NEARLY 20 years since the observation by Prichard and Gillam1 that beta-blockers lower blood pressure, the mechanism(s) for this drug-induced reduction in blood pressure still remain uncertain. This is apparent from the diversity of hypotheses still under consideration.2-5 Perhaps the only point of agreement is that more than one mechanism must be invoked to explain the blood-pressure-lowering action of these drugs. Since the reduction in mean arterial pressure (MAP) produced by these beta-blocking agents is only about 10–20 mm Hg, fractionating this effect among several causal mechanisms poses formidable experimental problems.

The most puzzling feature of the antihypertensive response to beta-blockers is the latency of several hours required before MAP falls. Even if these drugs are given intravenously in doses that produce high-level blockade of cardiac as well as renal juxtaglomerular apparatus (JGA) beta-receptors, the fall in blood pressure is delayed.6 Blockade of beta-receptors at these sites produces an immediate fall in cardiac output (CO) and a decrease in the activity of the renin-angiotensin system. Clearly these effects, either alone or together, are not sufficient to initiate the fall in blood pressure. This is because of a systemic vasoconstrictor response, that is, an elevation of total peripheral resistance (TPR) that accompanies the fall in CO and appears to be evoked through reflex mechanisms.7 The fall in blood pressure that eventually occurs is coincident with the attenuation or abolition of this constrictor response.8-10 As demonstrated by studies using a variety of beta-antagonists, the major determinant of the antihypertensive response to the chronic administration of these agents is a reduction in CO.8-10

Hypotheses most favored to explain the initial delay in the fall of MAP include blockade of beta-receptors at sites additional to the heart and JGA: for example, in the central nervous system (CNS); at presynaptic sites of the sympathetic constrictor nerve terminals; and sites on arterial baroreceptors.2-4,5 It has been postulated that beta-blockade at one or more of these locations is responsible for the diminution of the early vasoconstrictor response. This then allows the effects of cardiac beta-blockade — or in the case of high renin patients, blockade of JGA receptors — to be manifested. Although there is some support for each of these hypotheses, much controversy still exists. Certainly none has been generally accepted as an explanation for the initial fall in MAP.

In his recent review, Lewis7 referred to the possible role of autoregulatory mechanisms in the antihypertensive action of beta-blockers. He did not press these claims of autoregulation as compared to other hypotheses. But Simon et al.11 have been recent advocates of this theory, and the latest supporters are Colfer et al.12 in this issue of Hypertension. Using mainly a noninvasive method, Colfer et al.12 measured CO in patients more frequently than in previous investigations in humans. The first part of their study was performed over 2 days after hospitalization. The patients remained mobile during this time. Baseline measurements were obtained before treatment and
during the first 30 hours after medication with 1-timolol. The second part of the study was performed as an outpatient investigation with measurements made after an overnight fast at 3 and 6 weeks of beta-blockade.

The CO fell rapidly, whereas a significant reduction in MAP was observed at 3 hours only and reached its nadir at 8–10 hours. Surprisingly, at this latter time CO had now risen to a level higher than the pretreatment baseline value. Thus, the early fall in MAP was due entirely to a reduction in TPR. In contrast, with chronic therapy the fall in MAP resulted from a reduction in both CO and TPR.

On the basis of these hemodynamic changes, the initial reduction in blood pressure has been interpreted to be due to peripheral vasodilation on the basis of an autoregulatory mechanism. This vasodilatory response together with cardiac beta-blockade is considered to account for the long-term reduction in blood pressure. It is postulated that the initial lowering of CO produces tissue underperfusion, which sets in train an autoregulatory vasodilator response. In turn, this contributes to the abolition or attenuation of the reflex elevation of TPR. This vasodilator response, according to this hypothesis, is considered important in the initiation and maintenance of the hypotensive response.

Role of Autoregulation

In its common usage, autoregulation of blood flow refers to the many relatively rapidly acting local regulatory mechanisms controlling resistance vessel tone in the different vascular beds. Another usage, so-called long-term autoregulation, refers to more chronic adaptations in blood flow that have been invoked to explain the hemodynamic patterns associated with the development of hypertension. Because of the slow time course of long-term autoregulation, Lewis considered that this mechanism could explain the long delay before the initial fall in MAP with beta-blockers.

Autoregulation, in its regular usage, includes all local regulatory mechanisms that help to maintain the constancy of regional blood flow, despite changes in perfusion pressure and those mechanisms that alter blood flow during changes in metabolic activity. The local regulators of vascular muscle tone include physical factors (such as transmural pressure, osmolality, and temperature) and chemical stimuli (such as changes in pH, oxygen and carbon dioxide tension, metabolites, and local hormones). Changes in vascular tone mediated by these local regulators occur rapidly, over seconds or minutes, but not over hours or days. Thus, these regulators are of great importance in the moment-to-moment control of blood flow in the intact organism. Indeed, under the closed-loop conditions normally operative in the intact organism, a circulatory response to a disturbance or drug can be considered as the sum of evoked neural plus hormonal plus local effects. These local regulators do not appear to have a long memory for any particular level of absolute blood flow or metabolism. Moreover, like the CNS control systems that regulate the circulation, the local systems regulating the blood flow of different organ beds operate as variable-reference servocontrol systems, and not as though they had a fixed setpoint, as in the case of a simple thermostat. For example, in the cerebral circulation, the blood flow level that is maintained over a given range of transmural pressures varies in proportion to the carbon dioxide tension.

It is doubtful whether any of these rapidly acting normal autoregulatory mechanisms is capable of explaining the slow onset of the initial hypotensive response to beta-blockers. The reduction in CO will induce tissue hypoperfusion, but this will quickly be countered by local vasodilator effects. The rapidity of the response can be demonstrated under open-loop conditions of autonomic blockade. With an acute reduction in CO, as occurs when the Valsalva maneuver is undertaken during autonomic blockade, peripheral vasodilatation occurs within 30 seconds and its magnitude is proportional to the reduction in CO. In the intact organism these rapidly occurring local effects will be present during the early phase of beta-blockade and will oppose the neurohumorally mediated increases in vascular tone. Thus, the elevated TPR at this time will already include a component due to the local effects.

What about long-term autoregulation? This concept was first introduced by Borst and Borst de Geus and by Ledingham and Pelling and has since received strong support from Guyton and co-workers. It purports to explain how the high CO pattern of early hypertension is transformed into a high TPR pattern when hypertension is fully
established. The mechanism envisaged is that the initial elevation of MAP occurs via an elevation in CO. This increase in CO results in tissue overperfusion and the rise in MAP triggers a myogenic response which, over a period of days and weeks, leads to a compensatory rise in TPR. This increase in TPR is associated with a restoration of CO to a level similar to the initial value. Even under experimental conditions considered to provide maximal support for this hypothesis, 24 the time course is so divergent from that of "normal" autoregulation that a different process must be involved. In my opinion, current evidence does not support the existence of a special type of long-term autoregulation to explain the hemodynamic changes during the development of hypertension. 17 24

An alternative hypothesis has recently been formulated to explain the changing hemodynamic patterns that occur with the development of hypertension. This theory takes into account the changing hemodynamic amplifier capacities that occur during the course of hypertrophy of the musculature of the heart and resistance vessels. 24 25 Nevertheless, is there experimental support for the converse type of long-term autoregulation resulting from a reduction of CO due to medication with beta-blockers? This type of autoregulation should produce peripheral vasodilatation of gradual onset leading to an attenuation and even to reversal of the early vasoconstrictor response. The theory predicts considerable restoration of the initially low CO toward the baseline value. Subsequently, with prolonged beta-blockade only part of the hypotensive response should be due to a reduction in CO, whereas the remainder should be due to a reduction in TPR.

In the study of Colfer et al., 12 the findings associated with the initial fall in MAP during the in-hospital phase of the investigation appear, at first sight, to be consistent with the autoregulatory hypothesis. However, it is odd that the initial fall in MAP is due to such marked reduction in TPR that CO actually increases to a level above the pretreatment baseline value. Implicit in the theory of long-term autoregulation is a "memory" for the pretreatment blood flow at a given level of metabolism. On this basis, one might expect partial restoration of the low CO. Overcorrection, however, as observed by Colfer et al., 12 should not occur.

In addition to these physiological considerations, a major problem in interpreting the study by Colfer et al., 12 is its experimental design. One cannot be certain which hemodynamic changes associated with the early fall in MAP were due to timolol and which were due to changes in the diurnal pattern of activity of their subjects. Beta-blockers do not markedly alter body oxygen consumption. Thus, the observed parallel increases in CO and oxygen consumption suggest that the rise in the former was metabolically determined. Indeed, such a possibility is raised by the authors in their discussion. Given these problems with the interpretation of the hemodynamic changes, their explanation that is based on long-term autoregulation remains questionable.

To obviate these problems, it is essential that the design of the study permit background effects to be distinguished from those produced by the drug. The correlation analysis between the early and later hemodynamic events employed by the authors does not compensate for the absence of an appropriate design. Only by having an additional placebo study under circumstances similar to those occurring during the first part of the timolol investigation would it be possible to evaluate which effects are drug-related.

Are there other studies relevant to the long-term autoregulation theory and the antihypertensive action of beta-blockers? Simon et al. 11 observed partial restoration of CO over the first 48 hours after commencing atenolol. During this period, TPR fell to the original baseline level following an initial vasoconstrictor response. However, the restoration of CO was only transient, and it fell again to a level close to the original nadir 4 days after the start of medication. At that time, TPR was close to the baseline value. These results do not support the long-term autoregulation hypothesis, since the reduction in CO after several days should have been less marked and the fall in TPR should have been greater. In a study performed in conscious rabbits, the animals were infused over a 3-hour period with either three doses of propranolol or with dextrose (control) on four separate experimental days. Although CO fell to a similar extent with all three doses of beta-blocker, MAP was reduced significantly only by the two highest doses. 26 This implies that the dose of the beta-blocker, and not just the fall in CO, is an important determinant of the hypotensive response to these drugs.
During the chronic phase of their study, Colfer et al.12 found that the reduction in MAP was caused by a fall in both CO and TPR. Although this hemodynamic pattern would be anticipated on the basis of long-term autoregulation, there are doubts again about the interpretation of these findings. Baseline measurements were performed only in the first part of the study and then after breakfast following a 1-day stay in the hospital. By contrast, the hemodynamic measurements made after 3 and 6 weeks were performed under outpatient conditions after an overnight fast. It is difficult to know whether the chronic changes in CO can be appropriately referred to a baseline value obtained under different conditions. This is of paramount importance in assessing the data. The problem could have been avoided by separating the first and second phases of the investigation. Baseline measurements for the second part of the study could then have been obtained under the same conditions used to assess the effects of timolol.

Other investigators have reported different hemodynamic effects after prolonged medication with various beta-blockers.2.4.5.810 In most studies the fall in MAP could be entirely accounted for by the reduction in CO, whereas TPR was often somewhat raised or, at least, no lower than the control value. These findings are not in accord with the long-term autoregulation hypothesis. Only Franciosa and colleagues27 28 have found complete restoration of CO during chronic administration of timolol, in accordance with the theory. By contrast, in an extensive investigation Lund-Johansen and Ohm10 observed a reduction in CO and an elevation in TPR with timolol and many other beta-blockers. Control groups have not been used in any of the chronic studies, although some investigators have performed repeated long-term measurements in untreated hypertensive patients.29 In the absence of a control group, standardizing conditions at the time of hemodynamic measurements is of paramount importance.

How Do Beta-Blockers Lower Blood Pressure?

We still do not know the mechanisms that initiate the fall in MAP during administration of beta-blocking drugs. The most likely explanation is that blockade of beta-receptors involves sites additional to the heart in the attenuation or abolition of the early rise in TPR.4.5 There is now little doubt that reduction in CO through cardiac beta-receptor blockade is the major hemodynamic cause of the chronic reduction in blood pressure. There is no evidence that a special type of “long-term” autoregulation is involved in the hypotensive response. Current evidence favors the view that the fall in blood pressure is entirely due to the specific beta-adrenergic blocking properties of these drugs.

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