More on Paradoxical Pressor Effects of Nonselective β-Blockers

A pressor effect of nonselective β-blockers has been reported from the very beginning. It was observed in patients with emotional stress, low renin hypertension, and increased sympathetic activity, as well as in patients with untreated pheochromocytoma, clonidine withdrawal, abuse of cocaine, and subcutaneous administration of epinephrine. The most consistent finding in these reports was the situation of increased sympathetic activity. It was hypothesized that α-receptor-mediated vasoconstriction unopposed by β-receptor-mediated vasodilation might be responsible. In situations of increased sympathetic activity, this mechanism might override the otherwise hypotensive activity of nonselective β-blockers. To test this hypothesis, investigators started to design controlled trials comparing β₁-selective and nonselective β-blockers. On the one hand, β₁-selective blockers have a weak binding potency at the β₂-receptor site and thus are less likely to produce this pressor effect. On the other hand, however, the selectivity is not absolute, but dose-dependent (eg, metoprolol and atenolol lose their β₂-selectivity with incremental doses). Correspondingly, the different effects of β₂-selective drugs on peripheral vascular resistance compared with nonselective compounds seem to be dose dependent. Finally, even the heart does contain not only so-called cardioselective β₁ but also otherwise vasodilative β₂-adrenergic receptors.

If epinephrine is administered, mean arterial pressure hardly changes. This is so because epinephrine stimulates both α- and β-receptors. α- Receptor stimulation causes vasoconstriction; β₂-receptor stimulation vasodilation. The net effect is that mean arterial pressure remains essentially unchanged. The effect is different if patients have been pretreated with a nonselective β-blocker. Pretreatment with propranolol, for example, causes an increase of mean arterial pressure of 20 to 30 mm Hg, because the vasodilative β₂-receptors are blocked by nonselective β-blockers, and thus, epinephrine is no longer capable of a vasodilative effect. This very thing does not happen in case of pretreatment with metoprolol or atenolol, β₁-selective blockers, because of their low binding potency at the β₂-receptor site. By now, this phenomenon has been reported by four groups, so it cannot be easily ignored. The effect has not yet been examined in patients with enhanced receptor sensitivity; patients with acute anxiety syndromes overreact to infusion of epinephrine compared with psychologically stable subjects. Neither has the effect been examined after administration of norepinephrine, which is a more potent vasoconstrictor than epinephrine. This is even more important because two kinds of sympathetic overactivity have been recognized: a norepinephrine effect by release of norepinephrine from the sympathetic nerve endings, and a epinephrine effect mediated mainly by indirect release of epinephrine from the adrenal medulla, nowadays also called the aggressive and defensive sympathetic reactions, respectively. Moreover, there are miscellaneous forms (for example, handgrip). Obviously, daily life stress involves more complicated processes than the infusion of epinephrine does.

In normotensive subjects who are being treated with saline or atenolol, blood pressure is hardly influenced by two cigarettes. Pretreatment with propranolol, however, does cause a significant rise of diastolic blood pressure of 12 mm Hg. The same effect is seen after chronic treatment with nonselective β-blockers, as reported by three groups. Nicotine is just like caffeine and insulin: a drug in daily life that causes a substantial rise of plasma epinephrine and can thus be used as a model for pharmacological stress. As a matter of fact, insulin has been quite successful in demonstrating a pressor response from propranolol (increase of diastolic blood pressure from 80 to 90 mm Hg), whereas pretreatment with β₁-selective β-blockers even caused a slight decrease of diastolic blood pressure, from 80 to 65 mm Hg. What about caffeine? It has been less successful than nicotine and insulin. In some studies, no difference was found between pretreatment with a β₁-selective and a nonselective β-blocker. This failure was ascribed to an increase of plasma epinephrine of <200%, which was the lowest level to cause a pressor response to infusion of epinephrine. Much more coffee would be needed, or the same quantity together with a bit of nicotine, as demonstrated by Freestone and Ramsay. After pretreatment with the nonselective β-blocker oxprenolol for 6 weeks, 500 mL coffee and two cigarettes caused an increase of systolic blood pressure of 12.1±3.6 mm Hg and of the diastolic blood pressure of 9.1±2.6 mm Hg (both P<.01). Other workers, however, did find that the pressor effect disappeared in heavy smokers after more than 4 weeks of treatment. What little is absolutely true is documented by the paper of Shepherd reporting an increase from 140/80 to 230/112 mm Hg during hypoglycemia in a patient who had been treated with the β₁-selective blocker metoprolol for many years. Finally, whether the absence of any cardiovascular response to hypoglycemia is a true advantage is uncertain. Other types of stress to study differences between the two β-blockers are (1) environmental stress, such as cold, loud noise, and pain; (2) mental stress, such as arithmetic; and (3) physical stress, such as handgrip and different types of dynamic exercise. Most of these stress models cause smaller increases of catecholamines in the laboratory than the infusion of catecholamines does. Nonetheless, subtle differences between β₁-selective and nonselective β-blockers could repeatedly be demonstrated. For example, loud noise caused a significant increase of blood pressure of 10 mm Hg and also of peripheral vascular resistance in hypertensive patients treated with propranolol. In the case of metoprolo, this was not so. Similar effects of nonselective β-blockers were observed with mental arithmetic and physical stress tests such as handgrip. The effects were demonstrated in both acute and chronic studies. After dynamic exercise, local metabolic factors probably override the antagonistic effect on vasodilation. However, in a category of low anaerobic metabolism, namely long-distance runners, performance was impaired by 30% when the subjects received propranolol but by only 10% when they received atenolol. Karlson attributed this effect to prevention of β₁-receptor-mediated vasodilation. In recent years, controlled and double-blind studies on pressor effects of nonselective β-blockers have been performed in patients with acute psychosis, acute hospitalization, surgery, and unstable angina pectoris. During surgery, under anesthesia, an increase of blood pressure is generally no problem. The anesthesiologist generally has less trouble with high than with low blood pressure because of the hypotensive effects of most anesthetic drugs. In unstable angina pectoris, an increase of blood pressure of 30 mm Hg is certainly unfavorable because the double product (systolic blood pressure times heart rate), which is an estimate of myocardial oxygen demand, increases. Indeed, nonselective β-blockers were less effective than β₁-selective β-blockers in unstable angina pectoris. As can be seen, the pressor responses appear exclusively in situations of increased sympathetic activity. An increased release
of norepinephrine from sympathetic nerve terminals and increased levels of plasma norepinephrine are consistent findings in patients on nonselective \( \alpha \)-blockers. This is so because blockade of \( \alpha_2 \)-receptors that are present on the sympathetic nerve endings largely enhances the release of norepinephrine. Consequently, this may be a situation to demonstrate a pressor response from nonselective \( \beta \)-blockers as well. Indeed, in young hypertensive patients, the nonselective \( \alpha \)-blocker phenolamine caused a mean fall in blood pressure of 16.5 mm Hg and an increase in mean heart rate of 19 beats per minute. After pretreatment with propranolol, the mean fall in blood pressure was only 4.7 mm Hg (before versus after, \( P<.01 \)), whereas heart rate hardly increased.\(^22\) Also, other groups have demonstrated that propranolol antagonizes not only the increase in heart rate but also the hypotensive activity of nonselective \( \alpha \)-blockers.\(^30\) On the other hand, no such effect can be expected from the more modern \( \alpha_1 \)-selective \( \alpha \)-blockers like prazosine that block predominantly the vasoconstrictive postsynaptic \( \alpha_1 \)-receptors. The absence of a protective effect against hypotension in another study\(^32\) shows that it is a subtle mechanism we’re dealing with: if a pressor effect due to \( \beta \)-blockade is countered by a vasodilator effect via the \( \alpha \)-receptors and a decrease of cardiac output via the \( \beta \)-receptors, the net effect may as well be a considerable decrease of blood pressure. 

Orthostatic hypotension based on autonomic neuropathy has been treated successfully with nonselective \( \beta \)-blockers, although most reports were case histories without control observations.\(^10\) To eliminate potential biases as seen with uncontrolled studies, we performed a double-blind placebo-controlled study in 11 patients with symptoms of orthostatic hypotension.\(^23\) All patients had vagal neuropathy and largely elevated levels of plasma catecholamines as seen with hyperadrenergic diabetic syndrome. Different \( \beta \)-agonists (terbutaline and orciprenaline) did not reduce the fall of blood pressure on standing, nor did the \( \beta \)-blockers acebutolol and metoprolol. Only the nonselective \( \beta \)-blockers propranolol and pindolol significantly reduced or practically abolished the fall. This effect was confirmed by a 3-week trial with pindolol.\(^23\) As cardiac output was reduced, the effect was ascribed not to positive inotropic intrinsic sympathomimetic activity effect but rather to prevention of \( \beta \)-receptor vasodilation. Roughly, orthostatic hypotension can be distributed into two categories, a hypoadrenergic form with very low and a hyperadrenergic form with very high plasma catecholamine levels. The former category may benefit from intrinsic sympathomimetic activity\(^24\) and from \( \beta \)-agonists like xamoterol.\(^25\) The latter category probably does not, because \( \beta \)-receptors are already stimulated maximally. This explains why xamoterol did not have any beneficial effect in diabetes with orthostatic hypotension and presumably hyperadrenergic status.\(^26\)

Paradoxical pressor effects of nonselective \( \beta \)-blockers have been reported in more than 60 articles. The pressor effects are probably due to \( \alpha \)-receptor-mediated vasoconstriction unopposed by \( \beta \)-receptor-mediated vasodilation. In situations of increased sympathetic activity, this mechanism may override the otherwise hypotensive properties of nonselective \( \beta \)-blockers. Some patients seem to be at risk, for example, patients with unstable diabetes mellitus, athletes who perform a lot of isometric exercise, and heavy smokers. In these patients, the preference for a \( \beta_1 \)-selective \( \beta \)-blocker seems reasonable. In 1988, we reviewed the articles on this subject published at that time. Our conclusions have been adopted by Goodman & Gilman, *The Pharmacological Basis of Therapeutics.*\(^27\) In recent controlled and double-blind studies, the pressor effect has been demonstrated during increased sympathetic activity due to unstable angina pectoris,\(^23\) surgery,\(^28\) and acute hospitalization.\(^19\) Although the clinical relevance of the phenomenon in terms of permanent harm has not been elucidated so far, we may ask: do we require the very proof of it by exposing mankind to a less effective and potentially hazardous compound? \( \beta \)-Blockade, if not hazardous, does not help to reduce blood pressure either,\(^28\) although initially it was thought to do so.\(^29\) We should add that there are more reasons for choosing a \( \beta_1 \)-selective blocker, e.g., bronchus constriction especially in patients with chronic obstructive pulmonary disease, delayed recovery from hypoglycemia in diabetes mellitus, and severe hypertrophic cardiomyopathy. The pressor effects have also been described with nonselective \( \beta \)-blockers with ISA (table)\(^30\) or with additional \( \alpha \)-blocker properties (labetalol).\(^31\) This is not too much of a surprise because these compounds do block \( \beta \)-receptors, although maybe less vigorously. Moreover, labetalol is not that good for additional \( \alpha \)-blockade, since it lacks \( \alpha \)-selectivity. Carvedilol, which is \( \alpha \)-selective, may be a better choice, but even this compound does block \( \beta \)-receptors.

The reverse of the medal is that the results of secondary prevention studies of myocardial infarction are slightly in favor of nonselective \( \beta \)-blockers. Perhaps this is partly due to the presence of mostly normotensive subjects in this category. Still, even in these patients, the beneficial effect of nonselective \( \beta \)-blockade is lost by the factor of smoking.\(^12\)

### References


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**Women and Coronary Artery Disease**

The publication of Murabito et al. discusses the Framingham data on coronary disease that has been used as a basis for looking at the presentation and prognosis of women with coronary disease. In their article, they acknowledge that the clinical diagnosis of angina in women is frequently incorrect, with perhaps half of these women having no significant epicardial coronary disease. If one reduces the number of women with an anginal presentation of coronary disease by a factor of 50% (as perhaps only half of these women actually had coronary disease), then Table 1 would show that the percent of women with angina as their initial presentation of coronary disease is 31%. This is similar to the 32% observed in men. With regard to prognosis, it has been shown that women with chest pain and normal coronaries have a good prognosis. If one assumes that the myocardial infarctions and coronary heart disease deaths in women with angina occurred in those women who actually have coronary disease (roughly half the population), then the rates of these events in this population would be double the values shown in Table 3. This would be a 2-year rate of myocardial infarction of 12.4% and a 10-year rate of 35.6%, similar to the rates of 14.3% and 33.4% observed in men. The rate of coronary heart disease death would be 7.6% at 2 years and 33.4% at 10 years as compared with 5.5% and 28.2% for men.

These dramatic changes in presentation rates and outcomes given a correction factor of 50% are crude estimates. The actual number of women with angina who actually had coronary disease cannot be determined from the available data. This reinforces the urgent need for better data on cardiovascular disease in women, with a more rigorously defined database. Data acquired on a clinical basis without angiographic confirmation of coronary disease must be used with extreme caution and should not be construed to mean that women with angina and coronary disease have a benign prognosis.

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**References**


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**Reply**

We strongly agree with Dr Horton’s concern regarding the clinical diagnosis of angina in women. We repeatedly cautioned that after the onset of angina, women are expected to fare better than men because fewer women than men with clinically diagnosed angina actually have underlying coronary disease.

While we agree that there is greater misclassification of coronary disease status in women with clinically diagnosed angina than in men, we believe that the 50% misclassification error suggested by Dr Horton is excessive. The correction factor of 50% suggested by Dr Horton was derived from a group of women under 50 years of age with clinical angina by history, which was defined as “pain somewhere in the upper half of the body precipitated by walking and relieved within 15 minutes by rest.” A study sample more representative of our population comes from the Coronary Artery Surgery Study Registry, where the prevalence of significant coronary disease was 81% in women 60 to 69 years of age with definite angina. In that study, significant coronary artery disease occurred more frequently in older patients as well as in those with a
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Circulation. 1994;90:2157-2159
doi: 10.1161/01.CIR.90.4.2157

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