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Sensitivity to insulin during treatment with atenolol and metoprolol: a randomised, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients

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Abstract

***Objective*—To compare the effects of metoprolol and atenolol on carbohydrate and lipid metabolism and on insulin response to an intravenous glucose load.**

***Design*—Randomised, double blind, double dummy, controlled crossover trial.**

***Setting*—University Hospital, Uppsala, Sweden.**

***Patients*—60 Patients with primary hypertension (diastolic blood pressure when resting supine 95-119 mm Hg on at least two occasions during four to six weeks of treatment with placebo) randomised to receive either metoprolol (n=30) or atenolol (n=30) during the first treatment period.**

***Interventions*—Placebo was given for a run in period of four to six weeks. Metoprolol 100 mg twice daily or atenolol 25 mg twice daily was then given for 16 weeks. The two drugs were then exchanged and treatment continued for a further 16 weeks.**

***End point*—Evaluation of effects of treatment with metoprolol and atenolol on glucose, insulin, and lipid metabolism and glucose disposal mediated by insulin.**

***Measurements and main results*—Reduction of blood pressure was similar and satisfactory during treatment with both drugs. Glucose uptake mediated by insulin was measured during a euglycaemic hyperinsulinaemic clamp to evaluate patients' sensitivity to insulin. Glucose uptake decreased from 5·6 to 4·5 mg/kg/min when patients were taking metoprolol and from 5·6 to 4·9 mg/kg/min when they were taking atenolol. Both drugs caused a small increase in fasting plasma insulin and blood glucose concentrations and glycated haemoglobin concentration. Despite decreased sensitivity to insulin the increase in insulin concentration in response to an intravenous glucose tolerance test was small, suggesting inhibition of release of insulin. Very low density lipoprotein and low density lipoprotein triglyceride concentrations were increased with both drugs and high density lipoprotein cholesterol concentration was decreased. Low density lipoprotein cholesterol concentration was not affected.**

***Conclusions*—Long term use of metoprolol and atenolol causes metabolic abnormalities that may be related to the increased incidence of diabetes in patients with hypertension who are treated pharmacologically. These results may help to explain why the two drugs have failed consistently to reduce the incidence of coronary heart disease in several large scale studies.**

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Introduction

During the past 20 years there has been much emphasis on detecting and treating hypertension, which is an important risk factor for cardiovascular disease,[1] and several large scale trials have shown that a reduction in blood pressure is associated with a decrease in cardiovascular morbidity and mortality.[2-5] Some of the drugs used to treat hypertension, however, have adverse effects, including disturbances of serum lipid concentrations and glucose metabolism.[5-7] Treatment with thiazide diuretics and β blockers has been associated with an increased incidence of impaired glucose tolerance[6] and diabetes.[5,7] Few attempts have been made, however, to evaluate specific influences of pharmacological treatment of hypertension on glucose metabolism—for example, to determine whether it decreases secretion of insulin or sensitivity to insulin, or both. Sensitivity to insulin may be important as studies have shown that hypertension is accompanied by resistance to insulin.[8-10]

We evaluated the effect of long term treatment with two widely used β_1 adrenergic blockers, metoprolol and atenolol, on glucose disposal mediated by insulin and examined their effects on glucose, insulin, and lipid metabolism.

Patients and methods

CRITERIA FOR INCLUSION

Patients were recruited from a health screening survey in Uppsala, Sweden. All had primary hypertension, defined as a stable diastolic blood pressure when resting supine of 95-119 mm Hg on at least two occasions during four to six weeks of treatment with placebo. Any current antihypertensive treatment was stopped and a placebo was given single blind for four to six weeks. Patients with newly detected hypertension were followed up for three to four months to make sure that their raised blood pressure was stable before they entered the single blind placebo period.

CRITERIA FOR EXCLUSION

Criteria for exclusion were: clinical or laboratory evidence of hepatic or renal disease, obstructive pulmonary disease, Raynaud's disease, or thyroid dys-

function; a history of cardiovascular disease, major gastrointestinal surgery, or renal impairment; diabetes (except in one subject with non-insulin dependent diabetes controlled by diet); other endocrine diseases; contraindications to treatment with β blockers; and treatment with drugs for other diseases.

DESIGN OF STUDY

The study was a controlled, randomised (with a block size of four), double blind, double dummy crossover trial done over nine months divided into three treatment periods. The first period was a single blind washout phase (four to six weeks) during which the patients were given one placebo that matched atenolol and one placebo that matched metoprolol twice daily. In the second period (four months) the patients were randomised and given fixed doses of either metoprolol 100 mg twice daily (n=30) or atenolol 25 mg twice daily (n=30) and placebo that matched the alternative drug. During the third period (four months) metoprolol and atenolol were exchanged.

Compliance with treatment was assessed in all patients by interview and pill count. Subjective symptoms were evaluated by visual analogue scales. Questions were asked about physical activity during leisure and at work and answers indicated on a four point scale. Dietary habits were investigated. All patients entering the study were given a thorough physical examination by one doctor (TP), and all blood pressure measurements were made by the same two nurses. Metabolic investigations were performed at the end of each period in the morning, 10-14 hours after the last dose of the drug. The methods of these investigations have been described in another study.[9]

Fully informed consent was obtained from all subjects. The protocol was approved by the human ethics committee of the medical faculty of Uppsala University.

BLOOD PRESSURE AND HEART RATE

Systolic blood pressure was defined as Korotkoff-phase I and diastolic as phase V. Measurements were made on the right arm to the nearest mm Hg with a mercury sphygmomanometer: three measurements were made in the supine position after the patients had rested for 10 minutes, and two after they had stood for one minute. The means of these measurements were used in the analyses. A large cuff was used when appropriate. Heart rate was recorded before each blood pressure measurement.

METABOLIC INVESTIGATIONS

Blood samples were taken and urine collected after an overnight fast. An intravenous glucose tolerance test was performed by injecting 300 mg glucose/kg body weight.[9] Plasma glucose concentration was determined by the glucose oxidase method (Optimate, Ames-Gilford). The rate of disappearance of glucose was expressed as a k value calculated from the formula $k=100\times\log_e 2/T½$; T½, the time (minutes) required for the glucose concentration to be halved, was determined from the best fit of the measured values on semilogarithmic paper.[11] Immunoreactive insulin in plasma was assayed by a commercial radioimmunoassay kit (Phadeseph insulin radioimmunoassay, Pharmacia). The peak insulin response was defined as the mean of the values obtained at two, four, and six minutes. The average fasting plasma insulin concentration was calculated from the values in four samples taken on two separate days. Glycated haemoglobin concentration was measured by high performance liquid chromatography.[12] Lipoproteins were analysed by ultracentrifugation and precipitation (with phosphotungstate and magnesium chloride).[9] Triglyceride and cholesterol concentrations were measured by enzymatic techniques (Boehringer Mannheim) with a Multistate III I/LS centrifugal analyser (Instrumentation Laboratories). Serum concentrations of free fatty acids were determined by an enzymatic colorimetric method with a commercial kit (Wako Chemicals) adapted for analysis with a Multistat III analyser. All other tests were carried out in the department of clinical chemistry of the University Hospital. Body mass index was calculated as weight (kg)/(height (m))^2.

INSULIN SENSITIVITY

The euglycaemic hyperinsulinaemic clamp technique was used to estimate the sensitivity of patients to insulin while they were taking placebo and at the end of each treatment period.[13] The technique has been described in detail.[9] The rate of infusion of insulin (Actrapid Human, Novo) was 56 mU/m^2/min in all subjects, resulting in a mean plasma insulin concentration of 98 mU/l (range 79-129). The chosen plasma glucose concentration during the clamp study was 5·2 mmol/l. The mean (SD) steady state plasma glucose concentration during the clamp in patients taking placebo was 5·2 (0·3) mmol/l, and there was no significant change in concentration during different treatment periods. The coefficient of variation for the steady state plasma glucose concentration for a single clamp was less than 4·5% on all occasions (mean 3·4 (1·0%)), and there were no significant changes in the coefficient of variation between different treatment periods.

The amount of glucose taken up (mg/kg/min) during each clamp study was calculated for each 20 minute interval after the first 20 minutes. The mean rate of glucose uptake for the last 60 minutes of the clamp was used as the main target variable. The index of sensitivity to insulin, a measure of sensitivity of tissue to insulin expressed per unit of insulin, was calculated by dividing the amount of glucose taken up by the mean insulin concentration during the same period of the clamp.[13] The insulin concentrations attained during the insulin infusion (about 98 mU/l) were sufficient to suppress production of glucose by the liver in hypertensive patients with insulin resistance.[8 14-18] Urinary losses of glucose were negligible under euglycaemic conditions.

STATISTICAL ANALYSES

Two way analysis of variance was used to test changes within and between groups over time. As the data were unbalanced because subjects dropped out or values were missing, or both, the mean values were not suitable for comparison. The results are presented as least square means[19] because they form the basis of the tests and estimates in the analysis and take the imbalance into account. The various tests of contrast use functions of the residual variance as the error term and not functions of the variance of the group multiplied by time. The square root of the residual variance is therefore presented in the tables. The results of the two arms combined are presented. All comparisons were made against the results obtained in the placebo period.

Results

ANTIHYPERTENSIVE TREATMENT

Sixty two patients met the criteria for entry and were enrolled in the placebo run in period, but two failed to qualify during this period. Thus 60 patients were given active drug treatment (table I). Twenty seven had been taking antihypertensive drugs before the placebo period: selective β blockers (13), pindolol (4), diuretics (6), calcium channel blockers (5), and angiotensin converting enzyme inhibitors (3). Four patients had

been receiving combined treatment. Two patients did not complete the last treatment period (with metoprolol in both cases). One withdrew because his hands and feet became cold when he was taking the drug; the other moved away from the area. The pill count showed good compliance (all subjects took >95% of tablets). Diet and physical activity did not change during the study. There were no carryover effects between drugs, nor were there differences in the effects of the drugs between patients who had and had not been treated for hypertension previously.

BLOOD PRESSURE

The adjusted mean blood pressure, both supine and standing, decreased significantly during treatment with both drugs (table II). The reduction in supine pressure in all patients was 15/13 mm Hg when they were taking atenolol and 14/12 mm Hg when taking metoprolol. Both drugs caused a significant decrease in heart rate.

INSULIN SENSITIVITY AND GLUCOSE UPTAKE

Sensitivity to insulin decreased during treatment with metoprolol and atenolol in each clamp period of 20 minutes compared with the corresponding value during the clamp when the patients took placebo, although the area under the insulin curve during the clamp study increased by 7·6% (p=0·029) and 11% (p=0·002) for metoprolol and atenolol respectively.

The mean glucose uptake (during the last 60 minutes of the clamp) during treatment with placebo was 5·6 mg/kg/min. This decreased by 1·1 mg/kg/min (p<0·0001) during treatment with metoprolol and by 0·7 mg/kg/min (p<0·0001) during treatment with atenolol. The difference between the two drugs was significant (p=0·018).

The index of sensitivity to insulin for the last 60 minutes of the clamp decreased from 5·8 to 4·2 when patients were taking metoprolol (p<0·0001) and from 5·8 to 4·5 when patients were taking atenolol (p<0·0001), showing that disposal of glucose decreased during the two regimens. The difference between the two drugs was not significant (figure).

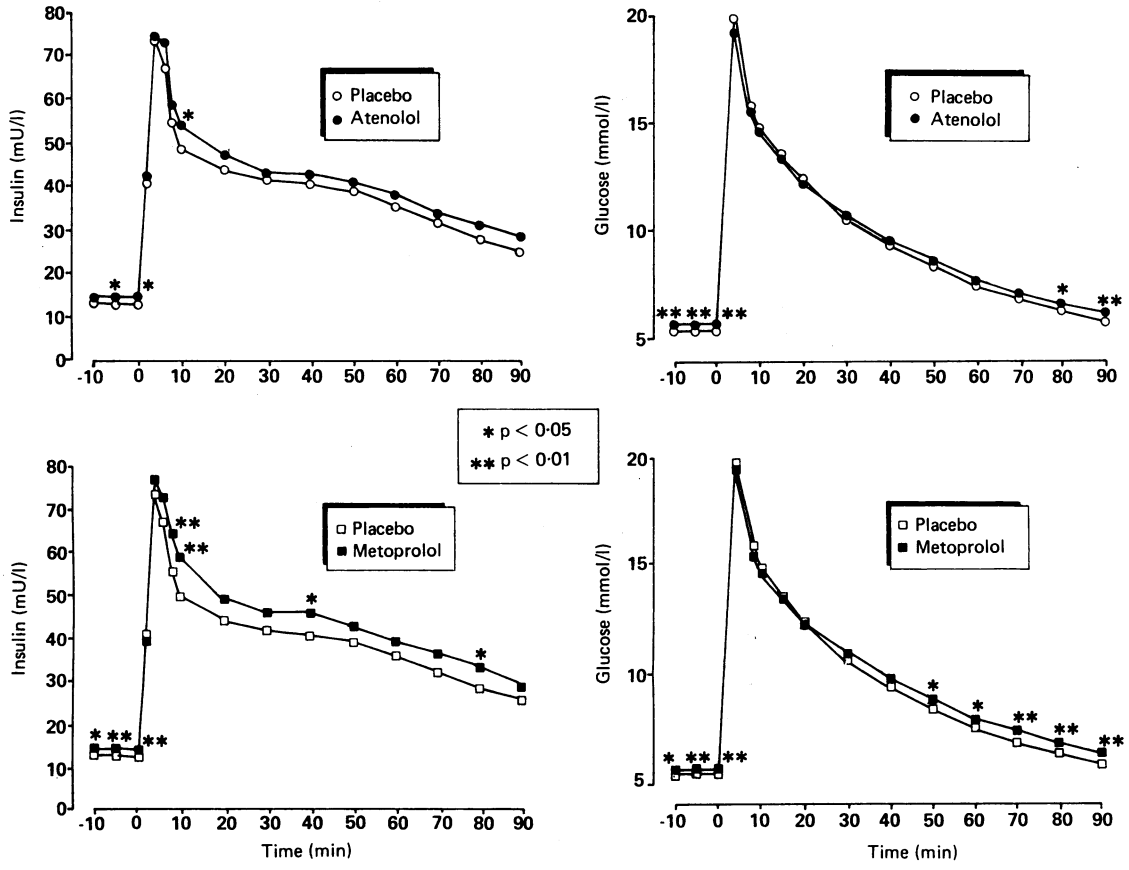
TABLE I—*Clinical characteristics of hypertensive patients*

	Men (n=36)	Women (n=24)
No (%) newly diagnosed as having hypertension	19 (53)	14 (58)
Mean (SD) age (years)	56·2 (11·9)	57·2 (8·1)
Mean (SD) body mass index (kg/m²)	29·4 (4·5)	31·2 (6·4)
Mean (SD) ratio of waist to hip circumference	0·95 (0·05)	0·89 (0·08)
No (%) smokers	9 (25)	5 (21)

TABLE II—*Adjusted mean systolic and diastolic blood pressures and heart rate in patients supine and standing while taking placebo, effects of metoprolol and atenolol, and difference between effects of the two active drugs*

Variable	During treatment with placebo (n=60)	Effect of treatment with metoprolol (n=58)	Effect of treatment with atenolol* (n=60)	Difference between effects of metoprolol and atenolol	Square root of residual variance
Systolic blood pressure (mm Hg):					
Supine	163	−14	−15	1·4	10·2
Standing	158	−15	−15	0·3	10·0
Diastolic blood pressure (mm Hg):					
Supine	101	−12	−13	1·3	5·2
Standing	105	−12	−12	0·2	5·5
Heart rate (beats/min):					
Supine	69	−9	−9	0	5·2
Standing	77	−11	−11	0	6·3

*p<0·001 For all values.



*Plasma insulin and glucose concentrations during intravenous glucose tolerance test in 60 hypertensive patients receiving atenolol (top) and metoprolol (bottom). *p<0·05, **p<0·01*

FASTING INSULIN AND GLUCOSE CONCENTRATIONS AND RESPONSE TO INTRAVENOUS GLUCOSE TOLERANCE TEST

Table III and the figure show data on fasting plasma insulin and glucose concentrations and other variables and the responses of plasma insulin and glucose concentrations during the intravenous glucose tolerance test before and after treatment with metoprolol and atenolol. Fasting plasma insulin concentration increased significantly during treatment with both drugs, and the insulin concentrations at the end of the glucose tolerance curve tended to be higher than during treatment with placebo. Plasma insulin concentrations were somewhat higher with metoprolol than atenolol, and peak insulin concentration was increased with metoprolol (from 65 to 71 mU/l, p=0·042). Fasting plasma glucose concentration also increased (significantly) during both treatment periods, as did glucose concentrations at the end of the glucose tolerance curve, with higher values during treatment with metoprolol.

The k value for the disappearance of glucose during the glucose tolerance test decreased during treatment with metoprolol (p<0·05), and glycated haemoglobin concentration increased during treatment with both drugs (p<0·001). Patients gained about 1 kg in weight during both drug regimens (p<0·001) (table III).

TABLE III—*Adjusted mean glycated haemoglobin (HbA_{1C}) concentration, k value obtained during glucose tolerance test, fasting plasma glucose and insulin concentrations, and body weight during treatment with placebo, metoprolol, and atenolol*

Variable	During treatment with placebo	During treatment with metoprolol	During treatment with atenolol	Square root of residual variance
HbA_{1C} (%)	4·6	4·9***	4·9***	0·5
k Value (%/min)	1·3	1·1*	1·2	0·4
Plasma glucose (mmol/l)	5·4	5·6***	5·6***	0·5
Plasma insulin (mU/l)	13	15**	15*	6
Weight (kg)	88·0	89·2***	89·3***	8·1

*p<0·05, **p<0·01, ***p<0·001.

SERUM LIPID CONCENTRATIONS

Very low density lipoprotein triglyceride and cholesterol concentrations increased during treatment with both drugs (table IV), as did low density lipoprotein triglyceride concentration, but low density lipoprotein cholesterol concentration did not change. High density lipoprotein cholesterol concentration decreased during both drug regimens, but the high density lipoprotein triglyceride concentration did not change. The ratio of low density lipoprotein to high density lipoprotein cholesterol increased by 4·4% (p=0·074) during treatment with atenolol. The ratio of non-high density lipoprotein cholesterol to high density lipoprotein cholesterol increased by 8·9% (p=0·0004) during treatment with metoprolol and 7·1% (p=0·003) during treatment with atenolol. Free fatty acid concentrations did not change significantly during any of the treatment periods.

TABLE V—*Subjective symptoms as evaluated by visual analogue scales during treatment with metoprolol and atenolol. No points were given for no disturbing symptoms and 100 points for intensive, maximally disturbing symptoms. Values are adjusted means*

Symptom	During treatment with placebo (n=60)	During treatment with metoprolol (n=58)	During treatment with atenolol* (n=60)
Palpitations	13·8	9·9*	8·0**
Tachycardia	11·9	7·6*	6·3**
Bradycardia	3·9	7·5**	5·6
Irregular heart activity	9·6	8·9	8·2
Headache	26·5	18·5*	17·8**
Breathlessness and wheezing	18·7	16·1	14·3
Sweating	18·3	18·6	15·7
Skin symptoms	5·5	6·1	5·7
Cold hands and feet	20·0	22·7	23·6
General fatigue	25·2	23·5	22·3
Muscular tiredness during effort	12·9	15·4	14·7
Decreased physical endurance	20·4	18·4	16·7
Difficulties in concentrating	11·5	12·9†	9·7†
Irritability	15·6	14·9	13·0
Forgetfulness	16·6	14·9	16·1
Dizziness	14·2	13·6	10·3
Sensations of fainting	4·7	5·8	5·4
Nightmares	6·1	8·9*	6·7
Insomnia	10·6	15·8*	11·4
Waking up during the night	16·5	20·1	15·2
Vivid dreams	11·0	13·9†	9·7†

*p<0·05, **p<0·01, ***p<0·001 Compared with treatment with placebo. †p<0·05 For differences between treatment with metoprolol and atenolol.

OTHER MEASUREMENTS IN BLOOD

Packed cell volume increased by about 3% (p<0·05) during treatment with both metoprolol and atenolol. Serum urate and creatinine concentrations also increased by about 3% (p=0·09). All results of routine tests were within the normal ranges.

ADVERSE REACTIONS

Subjective symptoms were evaluated by visual analogue scales (table V). Difficulty in concentrating and vivid dreams were more pronounced during treatment with metoprolol than atenolol. There was also a tendency to more nightmares and insomnia when patients were taking metoprolol. Some patients reported other minor subjective side effects, but only one withdrew from the study (he developed cold hands and feet).

Discussion

Sensitivity to insulin decreased significantly during treatment with metoprolol (20%) and atenolol (13%).

TABLE IV—*Adjusted mean serum cholesterol and triglyceride concentrations and plasma free fatty acid concentrations when patients took placebo, effects of metoprolol and atenolol, and difference between effects of the two drugs*

Variable	During treatment with placebo (n=60)	Effect of treatment with metoprolol (n=58)	Effect of treatment with atenolol (n=60)	Difference between effects of metoprolol and atenolol	Square root of residual variance
Serum cholesterol (mmol/l):					
Total	6·10	0·00	−0·08	0·08	0·39
VLDL	0·62	+0·20***	+0·14**	0·05	0·23
LDL	4·41	−0·06	−0·15**	0·08	0·42
HDL	1·03	−0·06**	−0·08***	0·02	0·10
Serum triglycerides (mmol/l):					
Total	2·04	+0·59***	+0·43***	0·15	0·59
VLDL	1·26	+0·54***	+0·41***	0·13	0·54
LDL	0·55	+0·06***	+0·04*	0·02	0·09
HDL	0·21	+0·016	0·00	0·01	0·05
Plasma FFA	0·59	−0·02	−0·04	0·02	0·15
VLDL triglycerides:VLDL cholesterol	2·20	+0·13*	+0·12**	0·02	0·33
LDL triglycerides:LDL cholesterol	0·13	+0·02***	+0·02***	0·00	0·02
LDL cholesterol:HDL cholesterol	4·40	+0·19*	+0·15	0·04	0·57
VLDL and LDL:HDL cholesterol	5·07	+0·45***	+0·36**	0·09	0·66

VLDL=Very low density lipoprotein. LDL=Low density lipoprotein. HDL=High density lipoprotein. FFA=free fatty acids. *p<0·05, **p<0·01, ***p<0·001 Compared with treatment with placebo.

During a euglycaemic hyperinsulinaemic clamp study glucose uptake occurs when patients are hyperinsulinaemic and is directly related to insulin concentration. Despite higher steady state plasma insulin concentrations during treatment glucose uptake was decreased. Thus the decrease in glucose disposal mediated by insulin was, if anything, underestimated. The glucose uptake corrected for the steady state insulin concentration, which is probably a better estimate of the degree of change, was 27% and 23% lower during treatment with metoprolol and atenolol respectively (figure). The steady state insulin concentrations attained during the euglycaemic clamps reflect the rate of metabolic clearance of insulin.[20] This may therefore be decreased by both metoprolol and atenolol. Two other studies have shown that clearance of insulin is reduced after blockade selective for the type of β adrenergic receptor.[21,22]

The reduction in sensitivity to insulin was also reflected by higher insulin and glucose concentrations during treatment with selective β blockers compared with placebo, both when the patients were fasting and after they had received an intravenous glucose load. In subjects with normal insulin secretion decreased sensitivity to insulin is compensated for by an increase in the amount of insulin released in order to preserve glucose homoeostasis—for example, in obesity. In this study the decreased sensitivity to insulin and increased fasting insulin and glucose concentrations were accompanied by a small increase in insulin response during the glucose tolerance test. During treatment with metoprolol insulin concentrations increased by 13% during the last 30 minutes of the test compared with values during treatment with placebo. In two groups of 60 year old men with normal blood pressure and blood glucose concentrations a similar difference in glucose disposal mediated by insulin was associated with a 100% increase in insulin concentrations during the corresponding period of the glucose tolerance test (T Pollare, unpublished observations). Thus the possibility cannot be ruled out that β selective adrenergic blockade,[23,24] like non-selective β adrenergic blockade, suppresses insulin secretion and that this may be one cause of the deterioration in glucose tolerance found in our study. The increase in glycated haemoglobin concentrations, reflecting higher average blood glucose concentrations, is further evidence that low glucose disposal mediated by insulin leads to decreased glucose tolerance during β selective blockade.

Treatment with non-selective β adrenergic blockers such as propranolol has been reported to lead to worsened control in diabetic patients and is also occasionally associated with precipitation of diabetes.[25] In some comparative studies,[26-28] but not others,[29] drugs selective for the β_1 receptor have offered some advantage over non-selective β blockers. Most studies of carbohydrate metabolism during β adrenergic blockade have been done on too few patients to show effects on fasting glucose and plasma insulin concentrations. This may explain why increased[30,31] as well as decreased[31,32] and unchanged glucose tolerance and insulin responses[33-35] have been found. With the intravenous insulin tolerance test as a crude measure one study found that both propranolol and metoprolol reduced sensitivity to insulin.[36] Furthermore, DeFronzo *et al* showed that infusion of propranolol during a euglycaemic clamp significantly reduced glucose uptake mediated by insulin.[37]

The change in fasting blood glucose and plasma insulin concentrations observed in our study was small and unlikely to play an important part as a risk factor for cardiovascular morbidity and death. On the other hand, decreased sensitivity to the peripheral action of insulin may impair glucose tolerance and cause diabetes. A longitudinal study of 1462 women showed that treatment with β blockers and thiazides was associated with a risk of diabetes in hypertensive patients.[7,38] We report similar results for men in a separate paper in this issue (p 1147). The impaired glucose disposal mediated by insulin during euglycaemic clamp shown in this study during treatment with β_1 selective adrenergic blockers, and similar effects of saluretics[39] may contribute to the precipitation of diabetes in susceptible people with hypertension. Both diabetes and impaired glucose tolerance increase the risk of cardiovascular disease.[40]

There are several possible explanations for the diminished glucose disposal mediated by insulin during β_1 selective adrenergic blockade. The decrease in cardiac output during β blockade may lead to reduced blood flow in muscles, thereby reducing the availability of glucose to the prime target tissue for glucose disposal.[41,42] There is further support for a haemodynamic explanation of the decreased sensitivity to insulin from studies of vasodilators, as prazosin[9] and captopril,[43] both of which increase blood flow in skeletal muscle, increase sensitivity to insulin.

The density of capillaries in skeletal muscle correlates with plasma insulin concentration.[44] Lillioja *et al* showed that insulin action is determined by the density of the capillary supply to skeletal muscle, particularly around the type 1, oxidative, slow twitch fibres.[45] Type 1 fibres are more sensitive to insulin and are equipped with more β adrenergic receptors than type 2, glycolytic, fast twitch fibres. Subjects with a high proportion of slow twitch fibres are apparently more sensitive to the action of β blockers as they have a more pronounced reduction in heart rate during treatment.[46] The decrease in sensitivity to insulin during β blockade in our study showed a weak ($r=0{\cdot}33$) but significant ($p=0{\cdot}037$) association with the change in heart rate. β_1 Selective blockers have been shown to reduce maximum oxygen uptake during an exercise test.[46] Thus β blockers may interfere with the capacity for glucose oxidation in insulin sensitive type 1 fibres. β Blockade may also influence glucose metabolism by its effect on the release of growth hormone.[14,47]

Free fatty acid concentrations are either unchanged, as in our study, or decreased during β blockade, thus excluding the possibility of resistance to insulin mediated by an increased supply of fatty acids to skeletal muscle.[48] Our data support previous observations that free fatty acid concentrations return to pretreatment values after six months of treatment.[49]

An increase in body weight has been noted in other studies during β blockade.[5] The reason for this is not fully understood, although a lower metabolic rate may be contributory.[37,50] In our study weight gain was associated with a significant increase in waist circumference ($p=0{\cdot}01$) during treatment.

Our results confirm that β selective blockade has little influence on serum cholesterol and low density lipoprotein cholesterol concentrations but decreases high density lipoprotein cholesterol concentration by about 7%.[51] The atherogenic index (very low density lipoprotein plus low density lipoprotein/high density lipoprotein cholesterol) increased significantly during both treatments. In agreement with other studies the most striking change in lipid metabolism during β blockade was an increase in serum triglyceride and very low density lipoprotein triglyceride concentrations.

The changes in basal glucose and plasma insulin concentrations shown during β selective blockade in this study may provide a link between insulin resistance and abnormal lipid metabolism. Increased serum triglyceride and decreased high density lipoprotein cholesterol concentrations are directly and inversely related to plasma insulin concentrations. There may, therefore, be a series of events which starts with a

β blocker inducing a decrease in glucose disposal mediated by insulin and eventually ends with an increased burden of risk factors for ischaemic heart disease. During this course of events an increased serum triglyceride concentration, decreased serum high density lipoprotein cholesterol concentration, and impaired glucose tolerance or diabetes are direct consequences of insulin resistance and hyperinsulinaemia. People who already have some resistance to insulin when essential hypertension is detected may be particularly susceptible to environmental influences that increase the resistance.

The metabolic side effects shown in this study are small, but as 30-50% of people over 60 are treated for hypertension in Sweden the effects of antihypertensive treatment on the incidence of ischaemic heart disease in the whole community should not be underestimated.[52] The association between antihypertensive treatment and resistance to insulin should be subject to further studies. Non-pharmacological treatments for hypertension should also be investigated, especially as such treatment may influence other risk factors for cardiovascular disease and death.

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Correction

Prevalence of diabetes in a predominantly Asian community: preliminary findings of the Coventry diabetes study

A printers' error occurred in the list of authors of this paper by Dr D Simmons and others (7 January, p 18). The first author is Dr D Simmons and not Dr S Simmons as published on the cover of this issue.