Adrenergic Vasoconstriction as a Cause of Inadequate Hypotensive Response to Beta-Adrenergic Blockade

WILLEM H. BIRKENHAGER, M.D., AND PETER W. DE LEEUW, M.D.

SUMMARY This overview is concerned with the causes of nonresponsiveness to the hypotensive action of beta-adrenergic blocking drugs. The overall hemodynamic response, i.e., a secondary decrease in peripheral vascular resistance, is unrelated to the primary decrease in cardiac output. The reduction in vascular resistance may be triggered by mechanisms residing in the central nervous system, the arterial baroreceptor area, or the prejunctional beta-receptor. None of these mechanisms seem to be entirely responsible. Studies in responders vs nonresponders tend to equate nonresponsiveness with alpha-adrenoceptor-mediated vasoconstriction. Although circulating catecholamines are relatively poor indices of sympathetic activity, studies focusing on the renal-neural area appear to show clearly differential profiles between responders and nonresponders. Such findings, in relation to experimental data on the renal nerves as selective neural amplifiers, may provide a renewed interpretation of the centrally mediated hypotensive mechanism of beta-adrenergic blockade.


Key Words • arterial pressure • cardiac output • vascular resistance • betablockers • propranolol • responders • nonresponders • norepinephrine

PRESSOR mechanisms interfering with the hypotensive effect of treatment may stem from the primary condition (pheochromocytoma, adrenal medullary hyperplasia), but far more common is the problem of resistance patterns based on physiological counterregulatory responses to the drug's mechanism. Diuretics induce hyperreninism and hyperaldosteronism. Vasodilators, acting directly on vascular smooth muscle tone, trigger an all-out response consisting of increased sympathetic nervous activity manifested by hyperkinetic circulatory response, together with hyperreninism and fluid-sodium retention. These mixed reactions do not allow a separate assessment of an adrenergically-mediated component of vasoconstriction. In fact, the beta-blockers are presently the most widely used drugs, in which nonresponse may be analyzed in terms of sympathetic vasoconstriction. In this review, we will therefore focus on beta-adrenergic blockers.

Overall Hemodynamic Response Pattern to Beta-Adrenergic Blockade

Both in normotensives and in hypertensives, the immediate hemodynamic response at rest to any beta-blocking agent unless it has potent intrinsic sympathomimetic activity (ISA') is characterized by a fall in cardiac output; and even ISA drugs show a fall in cardiac output during exercise. After a shorter or longer time lag, arterial pressure decreases. The initial nonresponse on the part of arterial pressure must reside in an increase in peripheral vascular resistance. Originally this had been attributed to blockade of the vascular beta2-receptor, but this mechanism seems to be rather unimportant, when the local effects of propranolol or the results of beta2-selective blockade are taken into account. The observation that plasma catecholamines rise within 1 hour after i.v. injection of propranolol is probably not due to some pharmacological interference with reuptake. The most likely explanation is that sympathetic nervous system activity is increased by a reflex mechanism. This vasoconstrictor effect subsides in the responders whether cardiac output remains reduced or calculated peripheral resistance returns to or below control levels. Interestingly, a recent review has demonstrated that the onset of blood pressure reduction during long-term treatment with different beta-blockers was always associated with a fall in vascular resistance at any given level of cardiac output, even when the latter was not decreased at rest by virtue of the presence of ISA.

Possible Mechanisms Responsible for the Secondary Decrease in Total Peripheral Vascular Resistance

It is highly probable that, at some level along the sympathetic nervous axis, an adaptation occurs that
ultimately abolishes at least partly the vasoconstrictor response initiated by the reduction in cardiac performance. Descending from central to peripheral levels, the central nervous system, the baroreceptors, and the peripheral receptors will pass muster.

Central Nervous System

It has been demonstrated that experimental intraventricular administration of beta-blockers reduces arterial pressure. When propranolol is infused into the vertebral artery, impulse traffic in splanchnic nerves is reduced; however, this effect is not seen during infusion of practolol. The crucial problem, as reflected in the latter experiment, is that the central hypothesis fails to explain that beta-blockers which do not readily cross the blood-brain barrier (practolol, sotalol, atenolol, metoprolol) are in no way inferior to those beta-blockers that are characterized by a high lipid partition coefficient. The central nervous echelon may still play a crucial role, however, albeit in an indirect way (see below).

Arterial Baroreceptor Reflexes

Pritchard and Gillam suggested in one of their early papers that beta-adrenergic blockade might act by modulating the baroreflex. In that area of research, a great deal of controversy has arisen. A baroreflex alteration by beta-blockade has been reported in animals and humans, in terms of a propranolol-induced augmentation of the bradycardic response to increases in pressure. Others have reported, however, that this effect occurred only in young subjects or not at all. Even if the baroreflex is reset, this may be a nonspecific consequence of the hypotensive effect of treatment rather than the beta-blockade per se.

Prenjunctural Beta-receptors

A betareceptor site has been identified at sympathetic nerve endings. Circulating epinephrine may raise arterial pressure by acting on prejunctural beta-adrenergic receptors, with enhancement of no adrenergic transmission. Since stimulation of these receptors facilitates norepinephrine release, blockade of the same units is very likely indeed to reduce the release of neurotransmitter. The vasoconstrictor nerve transmission would then be reduced or inhibited. Those who like to adopt this explanation still have to deal with two problems. First, why are the prejunctural beta, receptors receptive to selective beta blockers? Second, why should there be a time delay between the immediate postjunctural mode of action of beta-blockade on cardiac muscle and these prejunctural effects?

In brief, none of these theories appears to be conclusive at this stage.

Responders vs Nonresponders

Comparison between hemodynamic and hormonal alterations in responders and nonresponders to treatment with beta-adrenergic blocking drugs could yield interesting data. There have been surprisingly few studies in this area. All of these appear to agree that the decrease in cardiac output is of similar magnitude in responders and nonresponders. It is therefore tempting to relate the blood pressure fall in responders to a decrease in total peripheral vascular resistance. Despite the dubious aspects of relating a decrease in blood pressure to a calculated derivative of blood pressure, there is at present no reasonable alternative expression. Tarazi et al. have emphasized changes with time, implying that the evolution of vascular relaxation may be due to a complex cascade of events, and this is a common feature of such widely different drugs as beta-blockers and diuretics. It should be borne in mind, that during beta-blockade this process may need only a very short timespan in contrast to diuretics. A hemodynamic similarity (particularly when based on the crude parameters presently available) does not necessarily imply a pathophysiological commonality. The origin of the vascular wall change in responders is still unclear, as indicated in the previous section. In nonresponders, the lack of a decrease in peripheral vascular resistance may be determined to a large extent by persistent or enhanced neurogenic alpha-adrenoreceptor-mediated vasoconstriction. Despite the plausibility of this concept, the origin of such a mechanism in nonresponders vs its nonexistence in responders remains obscure.

Assessment of Sympathetic Nervous Indices in Responders and Nonresponders

Systemic Catecholamine Levels

There is a paucity of data on circulating catecholamines when responders are contrasted with nonresponders. In a small series, Amann et al. observed no differences in the course of propranolol treatment between the two groups. Both basal plasma norepinephrine and epinephrine levels were unchanged in responders and nonresponders alike. Despite current reservations with respect to the validity of circulating norepinephrine and epinephrine levels as indices of sympathetic nervous system activity, we designed a compact study to compare patterns in responders and nonresponders.

Subjects were admitted to the hospital and after a pertinent investigation received either atenolol in an average daily dose of 100 mg (n = 23) or verapamil (n = 13; average dose 240 mg). Verapamil was chosen for comparison because it is supposed not to work through a neural mechanism. Those who responded well during 14 days in the hospital were discharged with continuation of the same drug. After a time lapse of 10 weeks, both treatment groups were split into subgroups of continuing responders (atenolol n = 15, verapamil n = 8) and secondary nonresponders (atenolol n = 8, verapamil n = 5). Noncompliance was excluded as far as possible by conventional means.

We found no difference with respect to plasma volume or active plasma renin concentration. Both plasma norepinephrine and epinephrine levels turned out to increase significantly in the group of nonresponders compared with the group of responders. The finding...
that norepinephrine and epinephrine tended to run parallel courses suggests that the failure to keep up the hypotensive response may be due to a widespread sympathetic reaction pattern. The function of epinephrine in the process of vasoconstriction has recently been clarified, in that its prejunctional uptake and its release together with norepinephrine appear to render it a true neurotransmitter.\textsuperscript{36,37} The rise of epinephrine levels (by adrenal medullary secretion?) may thus even overcome a (partial) blockade of prejunctional betareceptors. The possibility that circulating levels of catecholamines may have been influenced by impaired clearance mechanisms\textsuperscript{41} would to the best of our knowledge not have occurred during the use of a slow calcium channel blocker such as verapamil. The similarity of patterns suggests, therefore, that one is dealing with a true sympathetic nervous response. Nevertheless, one should still maintain some reservations when interpreting systemic catecholamine patterns, because of uncertainties with respect to re-uptake, clearance, and metabolism. To minimize such problems, we attempted to explore the renal hemodynamic and hormone secretional patterns in responders and nonresponders.

**Renal Vascular Circuit in Responders and Nonresponders**

The renal vascular circuit is an exquisite area in the study of hypertensive humans. Over the years, we have learned that it is also a sensitive model for measuring norepinephrine spillover.\textsuperscript{42-44} The experiment we wish to refer to in the present context was designed as follows. Twenty-five hypertensives were treated with propranolol up to 480 mg/day for a period of 2 weeks. Fifteen of them proved to be responders (patients in whom MAP fell at least 5 mm Hg and reached a level of 110 mm Hg or less) and the other 10 not answering these criteria were counted as nonresponders. Despite an equal fall in cardiac output in both groups, renal blood flow remained unchanged in responders, while it fell in nonresponders. Consequently, calculated renal vascular resistance dropped significantly in the responders and rose in the nonresponders (fig. 1). Norepinephrine secretion, as computed from renal blood flow and renal arteriovenous (AV) norepinephrine gradients, could be assessed only once in each patient (because this procedure was linked to diagnostic renal arteriography). Values obtained in the responders and nonresponders (during treatment) had therefore to be offset against the pattern observed in a group of 31 untreated hypertensives who were otherwise comparable to the study group. The results are presented in figure 2. The most salient finding was that norepinephrine secretion, which tends to decrease in responders, was sharply and significantly elevated in nonresponders. This dramatic increase in norepinephrine secretion rate was not reflected by systemic norepinephrine levels, which were rather similar in all three categories.

This finding seems to demonstrate rather convincingly the insensitivity of systemic norepinephrine levels as an index of neurogenic activity. At first sight this would seem to negate the previously described results. However, the circumstances were quite different in that the former patients were secondary nonresponders who were evaluated on an outpatient basis. The renal response may be supposed to fall in step with the systemic response. On the other hand, the profile of

\[\text{MAP (mmHg)}\]  

\[\text{RBF (ml/min /1.73m²)}\]  

\[\text{RVR (dyn sec cm /1.73m²)}\]  

\[\text{Renn secretion rate (µU/min)}\]  

\[\text{Renal norepinephrine release (ng/min)}\]  

\[\text{RESPONDERS} \quad \text{NON-RESPONDERS} \]

**FIGURE 1.** Changes in mean arterial pressure (MAP), renal blood flow (RBF), and calculated renal vascular resistance (RVR) in responders (left panel) and nonresponders (right panel) after treatment with propranolol for 2 weeks under standardized conditions of sodium intake.

\[\text{FIGURE 2.} \quad \text{Comparison of renal renin secretion (left panel) and norepinephrine release (right panel) in responders and nonresponders during treatment with propranolol. White bar = untreated; cross-hatched bar = propranolol-treated (responders); stippled bar = propranolol-treated (nonresponders).} \quad \star p < 0.01.\]
norepinephrine release as observed in nonresponders must be rather exceptional, since it is not at all reflected in circulating levels. This rise, with the decrease in renin secretion, is consistent with renal α-adrenoceptor stimulation.\(^4^\)

**The Kidney as a Determinant of the Hypotensive Response to Beta-Blockade**

In the aforementioned study, we depicted different profiles of the renal vascular-neurohumoral reaction in responders and nonresponders to treatment with propranolol. This stands out in sharp contrast to systemic norepinephrine levels which were not significantly different in responders and nonresponders in this short-term study. Admittedly, the concentration of norepinephrine in plasma represents a balance between release from sympathetic nerve endings and clearance by uptake and metabolism, while the measurements across the kidney probably are better correlated with transmitter release in a more purified fashion. Nevertheless, the patterns of norepinephrine secretion and circulation are so vastly different that the possibility of a particular role for the kidney merits consideration. Several lines of experimental evidence suggest that there is a neural link between the kidney and sympathoexcitatory centers in the brain.\(^5^\) More specifically, electrophysiological data relate the activities of renal afferent nerves and certain neural units in the AV3V region of rats.\(^6^\) The precise function of this renal-neural unit is as yet unclear, since both the severity\(^7\) and electrical stimulation\(^8\) of the renal afferents may induce attenuation of hypotension.

Although at this stage more experimental data are required, we propose the working hypothesis that the kidney serves as a signaling beacon guiding a centrally-mediated response to beta-adrenoceptor blockade. When the conditioning of the kidney allows a (relative) local vasodilation, the renal afferents transmit a positive feedback signal to induce general vasodilation. In nonresponders, the renal arterioles constrict, possibly by predominance of α-adrenoceptor tone (with norepinephrine production and renin suppression).\(^9^\) The renal afferents would then stimulate the strategic central neurons to counteract a fall in blood pressure. Thus, the concept of autoregulation focused on the kidney could be linked up with an indirect version of the central nervous system theory where beta-adrenergic blockade is concerned. Hopefully, the expanding experimental body of knowledge in regard to the renal-central axis will help to identify this potential source of hypotensive mechanisms.

**References**


2. Lund-Johansen P: Central hemodynamic effects of beta-blockers in hypertension. A comparison between atenolol, metoprolol, timolol, penbutolol, alfentanil, pindolol and bun-


4. Hanson L: Beta-adrenergic blockade in essential hyperten-


7. Åström M, Vallin H: Effect of a new beta-adrenergic blocking agent, ICI 66082, on exercise haemodynamics and airway re-


9. Adler-Gerhatschinsky E, Langer SZ: Possible role of a/β-adreno-

10. Tarazi RC, Dusan HP: Beta adrenergic blockade in hyperten-


Discussion

AGABITI-ROSEI: Have you any data on the effect of alpha-blockers in nonresponders? Is the hypotensive effect induced by alpha-blockade related to the increase in catecholamines that is observed in these patients?

BIRKENHÄGER: You can do this kind of study only once in an individual patient — but we have just started on a different approach.

PESSINA: Why was renin less suppressed by propranolol in your responders than in the nonresponders? Is it because responders have more renal ischemia?

BIRKENHÄGER: Possibly, but another explanation would be differences in the local baroreceptors between the two groups. It is rather typical for alpha-receptor stimulation that renin can be suppressed even without any measurable changes in renal blood flow. So we believe that in responders there is less alpha-stimulation than in nonresponders.

DIENSTL: Could there be a difference in the density of beta-receptors in the target organs between the two groups?

BIRKENHÄGER: From a general point of view there was no difference in systemic hemodynamic response, so I would doubt this theory.

DIENSTL: Your hemodynamic model is following Ohm’s law and therefore peripheral resistance is only calculated — not actually measured.

BIRKENHÄGER: I agree, but I was talking about cardiac output and heart rate.

BÜHLER: You found low renin secretion rate in the nonresponders. Maybe they were already low renin patients before treatment, which would explain why they did not respond to beta blockade.

BIRKENHÄGER: In terms of renin secretion, this possibility cannot be excluded. However, according to systemic renin levels that were assessed before treatment, the nonresponders were in the same category as the responders’ anticontrol hypertensives.
Adrenergic vasoconstriction as a cause of inadequate hypotensive response to beta-adrenergic blockade.
W H Birkenhäger and P W DeLeeuw

Hypertension. 1983;5:III31
doi: 10.1161/01.HYP.5.5_Pt_2.III31

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/5/5_Pt_2/III31