik et al. 1988). Hence, there appears to be little effect of atenolol or isradipine on gas exchange during exercise.

As serum concentrations of glucose, lactate and free fatty acids and RER during submaximal exercise were not altered following ingestion of either atenolol or isradipine compared to placebo, it is unlikely that alterations in the kinetics of energy production for active muscle cause the impaired exercise endurance demonstrated with both these agents. Other investigators have reported that serum glucose and blood lactate concentrations during submaximal exercise are unchanged after β-blockade (Lundborg et al. 1981; Van Baak et al. 1993), which concurs with the findings in this study.

While most investigators report that serum free fatty acid concentrations during exercise are reduced after β-blockade (Van Baak 1988), this is not a consistent finding (Wijnen et al. 1993). Derman (1993) found that free fatty acid concentrations were reduced during prolonged submaximal exercise only after 40 min of exercise. Similarly, Lundborg et al. (1981) report that the concentration of free fatty acids was significantly reduced after propranolol only after exercising for an hour and only after a longer period than this for the β_1-selective blocker, metoprolol. In this study, subjects were exercising at a

relatively higher workload and became exhausted earlier, so that data were only available up to 30 min of exercise. A reduction in free fatty acid concentration was not seen in this study. This demonstrates that the reduction in exercise endurance caused by atenolol is not related to free fatty acid availability. As outlined in Chapter 3, other studies have shown that it is unlikely that the reduction in exercise tolerance with β-blockers is related to the availability of free fatty acids (Van Baak et al. 1993).

In concordance with this study, serum lactate and glucose concentrations during submaximal exercise after calcium channel antagonist administration have previously been reported as being unchanged (Van Baak et al. 1987b, Derman et al. 1992; Gillies et al. 1996; Halperin et al. 1993; Kindermann 1987).

Heart rate and blood pressure during exercise were unaltered by isradipine. Exercising heart rate in hypertensive subjects has previously reported to be unchanged by dihydropyridine derivatives (Fariello et al. 1989; Halperin et al. 1993; Lund-Johansen et al. 1992; Omvik et al. 1988). Most reports show that these agents decrease systolic and diastolic blood pressure during submaximal exercise (Fariello et al. 1989; Gillies et al. 1996; Lund-Johansen et al. 1992; Omvik et al. 1988). However, other studies have demonstrated that systolic blood pressure is maintained in hypertensive subjects during submaximal exercise despite normalisation of the resting blood pressure (Halperin et al. 1993; Klein et al. 1983; Mayer et al. 1991). The findings of our study are in accordance with these latter studies.

Heart rate and systolic blood pressure during submaximal exercise were reduced by atenolol compared to placebo, which is in agreement with previous findings (Lundborg et al. 1981; Van Baak 1988).

The finding that both isradipine and atenolol impaired prolonged submaximal exercise capacity, whilst atenolol, but not isradipine, reduced maximal exercise capacity (Chapter 6), verifies the conclusion of McLenachan et al. (1991), that it is important to perform submaximal exercise testing in order to demonstrate

differences between anti-hypertensive agents. These differences are important, as submaximal exercise is the type of exercise which is most commonly performed by hypertensive patients.

In conclusion, the major findings of this study are that, in hypertensive patients who are able to maintain regular physical activity whilst ingesting atenolol and isradipine, submaximal endurance time was substantially reduced. Furthermore, RPE at 30 min were increased by both atenolol and isradipine compared to placebo. This reduction in prolonged submaximal exercise performance cannot be attributed to changes in serum lactate, glucose or free fatty acid concentrations or VO_2, RER, V_i during submaximal exercise. Moreover, the reduction in time to exhaustion during submaximal exercise following isradipine ingestion is not a result of changes in heart rate or blood pressure during submaximal exercise. The cause of the reduction in submaximal exercise performance following atenolol or isradipine ingestion is not directly apparent.

Chapter 8. Comparative effects of isradipine and atenolol on short duration high intensity exercise performance in physically active hypertensive patients.

8.1 Introduction

It was shown in Chapter 7 that submaximal exercise endurance was reduced after isradipine ingestion without alterations in blood pressure, heart rate, VO_2, RER, V_i or blood lactate, glucose or free fatty acid concentrations during exercise. This finding suggests that the premature fatigue results from mechanisms other than those affecting central haemodynamics, ventilation or substrate delivery during exercise.

It is possible that the site of the premature fatigue during exercise induced by β-blockade and also by other anti-hypertensive agents is due to alteration of skeletal muscle contraction and recruitment (Derman et al. 1991a). Furthermore, Noakes (1988) has suggested that it is failure of muscle contractility which determines the onset of fatigue, rather than limitations of oxygen delivery and utilisation.

The Wingate Anaerobic Test is a 30 sec bout of supramaximal exercise where the there is a high flux through oxygen independent pathways. This test has been shown to be highly reliable and reproducible (Bar-Or 1987). Hence, the Wingate Anaerobic Test is suitable to investigate the effects of anti-hypertensive agents on short duration high intensity exercise. As performance in a Wingate test is likely to be diminished when skeletal muscle contractile function is impaired, the Wingate test also provides a measure of skeletal muscle contractile function.

Few studies have examined the effects of calcium channel antagonists on skeletal muscle contractile function. Accordingly, this chapter examines the

effects of isradipine and atenolol on short duration high intensity exercise in active subjects with mild to moderate essential hypertension.

8.2 Methods

The study design is described in Chapter 4. Briefly, short duration, high intensity exercise performance was tested using a standard Wingate test as described by Bar-Or (1987).

8.3 Results

Technical problems with the equipment prevented data collection for 3 subjects. Results of the Wingate test were obtained for the remaining 8 subjects and are listed in Table 8.1. Neither isradipine nor atenolol influenced peak skeletal muscle power attained. The mean skeletal muscle power output over the 30 second test was also unaffected by either agent. Hence, the variables, power to weight ratio and total work done, which are dependent on the power output indices, were similarly unaffected following ingestion of isradipine or atenolol compared with placebo. The rate of fatigue during the test and the average pedal frequency were also unaltered following ingestion of either agent compared to placebo.

Table 8.1. Influence of isradipine, atenolol and placebo on short duration, high intensity exercise performance in active hypertensive patients.

Wingate test parameters	Placebo	Isradipine	Atenolol
Peak power (W)	603 ± 59	568 ± 83	581 ± 55
Mean power (W)	477 ± 56	420 ± 63	445 ± 55
Power:weight ratio (W/kg)	7.83 ± 0.51	7.38 ± 0.76	7.72 ± 0.48
Total work done (J)	28734 ± 3394	25189 ± 3752	26683 ± 3277
Average pedal frequency (revs/min)	87.5 ± 7.4	77.5 ± 9.8	81.4 ± 7.5
Fatigue rate (W/sec)	8.0 ± 1.1	8.4 ± 1.2	9.3 ± 0.9

Values are expressed as means ± SE. n = 8.

8.4 Discussion

This study found that, in hypertensive subjects who are able to maintain regular physical activity while ingesting isradipine and atenolol neither of these agents impaired the ability to perform short duration, high intensity exercise. Thus, power output during high intensity exercise of short duration measured during the Wingate test was not affected following ingestion of either atenolol or isradipine compared with placebo. The premature fatigue during prolonged submaximal exercise found after isradipine and atenolol ingestion is therefore not due to the inability of skeletal muscle to perform short duration, high intensity exercise.

This finding concurs with those of Gillies et al. (1996) and of Derman et al. (1993) where a tests of skeletal muscle contractile properties were unaffected following calcium channel antagonism. Derman et al. (1993) examined the effects of diltiazem in normotensive subjects on power output during bouts of maximum effort on an isokinetic cycle ergometer. Diltiazem had no effect on peak power, average power and work done at a variety of crank velocities during 10 second tests, or on total work done and rate of work decline during a 30 second isokinetic exercise test. Gillies et al.(1996) investigated the effects of amlodipine ingestion on skeletal muscle function by measuring the time taken for the torque produced by maximum voluntary isometric contractions of the quadriceps muscle to fatigue to 70% of the strength of the initial contraction. These authors found that amlodipine ingestion by physically active hypertensive patients did not alter skeletal muscle function either before of after prolonged submaximal exercise.

This finding also concurs with most studies which have examined the effect of β-blockers on skeletal muscle power output during high intensity exercise of short duration, which report no effect of β-blockade on the ability to generate power (Derman et al. 1993; Rusko et al. 1980; Yoroko et al. 1990). However, others have found a reduction in power output during high intensity exercise of short duration following β-blockade (Kaiser 1984).

While most tests of skeletal muscle contractile properties have been found to be unaffected by β-blockade (Alway et al. 1988; Derman et al. 1993; Rusko et al. 1980), subjects who fatigue prematurely after β-blockade have reduced muscle power output during short term, high intensity exercise when it is measured immediately after the completion of prolonged submaximal exercise (Derman et al. 1991a; Karlsson et al. 1983). This finding provides evidence that there is impaired skeletal muscle contractile function after exercise following β-blockade. Further, in the study by Derman et al. (1991a), subjects who terminated exercise prematurely following β-blockade had increased integrated electromyographic activity and increased minute volume during prolonged submaximal exercise. This suggests that the subjects had an alteration in skeletal muscle recruitment patterns and increased perception of effort after β-blockade, perhaps as a result of impaired skeletal muscle function. It is possible that skeletal muscle function may also be impaired during or after prolonged submaximal exercise after ingestion of calcium channel antagonists. Gillies et al. (1996) did not find evidence of impaired skeletal muscle function, measured by the torque achieved during maximal voluntary isometric contractions of the quadriceps muscle, after prolonged submaximal exercise following amlodipine ingestion. However, this study did not demonstrate an impairment of submaximal exercise performance after amlodipine ingestion. It is important that further research is done to investigate the effects of isradipine, or other calcium channel blockers which are found to impair submaximal exercise performance, on skeletal muscle function after prolonged submaximal exercise.

Chapter 9. Summary and conclusions.

The principal finding of this thesis is that, in hypertensive patients who are able to maintain regular physical activity whilst ingesting atenolol and isradipine, prolonged submaximal exercise performance was impaired after ingestion of isradipine and of atenolol compared to placebo, whilst maximal exercise performance is reduced after ingestion of atenolol only.

Submaximal exercise endurance was impaired equally after atenolol and isradipine. The reduction in submaximal exercise endurance of 40% seen after atenolol ingestion is consistent with reports in the literature, where the time to exhaustion during prolonged submaximal exercise is reported to be reduced by 10-50% by the ingestion of β-blocking agents (Van Baak 1988; Van Bortel et al. 1991; Vanhees et al. 1988).

Maximal exercise capacity was reduced after atenolol ingestion with an 8% reduction in VO_2max. Peak workload, test duration and V_i were correspondingly reduced during β-blockade with atenolol. No impairment of maximal exercise was seen with isradipine.

RPE during submaximal exercise was raised after atenolol and isradipine ingestion. Neither agent altered submaximal exercise V_i or VO_2 suggesting that the impairment in exercise endurance is not due to changes in ventilation or the provision and utilisation of oxygen by the muscles. Neither agent altered RER, blood lactate, glucose or free fatty acid concentrations during prolonged submaximal exercise. This finding suggests that the reduction in submaximal exercise performance was not due to an impairment of energy production for active muscle following either atenolol or isradipine ingestion.

Submaximal exercise blood pressure and heart rate were reduced by atenolol but were unaffected by isradipine. Hence, premature fatigue and increased

RPE during prolonged submaximal exercise after isradipine ingestion cannot result from changes in blood pressure or heart rate during exercise.

The conclusion that both atenolol and isradipine reduced submaximal exercise capacity, while atenolol, but not isradipine, decreased maximal exercise performance, demonstrates the importance of performing tests of submaximal exercise endurance in order to reveal an effect on exercise capacity of an anti-hypertensive medication. Isradipine ingestion did not reduce maximal or short duration, high intensity exercise capacity but did cause a reduction in prolonged submaximal exercise capacity which was equal to that of atenolol. This is significant as submaximal exercise is the form of exercise testing most analogous to the exercise that most individuals actually perform.

The second important finding in this study is that neither isradipine nor atenolol affected the ability to perform short duration, high intensity exercise. Power output during short duration, high intensity exercise as measured in the Wingate test was not affected by either atenolol or isradipine. The premature fatigue during prolonged submaximal exercise found after isradipine and atenolol ingestion is therefore not due to factors which would also limit the ability of skeletal muscle to perform short duration, high intensity exercise before a bout of prolonged exercise. As outlined in Chapter 8, there is evidence that after β-blockade, skeletal muscle contractile function is impaired immediately following prolonged submaximal exercise in those subjects who become fatigued prematurely during the prolonged exercise bout (Derman et al. 1991a; Karlsson et al. 1983). It is possible that calcium channel antagonists which reduce submaximal exercise performance might also impair skeletal muscle function during prolonged submaximal exercise. Further research is required to investigate if this effect does indeed occur.

The dosages of isradipine and atenolol used in this study were not equipotent. Atenolol reduced resting blood pressure by approximately 5 mmHg more than did isradipine. Isradipine has a dose dependent effect for the reduction of blood pressure (up to 5 to 7.5 mg twice daily) and for the presence of side

effects (Dahlöf 1989; Simonsen & Sundstedt 1989). Similarly, previous reports in the literature describe the reduction in exercise performance seen with β-blockers as a dose related phenomenon (McKelvie & Jones 1991). It is possible that the reduction in submaximal exercise performance seen after isradipine ingestion in this study is also dose related. If this is so, and had the dosages of the 2 medications been equipotent, then the impairment in submaximal exercise tolerance after isradipine ingestion may have been greater than that seen after atenolol ingestion, and a reduction in maximal exercise tolerance may have become apparent.

Recommendations are constantly being sought as to which anti-hypertensive medications are most suitable to patients who are physically active (Chick et al. 1988; Gordon & Duncan 1991; Houston 1992; Lund-Johansen 1987; Van Baak 1994). As the effect of many of the first line anti-hypertensive agents, such as the newer calcium channel blockers and angiotensin converting enzyme inhibitors, on submaximal exercise capacity have yet to be investigated, it is not possible to make definite statements that some anti-hypertensive medications do not effect exercise capacity. The findings that patients ingesting calcium channel blockers generally do not complain of reduced physical capacity (Lund-Johansen 1987), and that these agents do not impair maximal exercise performance in hypertensive subjects (Ashmore et al. 1990; Fariello et al. 1991; Gosse et al. 1992; Halperin et al. 1993; Keleman et al. 1989; Pool et al. 1985; Szlachcic et al. 1987) suggest that calcium channel blockers may indeed be a good choice of medication for physically active hypertensive patients. However, this study demonstrates that, in subjects who are able to maintain regular physical activity while ingesting atenolol or isradipine, isradipine impairs submaximal exercise tolerance to the same extent as does atenolol. Therefore, in these patients, calcium channel antagonists cannot be recommended above atenolol on the basis that they are superior to atenolol in terms of maintaining exercise capacity.

However, despite the fact that the same extent of impairment in prolonged submaximal exercise capacity, and a similar increase in RPE during

submaximal exercise, was found after isradipine ingestion as after atenolol ingestion in this study, the subjective experience of fatigue during physical activity was greater after atenolol than after isradipine, as indicated by the reported side effects. It may be this subjective experience of fatigue during physical activity that determines whether or not physically active hypertensive patients will be compliant with their medication. On this basis, it would be logical to recommend calcium channel antagonists above β-blockers for the treatment of hypertension in physically active patients.

Whilst there may be differences in the extent to which different classes of anti-hypertensive drugs cause impaired exercise performance, there may also be differences between drugs of the same class. Non-selective β-blockers cause a greater reduction in submaximal exercise capacity than do β_1-selective blockers (Anderson et al. 1985). As described in Chapter 7, a similar investigation to this study by Gillies et al. (1996), demonstrated that ingestion of the dihydropyridine derivative, amlodipine, did not impair prolonged submaximal exercise performance. The discrepancy between the finding by Gillies et al. (1996) and the finding that isradipine did impair prolonged submaximal exercise performance, underlies the importance of testing the effects of each specific medication on exercise performance. Recommendations must then be made regarding specific anti-hypertensive agents and not a particular class of drug.

In conclusion, the findings of this thesis are that, in physically active hypertensive patients who are able to maintain regular physical activity while ingesting atenolol or isradipine, isradipine and atenolol impaired submaximal exercise endurance to the same extent. Maximal exercise performance was reduced by atenolol only. As most recreational and occupational exercise involves submaximal exercise, this demonstrates the necessity to perform submaximal exercise testing when assessing the effects of anti-hypertensive medications on exercise performance. On the basis of this and other studies (Myburgh & Gordon 1987) it is not yet possible to make claims that the calcium

channel antagonist agents are without effect on physical exercise performance in physically active hypertensive patients.

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