Antihypertensive Therapy and Insulin Sensitivity: Do We Have to Redefine the Role of β-Blocking Agents?

Stephan Jacob, Kristian Rett, and Erik J. Henriksen

Essential hypertension is, at least in many subjects, associated with a decrease in insulin sensitivity, whereas glycemic control is (still) normal. Metaanalyses of hypertension intervention studies revealed different efficacy of treatment on cerebral (cerebrovascular accidents [CVA]) and cardiac (coronary heart disease [CHD]) morbidity and mortality. Although CVA were reduced to an extent similar to that anticipated, the decrease in CHD was less than expected. These differences are likely to be caused by the different impact of concomitant cardiovascular risk factors, such as dyslipidemia, impaired glucose tolerance, and non-insulin-dependent diabetes mellitus on CHD and CVA. Frequently these cardiovascular risk factors are ineffectively controlled in hypertensive patients, and moreover, some of the widely used antihypertensive agents have unfavorable side effects and further deteriorate these particular metabolic risk factors. Therefore, the metabolic side effects of antihypertensive treatment have received more attention. During the past few years, studies demonstrated that most antihypertensive agents modify insulin sensitivity in parallel with alterations in the atherogenic lipid profile. α1-Blockers and angiotensin converting enzyme inhibitors were shown to either have no impact on or even improve insulin resistance and the profile of atherogenic lipids, whereas most of the calcium channel blockers were found to be metabolically inert. The diuretics and β-adrenoreceptor antagonists further decrease insulin sensitivity and worsen dyslipidemia. The mechanisms by which β-adrenoreceptor antagonist treatment exert its disadvantageous effects are not fully understood, but several possibilities exist: significant body weight gain, reduction in enzyme activities (muscle lipoprotein lipase and lecithin cholesterol acyltransferase), alterations in insulin clearance and insulin secretion, and, probably most important, reduced peripheral blood flow due to increase in total peripheral vascular resistance. Recent metabolic studies found beneficial effects of the newer vasodilating β-blockers, such as dilevalol, carvedilol and celiprolol, on insulin sensitivity and the atherogenic risk factors. In many hypertensive patients, elevated sympathetic nerve activity and insulin resistance are a deleterious combination. Although conventional β-blocker treatment was able to take care of the former, the latter got worse; the newer vasodilating β-blocker generation seems to be capable of successfully treating both of them. Am J Hypertens 1998;11:1258–1265 © 1998 American Journal of Hypertension, Ltd.

Cardiovascular disease is the leading cause of death in the Western world, and hypertension is one important cardiovascular risk factor. Essential hypertension is at least in part, an insulin resistant state, characterized by a reduced insulin sensitivity of glucose uptake, mainly in skeletal muscle. Moreover, in many cardiovascular risk patients, frequently additional atherogenic risk factors are present, such as dyslipidemia, obesity, glucose intolerance, and hyperinsulinemia. This characteristic pattern is described as the syndrome X, the metabolic syndrome, or insulin resistance syndrome, in which insulin resistance and the accompanying hyperinsulinemia are thought to play a major role.

INTERVENTION STUDIES WITH ANTIHYPERTENSIVES

The goal of antihypertensive intervention is to reduce the morbidity and mortality of cardiovascular events, such as cerebrovascular accidents (CVA) or coronary heart disease (CHD). Antihypertensive treatment with β-blockers or diuretics lowers cardiovascular mortality, however, metaanalyses of hypertension intervention studies revealed that the decrease in CHD was less than expected. These differences are likely to be caused by the different impact of concomitant cardiovascular risk factors, such as dyslipidemia, impaired glucose tolerance, and diabetes on CHD and CVA, which seem to be often ineffectively controlled. Moreover, as some of the widely used antihypertensive agents have unfavorable metabolic side effects, antihypertensive intervention itself could contribute to the observed discrepancy.

ANTIHYPERTENSIVE TREATMENT AND LIPIDS

Both β-blocker and diuretic treatment are known to evoke a deterioration of the atherogenic lipids. Although nonselective β-blockers have the most pronounced effect, β1-selective adrenergic receptor blockade still has significant detrimental effects on the lipid profile (Table 1). These metabolic changes are completely reversible after the drugs were discontinued.

ANTIHYPERTENSIVE TREATMENT, INSULIN SENSITIVITY, AND CARBOHYDRATE METABOLISM

Previous studies have revealed an increased prevalence of type 2 diabetes in hypertensives who had been treated with diuretics and nonselective β-adrenoceptor antagonists. Although it was known that these agents worsen metabolic control in diabetics, many previous studies did not report a deterioration of glucose tolerance in nondiabetics, as fasting and postload glucose levels, as well as glycosylated hemoglobin (HbA1c) had remained unchanged. But there is evidence that as long as the β cell can adequately compensate for diminished insulin sensitivity, hyperinsulinemia will overcome insulin resistance and glucose tolerance will remain normal, even in the presence of marked insulin resistance (Figure 1). Therefore, a lack of deterioration of glycemic control (fasting or postload glucose or HbA1c) cannot exclude an alteration in insulin sensitivity.

During the past few years, the influence of these different agents on insulin sensitivity were examined with the aid of sophisticated methods such as the hyperinsulinemic, euglycemic glucose clamp technique, a method that is considered the gold standard for determining insulin sensitivity. These clamp studies demonstrated that many of the widely used antihypertensive agents modify insulin sensitivity in parallel with alterations in the atherogenic lipid profile. α1-Blockers and angiotensin converting enzyme (ACE) inhibitors were shown to either have no impact on or even improve insulin resistance and the profile of atherogenic lipids. In case of the calcium channel blockers, most of them were found to be metabolically inert, one study described a reduction of insulin sensitivity by nifedipine (Figure 2). The thiazide diuretics and β-adrenoreceptor antago-

<table>
<thead>
<tr>
<th>Table 1. Effects of β-Blocker Treatment on Metabolic Risk Factors</th>
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<tbody>
<tr>
<td><strong>Insulin Sensitivity</strong></td>
</tr>
<tr>
<td>Propranolol</td>
</tr>
<tr>
<td>Metoprolol*</td>
</tr>
<tr>
<td>Atenolol*</td>
</tr>
<tr>
<td>Pindolol</td>
</tr>
<tr>
<td>Dilevalol</td>
</tr>
<tr>
<td>Carvedilol</td>
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<tr>
<td>Celiprolol</td>
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*Mean value of cited studies.
nists further decrease insulin sensitivity and worsen dyslipidemia (Figures 2 and 3). These changes are reversible after the drug is discontinued, even after long-term use. In case of the thiazides, the metabolic side effects were shown to be mainly associated with the loss of potassium and were found to be dose dependent, as the lower doses did not impair insulin sensitivity.

CORONARY HEART DISEASE PARADOX

Although both \(\beta\)-blockers and diuretics showed a clear beneficial effect on cardiovascular mortality, their effect on CHD mortality was less than anticipated. The above described metabolic investigations (mainly glucose clamp studies), in addition to the retrospective data, supported the hypothesis that the less than expected long-term beneficial effect of antihypertensive intervention on CHD, despite adequate blood pressure control, may be in part brought about by the unfavorable changes in lipid and carbohydrate metabolism induced by the agents used. Black called this phenomenon the “coronary heart disease paradox.”

These observations resulted in an increased awareness of metabolic side effects of chronic antihypertensive treatment, and brought into question the use of \(\beta\)-blocking agents as a first-line antihypertensive agent, especially in younger hypertensives, as lifelong treatment is mandatory.

POSSIBLE MECHANISMS BY WHICH CONVENTIONAL \(\beta\)-BLOCKER TREATMENT INCREASES METABOLIC RISK FACTORS AND INSULIN RESISTANCE

The mechanisms by which \(\beta\)-adrenoreceptor antagonist treatment modifies insulin sensitivity and cardiovascular risk factors are not yet fully understood, yet several possibilities exist (Table 2).

MUSCLE LIPOPROTEIN LIPASE

The activity of the muscle lipoprotein lipase (LPL) is reduced in insulin resistance. This enzyme interferes

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**FIGURE 1.** Vicious circle of insulin resistance and hyperinsulinemia. Peripheral glucose uptake is diminished because of the reduced insulin sensitivity. Therefore, plasma glucose clearance is reduced and postprandial blood glucose will remain slightly higher. Consequently, this will induce hyperinsulinemia to overcome the insulin resistance. Hyperinsulinemia, however, will evoke a downregulation of the insulin receptors, which will further exacerbate the insulin resistance, hence leading to a vicious cycle (see text).

**FIGURE 2.** Effects of subchronic treatment (>2 months) with diuretics, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, and \(\alpha_1\)-blockers on insulin sensitivity, as assessed by the glucose clamp technique (selection of studies).
with triglyceride clearance and thus lipid metabolism. β-Blocker treatment was shown to lower the activity of the LPL, and thus diminishes triglyceride clearance.9–11,25,26 Therefore, triglycerides will increase because of their impaired breakdown.9–11,25,26 In contrast, α1-blockers increase the activity of the LPL and hence decrease triglycerides, as shown in several studies11,14,26; these compounds also increase insulin sensitivity.14

LECITHIN CHOLESTEROL ACYLTRANSFERASE AND HDL CHOLESTEROL

The activity of the lecithin cholesterol acyltransferase (LCAT) plays a major role in the transport and metabolism of cholesterol and triglycerides and in the generation of HDL. The activity of this enzyme is reduced by β-adrenergic blocking drugs; hence, HDL-cholesterol will decrease. α1-Blockers, however, by stimulating LCAT, will increase HDL.10,11,26

BODY WEIGHT CHANGES

Many hypertensive patients are overweight, and obesity is a risk factor for hypertension.2 β-Blocker treatment is often associated with a significant weight gain,22 and thus the increase in body weight will further reduce insulin sensitivity. However, this mechanism does not seem to play a major role, as in the glucose clamp studies, a marked decrease in insulin sensitivity was also observed in those who had no change in body weight.17,20–23

INSULIN SECRETION

The early (first) phase of insulin secretion plays an important role in controlling postload glycemia; when this first phase is reduced, more insulin is needed in the second phase.2 Chronic treatment with β-blockers was shown to alter first phase insulin secretion.17,20,21 An impairment of first phase insulin secretion is also considered to be a key factor in the development of non-insulin-dependent diabetes mellitus (NIDDM).2

INSULIN CLEARANCE

Insulin clearance is reduced in insulin-resistant and hypertensive patients,2,28 and β-adrenoreceptor antagonist treatment appears to further attenuate it.17,20–23 For instance, in hyperinsulinemic glucose clamp studies it is regularly observed that higher plasma insulin levels during the steady state (SSPI) are achieved after treatment with a β-blocker,17,20–23 although the same amount of insulin (defined as milliunit per kilogram body weight per minute)13 is infused in each experiment. As the SSPI represents the net result of the rate of exogenous insulin administration (which is always constant) and endogenous insulin removal, lower SSPI values indicate a better insulin clearance and vice versa (Figure 1). In most of the hyperinsulinemic glu-

**FIGURE 3.** Effects of subchronic treatment (>2 months) with β-adrenergic receptor blocker on insulin sensitivity.
cose clamp studies, an increase of SSPI by ± 10% was observed after treatment with a β-blocking agent.\textsuperscript{17,20–23}

Therefore, it is conceivable that due to the reduced insulin clearance, plasma insulin increases; the resulting hyperinsulinemia could downregulate the insulin receptors and consequently lower insulin sensitivity (Figures 1 and 2). This mechanism could make a small contribution to the alterations in insulin sensitivity.

**ROLE OF BLOOD FLOW**

Another possible mechanism involves hemodynamic changes. In healthy individuals, insulin enhances blood flow and consequently, substrate delivery to the skeletal muscle, thus contributing to the augmentation of glucose disposal (Figure 4).\textsuperscript{29–32} However, in conditions of decreased insulin sensitivity (obesity, hypertension, or NIDDM), the hemodynamic effect of insulin is diminished.\textsuperscript{29–31} Insulin resistance of glucose metabolism has been shown to be associated with resistance of the vasculature to increase blood flow during hyperinsulinemia (Figure 3). In fact, reduced insulin-stimulated peripheral blood flow correlates with the lower glucose disposal in these different disease states.\textsuperscript{29–31}

Indirect evidence supports the relevance of this mechanism, as successful weight reduction in obesity was shown to improve total peripheral vascular resistance (TPR) and peripheral blood flow; this was closely correlated with the improvement of insulin sensitivity.\textsuperscript{30}

There is also evidence of a close relationship between insulin and the sympathetic nervous system\textsuperscript{33,34}; enhanced sympathetic activity was shown to

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**TABLE 2. MECHANISMS BY WHICH ANTIHYPERTENSIVE TREATMENT WITH β-BLOCKING AGENTS CAN ALTER INSULIN SENSITIVITY**

<table>
<thead>
<tr>
<th>Muscle LPL activity</th>
<th>Untreated Hypertension</th>
<th>Treatment With β- or β\textsubscript{1}-Selective Adrenergic Blocker</th>
<th>Metabolic Consequences</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCAT activity</td>
<td>?</td>
<td>Down</td>
<td>↓ Clearance of triglycerides</td>
<td>9–11, 25, 26</td>
</tr>
<tr>
<td>Body weight</td>
<td>↑</td>
<td>↑ Weight gain</td>
<td>↓ HDL</td>
<td>10, 11, 26</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td>=</td>
<td>↓ 1st phase</td>
<td>↑ Insulin sensitivity</td>
<td>2, 27</td>
</tr>
<tr>
<td>Insulin clearance</td>
<td>↓</td>
<td>↓</td>
<td>↑ Hyperinsulinemia</td>
<td>2, 17, 20, 21</td>
</tr>
<tr>
<td>Peripheral blood flow</td>
<td>↓</td>
<td>↓</td>
<td>↓ Substrate delivery</td>
<td>29–32</td>
</tr>
<tr>
<td>TPR</td>
<td>↑</td>
<td>(↑)</td>
<td>↓ Glucose uptake</td>
<td>35, 37</td>
</tr>
</tbody>
</table>

LPL, lipoprotein lipase; LCAT, lecithin cholesterol acyltransferase; TPR, total peripheral vascular resistance.

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**FIGURE 4. Interplay between hemodynamic and metabolic alterations (see text).**
be associated with an elevated TPR, which is also present in insulin resistance.\textsuperscript{33,34}

As in \(\beta\)-blocker-treated patients TPR is found unchanged or even slightly increased\textsuperscript{10,35}, this effect on peripheral blood flow could contribute to the unfavorable metabolic effect on insulin sensitivity. This hypothesis is supported by the observation that drugs, which reduce vascular resistance and improve peripheral blood flow by blocking \(\alpha_1\)-adrenergic receptors, enhance insulin sensitivity.\textsuperscript{14} ACE inhibitors, through inhibition of the kininase II, will increase bradykinin, which in turn causes vasodilation and hence improves capillary blood flow\textsuperscript{36} and insulin sensitivity.\textsuperscript{15,16}

Stimulation of \(\beta_2\)-receptors causes vasodilation. Therefore, nonselective \(\beta\)-adrenergic blockade would also prevent the \(\beta_2\)-stimulated increase in blood flow.\textsuperscript{40} In line with this theory, insulin sensitivity is more impaired with nonselective compared to \(\beta_1\)-selective adrenoreceptor blockers.\textsuperscript{17,20–23} Moreover, when \(\beta_2\)-receptors are stimulated in addition to \(\beta_1\)-blockade, as with celiprolol treatment, TPR is even decreased.\textsuperscript{10} Also, when a nonselective \(\beta\)-adrenoreceptor antagonist is combined with a vasodilating \(\alpha_1\)-blocking property, as in carvedilol,\textsuperscript{37} TPR improves. Indeed, these vasodilating \(\beta\)-blockers, such as dilevalol, carvedilol, and celiprolol, were shown not to impair insulin sensitivity, but even slightly improve it.\textsuperscript{22,23,38}

**NEWER VASODILATING \(\beta\)-BLOCKERS**

Recent metabolic studies evaluated the effects of newer vasodilating \(\beta\)-blockers, such as dilevalol, carvedilol, and celiprolol, on insulin sensitivity and the atherogenic risk factors. None of them decreased insulin sensitivity, as has been described for the \(\beta\)-blockers with and without \(\beta_1\)-selectivity (see Figure 3). Haenni and Lithell\textsuperscript{22} reported a 10% increase in the insulin sensitivity index after chronic treatment with dilevalol, a \(\beta_1\)-selective \(\beta\)-blocker with a \(\beta_2\)-agonistic effect; however, because of the toxic side effects, this compound was withdrawn from the market. In another recently published study, Malminiemi\textsuperscript{38} also described an improvement of insulin sensitivity by 35% after chronic administration of celiprolol, another \(\beta_1\)-selective \(\beta\)-blocker with \(\beta_2\)-agonistic properties, which persisted after 12 months of treatment. And our group found a 14% increase in insulin-stimulated glucose uptake during a hyperinsulinemic glucose clamp after 3 months of treatment with carvedilol.\textsuperscript{30} In addition, antihypertensive therapy with these vasodilating \(\beta\)-receptor blockers was shown to have favorable effects on lipid metabolism (see Table 1).\textsuperscript{22,38,39}

One could speculate from these observations that peripheral vascular resistance and peripheral blood flow play a central role in mediating the metabolic side effects of the drugs, as the \(\alpha_1\)-blocking or \(\beta_2\)-stimulating compound more than compensated for the detrimental effects of the nonselective \(\beta\)-blocker in carvedilol or \(\beta_1\)-selective \(\beta\)-receptor blockade in celiprolol. However, in studies with the fatty Zucker rat, we also found an increase in insulin-stimulated glucose uptake after short-term and chronic treatment with celiprolol.\textsuperscript{40} In this model of the isolated epitroclearis muscle, blood flow is not a factor; therefore, other factors must also play a role.

Interestingly, in carvedilol, the nonselective \(\beta\)-receptor blocking part would be expected to decrease insulin sensitivity by \(>30\)%, as it was shown for propranolol.\textsuperscript{21} The \(\alpha_1\)-blocking part would at most improve insulin resistance by 20%, as shown for prazosin\textsuperscript{14}; thus, the overall effect would still be an unfavorable effect on insulin sensitivity with a decrease by \(-10\)%.

Oxidative Stress and Endothelial Function: Potential Benefits of These \(\beta\)-Blockers

There is potentially an additional mechanism by which the two vasodilating \(\beta\)-blockers carvedilol or celiprolol could improve blood flow and metabolism, as both were shown to act as a scavenger of free oxidative radicals.\textsuperscript{41,42}

In type 2 diabetes, atherosclerosis, and hypertension, the vasodilator endothelial derived nitric oxide (EDNO) is diminished, possibly attributable to excessive production of reactive oxygen species (ROS).\textsuperscript{43} This could result in an impairment of endothelial function (ie, vasodilation), and consequently in an increase of TPR and in a decrease in insulin sensitivity due to the diminished peripheral blood flow and substrate delivery (Figure 4). Insulin-induced vasodilation was shown to be, at least in part, mediated through an augmented production of EDNO\textsuperscript{32} and this vasodilation was found to be decreased in insulin resistance.\textsuperscript{29–31}

Moreover, NO acts as a radical scavenger\textsuperscript{42,43}; thus, availability of EDNO will be reduced when superoxide anions are trapped, hence EDNO-dependent vasodilation will be diminished,\textsuperscript{43} and consequently, blood flow will be reduced (Figure 4). Superoxide production is increased in diabetic animals; and Roesen et al\textsuperscript{43} found an improvement in endothelial function in these animals after chronic treatment with a radical scavenger, vitamin E. As nitric oxide synthase activity, and hence NO availability, is enhanced when ROS are reduced,\textsuperscript{42} the radical scavenging property of antihypertensive therapy with these vasodilating \(\beta\)-blockers was shown to have favorable effects on lipid metabolism (see Table 1).\textsuperscript{22,38,39}
pertensive agents like carvedilol and celiprolol could improve endothelial function, peripheral circulation, and hence insulin sensitivity of glucose metabolism. And indeed, an association between insulin sensitivity and oxidative stress is currently discussed.44

CONCLUSION

In view of some retrospective data and metaanalyses, the metabolic side effects of the antihypertensive treatment have received more attention. Also, essential hypertension is, at least in many subjects, associated with a decrease in insulin sensitivity, whereas glycemic control is (still) normal. It seems that in the hypertensive subject, two major functions of insulin are impaired: there is insulin resistance of peripheral glucose uptake (primarily skeletal muscle) and insulin resistance of insulin-stimulated vasodilation (Figure 4).29–32 Many groups have shown that conventional antihypertensive treatment, both with β-blockers and diuretics, decrease insulin sensitivity by various mechanisms.15,17,18,21–23 Although low-dose diuretics seem to be free of these metabolic effects,24 there is no evidence for this in the β-adrenergic blockers. However, recent metabolic studies evaluated the effects of vasodilating β-blockers, such as dilevalol, carvedilol, and celiprolol, on insulin sensitivity and the atherogenic risk factors. None of them decreased insulin sensitivity, as has been described for the β-blockers with and without β1-selectivity.22,23,28

This supports the idea that peripheral vascular resistance and peripheral blood flow play a central role in mediating the metabolic side effects of the β-blocking agents, as the vasodilating action (either via β2-stimulation or α1-blockade) seems to more than offset the detrimental effects of the blockade of β (or β1) receptors. Further studies are needed to elucidate the relevance of the radical scavenging properties of these agents and their relevance in regard to their metabolic effects.

In many hypertensive patients, elevated sympathetic nerve activity and insulin resistance are a deleterious combination. Although the conventional β-blocker treatment was able to take care of the former, the latter got worse; the newer vasodilating β-blocker generation seem to be capable of successfully treating both of them.

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