Antihypertensive Treatment in Insulin Resistant Patients

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Epidemiological evidence suggests that treatment with $\beta$-blockers and diuretics increase the risk to develop diabetes. Prospective, randomized studies of antihypertensive drugs have demonstrated differences between different classes of drugs regarding effects on insulin sensitivity. Thus treatment with $\beta$-blockers or diuretics is associated with impairment in insulin sensitivity, whereas most modern calcium-channel blockers and angiotensin converting enzyme inhibitors are neutral. However, captopril treatment seems to be different and result in improvement of insulin sensitivity. The most pronounced improvements have been obtained with $\alpha_1$-blockers. In populations at high risk for diabetes, it may be justified to select drugs that improve insulin sensitivity when treating hypertension in insulin resistant individuals. (Hypertens Res 1996; 19 Suppl. I: S75-S79)

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In 1988 Gerald Reaven in his Banting lecture suggested that insulin resistance may be a fundamental phenomenon in the body, causing a number of cardiovascular risk factors to deteriorate (1). In particular blood pressure regulation has been demonstrated to be related to hyperinsulinemia and/or insulin resistance in several ways (2). The fact that insulin resistance may be the common denominator for regulation of several cardio-vascular risk factors associated with hypertension has created a new interest in the risk factor concept as such. A consensus has developed that any treatment should aim at lowering the total risk in an individual, not to treat a certain value of blood pressure or of blood lipids (3). This idea is not new but has reemerged partially as a result of G. Reaven's concept of an insulin resistance syndrome. However, other factors have also contributed to focus the interest on the importance of the whole risk factor pattern of the patient. Several of the large trials in the 80s concerning the effect of antihypertensive treatment on hard end points came up with rather poor results (4, 5). The hope had been that $\beta$-blockers should have a primary preventive effect on coronary heart disease similar to what they were known at that time to have in secondary prevention. This would be an extra bonus of treatment with $\beta$-blockers that would go beyond the effect on the risk obtained by reducing the blood pressure. Unfortunately, such effects could not be clearly demonstrated to exist. Several possible explanations for this were suggested. One explanation was suggested to be the metabolic effects of the drugs used in the 70’s and 80’s. It was earlier known that $\beta$-blockers lower the cholesterol concentration in high density lipoproteins and increase the triglycerides in very low density lipoproteins (6). Also diuretics were known to alter the lipoprotein pattern increasing both cholesterol (in low density lipoproteins) and triglycerides (in very low density lipoproteins) (7). Such lipoprotein patterns are associated with an increased risk of atherosclerotic heart disease in the general population. Altering them in this way with drugs may infer an increased risk that counteracts any beneficial effect of lowering blood pressure and counteracts any additional effect of $\beta$-blockers of the same kind as obtained in secondary prevention. Today this is still a hypothetical issue because no studies have controlled for these other effects of drugs. Unfortunately, there is no other certain way to find out about the clinical consequences of these induced lipoprotein patterns than by studying them in trials.

Two “schools” have emerged during the last couple of years. Prior to that most of the expert committees had suggested that the four major classes of antihypertensive drugs could be used as first-line alternatives. One of these groups, the WHO/ISH expert group has stuck to this view and also included $\alpha_1$-blockers among the first-line drugs (8). However, the other school, represented by e.g. the JNC V expert panel, recommends that only the classes of drugs that have been used in primary preventive studies and proved their effect on hard end points, in particular stroke, should be first-line drugs (9). The JNC V group recommend only $\beta$-blockers and diuretics as first line alternatives.

Since the 80’s considerably more has been learnt about the metabolic effects of antihypertensive drugs. We could demonstrate in randomised, prospective trials lasting 4-6 months that not only did $\beta$-blockers and diuretics alter the lipoprotein pattern but treatment with these two classes of
drugs was generally associated with a deterioration of insulin sensitivity (they induced insulin resistance) (10-13) with some exceptions (14). These results were in sharp contrast to the effects obtained with other drugs, representatives of the calcium channel blockers (11, 15-17), angiotensin converting enzyme (ACE) inhibitors (12, 13, 17, 18) and \( \alpha_1 \) blockers (18-20). In this paper we will review some old and recent results and put them in the context of primary prevention.

**Are the Metabolic Effects Class Effects?**

On average, \( \beta \)-blockers and diuretics reduce insulin sensitivity and calcium channel blockers and ACE-inhibitors are neutral whereas \( \alpha_1 \)-blockers improve insulin sensitivity. However, when the details from different studies are considered it becomes quite clear that the metabolic effects are not true class effects but are linked to specific characteristics of the drugs in question.

**Metabolic Effects of Different \( \beta \)-Blockers**

In a cross-over designed, randomised trial in 40 newly detected, previously untreated hypertensives, treatment with propranolol reduced insulin sensitivity by 32% whereas treatment with pindolol reduced it by only 17% (21). As this statistically significant difference in effect was obtained in the same patient population it seems very likely that these two \( \beta \)-blockers differ in this respect. In a later study, in another patient group of essential hypertensives, the selective \( \beta \)-blocker metoprolol succinate was compared with dilevalol. The latter drug is a non-selective \( \beta \)-blocker with \( \beta_2 \)-agonistic effect which is much more pronounced than that of pindolol. Metoprolol and dilevalol were also significantly different in their effects on insulin sensitivity. With dilevalol there was a 10% improvement in insulin sensitivity. In contrast, with metoprolol there was a reduction in insulin sensitivity by 15%, an effect of the same magnitude as seen in previous studies with selective \( \beta \)-blockers. The effects of dilevalol included a pronounced reduction of serum triglyceride concentrations by 25%. This indicates that the effect on insulin sensitivity was not spurious but was coupled to other metabolic effects like that on triglyceride metabolism.

**Metabolic Effects of Some Calcium Channel Blockers**

Diltiazem treatment was not associated with any effect on insulin sensitivity (11). However, on a later occasion an analysis of diltiazem concentrations in stored serum samples was done (22). A positive relationship between diltiazem concentration and change of insulin sensitivity was demonstrated. Furthermore, there was also a relationship between diltiazem concentration and the blood pressure reduction. In summary, the higher the concentrations of diltiazem were, the more was insulin sensitivity improved and blood pressure reduced.

A quite different relationship was found with another type of calcium channel blocker, nifedipine (15). Using the old tablet form nifedipine treatment was associated with a significant reduction of insulin sensitivity. This finding could of course be spurious but the significant relationship between the change in heart rate and the change in insulin sensitivity indicates that it was probably not a chance finding. This has been interpreted to be due to an effect of a reflexory increase in sympathetic tone increasing both heart rate and reducing insulin sensitivity.

With isradipine the effect was neutral with regard to both insulin sensitivity and serum lipids (16). This supports the notion that long acting calcium channel blockers of the dihydropyridine derivative type are not associated with untoward effects on insulin sensitivity. This is supported by the results from a study in which nifedipine was administered in the long acting GITS formulation (23). With that type of administration nifedipine treatment was associated with an improvement of insulin sensitivity.

**Metabolic Effects of \( \alpha_1 \)-Blockers**

Seven years ago we published the results of a rather small study in newly detected hypertensives who were treated with prazosin over a three-month period (19). At the end of that period insulin sensitivity had improved by about 25% and insulin concentrations were reduced during an i.v. glucose tolerance test by about 30%. In fact, these changes were so large that this group of treated hypertensives was no longer significantly different from normotensive controls in these regards.

It was therefore of interest to study the second generation of selective \( \alpha_1 \)-blockers that could be given once a day. In the first study with doxazosin there was no significant improvement of insulin sensitivity in the first double-blind part of the study (20). However, at the 12-month follow-up after an open prolongation of the treatment with nine months, doxazosin treatment was associated with the expected improvement in insulin sensitivity. Furthermore, subgroup analysis indicated that the most pronounced effect was found in those patients who had indications of insulin resistance at the outset of the study. Thus, those who had a triglyceride concentration above the median value had a pronounced reduction of serum triglyceride concentration above the median value had a pronounced effect on insulin sensitivity by doxazosin treatment and those who had a value below median value had practically no effect. If other variables, like HDL-cholesterol concentration or plasma insulin concentrations, were used to categorise subgroups above and below median value similar results were obtained. Therefore, in a second study with doxazosin, only hypertensive patients with hypertriglycerideremia were investigated (18). In this parallel group, double-blind study 42 patients were given either enalapril or doxazosin, by randomisation, for five months. At the end of that period patients given doxazosin had increased their insulin sensitivity by more than 20%. In parallel, serum triglyceride concentrations had decreased by 25%. In this particular study also possible mechanisms be-
hind these changes were investigated. Thus, an i.v. fat tolerance test was used to study the capacity for removal of triglyceride-rich lipoproteins from the circulation and heparin-releasable lipoprotein lipase was measured both in plasma after i.v. heparin injection and in adipose and muscle tissue biopsy specimens incubated in heparin containing medium. These analyses indicated an improvement of the removal capacity of triglyceride-rich lipoproteins by about 30% which was accompanied by an increase of lipoprotein lipase activity in post-heparin plasma. However, there was no corresponding increase of lipoprotein lipase activity either in adipose or in muscle tissue. Thus, the increase in lipoprotein lipase activity is probably related to some other phenomenon and not to a tissue specific increase in lipoprotein lipase. In order to investigate any possible effect of vasodilation by \( \alpha_1 \)-blockade measurements of femoral blood flow by Doppler ultrasound technique was carried out before and after five months of active treatment. Furthermore, blood flow was measured both before and at the end of the clamp investigations. There were no significant changes in femoral blood flow during either regime (18). However, when the individual changes in blood flow were related to the individual changes in insulin sensitivity and blood pressure respectively, significant correlations were found. However, the slope of the line of regression was unexpected indicating that an increase in femoral blood flow was associated with a decrease in insulin sensitivity. On the other hand, in the enalapril treated group there was an inverse relationship between the change in blood pressure and change in blood flow, as hypothesized (Fig. 2). The most profound effect in reduction of blood pressure was seen among those who actually demonstrated a decrease in femoral blood flow. In absolute terms the changes were small, in relative terms some were rather large. These results are surprising because doxazosin is a vasodilator and vasodilatation should be associated with improvement in insulin sensitivity. However, one must consider that vasodilatation may have different consequences depending on how it is brought about. If doxazosin treatment caused an increase in cardiac output then an increase in femoral blood flow should be understandable. However, doxazosin treatment does not increase cardiac output. Vasodilation of small resistance vessels and capillaries may not necessarily be associated with a change in femoral blood flow, indeed, this may be an unlikely phenomenon. The metabolic effect of vasodilation of small vessels and capillaries at unchanged cardiac output and unchanged femoral blood flow is brought about by a longer transit time in the capillaries. Such an effect would explain the changes both in triglyceride metabolism found in this study and on insulin sensitivity. First of all lipoprotein lipase molecules are attached to the endothelial lining in the capillaries. If more capillaries are opened up during doxazosin treatment more of the triglyceride-rich macromolecules will be exposed to lipoprotein lipase molecules. This would explain two test results in this study, the increase in post-heparin plasma lipoprotein-lipase activity and the increase in the capacity for triglyceride hydrolysis as reflected in i.v. fat tolerance test. In parallel, opening up of capillaries may increase the number of sites at which insulin and glucose can act, thereby increasing glucose disposal.

Fig. 1. Relationship between change in office blood pressure and change in femoral artery blood flow (measured with Doppler technique) during treatment with doxazosin.

Fig. 2. Relationship between change in office blood pressure and change in femoral artery blood flow during enalapril treatment.

Fig. 3. Relationship between insulin resistance and relative risk for diabetes in insulin-resistant hypertension.
Discussion

In general, \( \beta \)-blocker and diuretic treatments are associated with a rather profound decrease in insulin's action on glucose uptake in tissues. The mechanisms behind these changes are still not known. The different effects among the \( \beta \)-blockers are likely due to different effects of these \( \beta \)-blockers on nutritional blood flow. Thus, with pletysmography it has been demonstrated that dilevalol is a vasodilator (24) but selective \( \beta \)-blockers as well as non-selective \( \beta \)-blockers without intrinsic sympathetic activity are vasoconstrictors. These different effects will probably influence insulin action in muscle tissue. A common metabolic effect of \( \beta \)-blockers and diuretics (high doses) that were used in the 70s was to increase insulin resistance. Among Caucasians insulin resistance is a prerequisite for development of diabetes mellitus. If e.g. \( \beta \)-blocker treatment is added to over-weight and sedentary lifestyle three environmental factors act in concert and cause insulin resistance. Several cohort studies have now indicated that treatment with \( \beta \)-blockers and/or diuretics increase the risk for development of diabetes in late middle-age (25-27). In our own study we were able to adjust for all other known risk factors for diabetes (fasting insulin concentration, the insulin response to glucose stimulation, body mass index, blood pressure and glucose concentration) (26). Also after such adjustment treatment for hypertension at the 10-year follow-up was statistically associated with a significant risk for diabetes. This study and a similar one in women have now been supported by findings in a Finnish study in which some of the hypertensives were not treated with drugs for a period of about 3-4 years (27). In the comparison groups that were treated with either \( \beta \)-blocker or diuretics, the incidence of diabetes was 2-3-fold higher than in the untreated group of hypertensives. This is probably the best and most important study indicating the clinical impact of drug-induced insulin resistance.

In a Swedish prospective study diabetes occurring during treatment for hypertension was not associated with any impact on the risk for myocardial infarction (28). In contrast, such an association was found among those individuals in whom diabetes existed when hypertension was diagnosed and anti-hypertensive treatment started. There are several possible explanations for this discrepancy. One possibility is that the insulin resistance that is induced by drugs does not share the pathogenic mechanisms with the insulin resistance that is due to inborn errors of metabolism (or overweight or sedentary life style). One other possibility is that the insulin resistance that preceded the hypertension was more pronounced and had been standing longer and therefore had a more profound influence on the risk for myocardial infarction. It is not possible to state from the data of this study if a selection bias is responsible for the findings, or not. However, at the present time, it still seems to be set safety first not to impair insulin resistance further by treating hypertension in insulin resistant individuals by drugs that will worsen insulin sensitivity further. Alternative treatment modalities exist today among the angiotensin converting enzyme inhibitors, among the calcium channel blockers and among \( a_1 \) blockers that at least are neutral in metabolic respects and some of the drugs may indeed improve insulin resistance. In populations in which a large part have a genetically determined poor insulin response to glucose stimulation any impairment in other risk factors for development of diabetes must be avoided. In many populations the secular trend brings about a sedentary life style in sharp contrast to what was predominant in the past. Westernization of the diet in populations in Asia may also increase the risk for obesity and insulin resistance. Although the effects of drugs on insulin sensitivity may seem small they are probably of importance due to the fact that this type of treatment lasts for decades. It is obvious from Fig. 3 that in terms of risk for diabetes it matters if we choose a non-selective \( \beta \)-blocker or an \( a_1 \)-blocker. The difference in risk over a 10-year period is of the magnitude of a factor of 2-3. At least in European (29) and North American (30) hypertensive populations about half of the hypertensives are insulin resistant. This proportion may be different in other ethnic groups. However, most evidence indicates that the risk for diabetes is even larger in south-east Asians, particularly when they are subjects substantial changes in environmental risk factors connected with immigration to European countries. Not only the risk for diabetes but also the risk for myocardial infarction is multiplied. These immigrants are not characterised by hypercholesterolemia or smoking so their increased risk for myocardial infarction must depend on other factors. Their pronounced insulin resistance and associated disturbance in metabolism of triglyceride lipoproteins has been suggested to be one possible risk factor for myocardial infarction of importance in these populations. Any factors that may further impair insulin function in such populations, like sedentary life style, obesity and treatment of hypertension with \( \beta \)-blockers and diuretics should probably be avoided.

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