Assessment of the Contributions of Autoregulatory Mechanisms to the Antihypertensive Actions of Beta-Adrenergic Therapy

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The study by Colfer et al.1 in this issue of Hypertension again raises the issue of whether whole-body autoregulation plays a role in determining overall changes in total peripheral resistance (TPR) during the development or reversal of hypertension. This hypothesis remains controversial because the local tissue mechanisms responsible for either the functional alterations in smooth muscle vascular tone or the long-term restructuring of vascular beds seen in hypertension are poorly understood. This does not mean, however, that the hypothesis is not based upon a reasonable extrapolation of solid biological data.

Rapid local control, or "autoregulation" of tissue blood flow, has been characterized in nearly every organ system of the body. That is, either over- or underperfusion of an isolated tissue bed, brought about by raising or lowering the regional blood perfusion pressure, results in local adjustments of vascular resistance which return blood flow toward normal levels. Over the past 20 years, physiologists interested in the microcirculation have been preoccupied by these events. We have used the term long-term autoregulation, as reviewed elsewhere, to describe the observed vascular responses that occur over days and months.2,3

The question is not whether local regulation of vascular resistance occurs. Rather, are such mechanisms of sufficient strength to effect long-term changes of TPR in the intact organism? And, how do these mechanisms operate? The challenge has been, and remains, to develop techniques that can selectively determine the relative importance of various local factors that influence both acute and long-term control of regional blood flow.

It is easy to play the role of devil's advocate in this issue, since so many fundamental mechanisms regulating tissue blood flow remain a mystery. So far, the carefully controlled studies of regional and/or whole-body autoregulation have all examined responses within time frames that are very brief in nature (1 minute to 3 hours). Whether these responses persist over prolonged periods, such as days and months, remains to be determined. It is also not known whether the acute autoregulatory responses are replaced, overridden, or altered in sensitivity by long-term structural changes.

Physiologists interested in the microcirculation have demonstrated that considerable regional vascular heterogeneity exists. This raises the question of which vascular beds should best be studied. Recent data by Liard4 indicate that, in response to chronic blood volume expansion, nearly all body organs and tissues constrict very rapidly to normalize blood flow and then sustain these increases in vascular resistance for prolonged periods. An exception to this was skeletal muscle, which remained overperfused for several days before it gradually increased its resistance to flow. Liard's
studies suggest that much of the long-term whole-body autoregulation may be attributed mainly to events that occur in the skeletal muscle bed.

The role of autoregulation in the control of vascular resistance has often been disregarded because of the difficulty in experimentally controlling or measuring the many variables that could modify or mask the local events. A number of conditions must be met before concluding that whole-body autoregulation is or is not determining observed changes in peripheral resistance. Certainly, the heart must be capable of adequately increasing its cardiac output (CO) when subjected to an increased load, since clearly even in cardiac failure a large overexpansion of total blood volume will not increase CO or TPR by autoregulatory mechanisms. Importantly, the metabolic needs of the tissue must remain unchanged, or observed changes in CO may merely reflect the normal needs of the tissue rather than a response to over- or underperfusion. Systems responsible for the delivery of tissue oxygen (O₂) and other nutrients must also be normal. Does the factor that initiated the change of blood volume or CO also alter capillary filtration of fluids, or does it dilute plasma protein concentrations? This must also be ascertained. Clearly, many events can influence regional blood flow and obscure what at first seems to be a violation of the autoregulatory hypothesis.

Failure to consider the influence of the initiating stimulus on chronic renal function may complicate the interpretation of long-term autoregulatory responses. For example, in the case of hypertension, unless renal excretory function were reduced along with, or as a consequence of, the elevation of mean arterial pressure (MAP), sodium and water would presumably be lost as a result of the excess renal perfusion pressure (if one accepts the phenomenon of pressure diuresis), and blood volume would consequently be reduced. The autoregulatory hypothesis predicts that TPR and MAP would return to normal in this event. Conversely, in the case of an antihypertensive agent such as the beta-adrenergic inhibitor used in the present study, unless renal excretory function were enhanced, the lowered renal arterial perfusion pressure would result in the retention of excess volume. This would trigger autoregulatory events to maintain an elevated TPR and MAP.

These and other complexities related to the application of the autoregulation theory have been discussed elsewhere. Unfortunately, they have often been overlooked both by individuals attempting to apply the theory of autoregulation and by those opposing the theory. The article by Colfer et al. is a case in point. The authors have determined the sequential hemodynamic and endocrine events following administration of a non-selective beta-adrenoreceptor blocking agent. Sequential hemodynamic studies of this sort can provide useful insights regarding the long-term mechanisms involved in the regulation of vascular resistance. But, as seen by the request for editorial comments regarding this study, interpretation of the observed hemodynamic changes can be difficult.

The results in this study were viewed within the context of three time frames: the acute (0.5 – 1 hour), early (5 – 24 hour), and late (6 week) phases. The acute phase was associated with an immediate fall of CO and MAP and a rise of TPR. The mechanisms responsible for this acute phase were not studied. Nevertheless, the authors used this initiating event to hypothesize that the initial 10% fall in CO resulted in tissue underperfusion with a resulting autoregulatory decrease of TPR over the next 24 hours. The major evidence for this was that ‘‘the magnitude of the initial reduction in blood pressure is significantly correlated to the magnitude of the immediate reduction in CO and to the immediate rise in A-V O₂ difference that preceded the blood pressure reduction.’’

The acute reduction of CO, if this is all that had occurred, could have initiated an immediate peripheral vasodilation via an autoregulatory response. But, something would have had to sustain this response. In these studies, at the time blood pressure had begun to fall toward normal levels, CO was rising to nearly 20% above its control value. This would not only have eliminated the signal for autoregulatory vasodilation, but also, according to our understanding of autoregulation, would have caused local vasoconstriction. To attribute the decrease in TPR in the early (5 – 24 hour) phase and the late phase to autoregulation, a sustained tissue flow deficit (albeit slight) would have had to have been induced over the period of time studied. Furthermore, since the elevation of CO seen at Hours 5–8 was twice as great as the acute initial fall of CO, the reduction in TPR observed during the latter half of the first day following beta-blockade is not consistent with the autoregulatory hypothesis.
It is meaningful that tissue $O_2$ utilization was increased during this early phase following beta-blockade. Although the reason for this apparent increase in tissue metabolic rate is unclear, autoregulatory mechanisms would be expected to decrease TPR and raise CO during this period, as was observed. Such a response, though, should not result in antihypertensive actions since the decrease in resistance would be offset by an increase in CO. The increased $O_2$ utilization with beta-blockade is in itself rather puzzling, however. Animal studies have indicated that $O_2$ utilization tends to decrease following beta-blockade, which would tend to lower CO. The increase in $O_2$ utilization and CO observed in the present study may not be related to the drug treatment. As acknowledged by the authors, postprandial increases in metabolic rate have been associated with elevations of CO, together with a small decrease of MAP in both normal and hypertensive subjects. The extent to which the changes in TPR were related to feeding was not ascertained. Beta-blockade undoubtedly could initiate many complex changes throughout the body, including metabolic alterations and changes within the central nervous system. Such possibilities were not and could not be fully explored in the present study. Studies of normal control subjects could have helped resolve some of these issues.

In summary, it is difficult to deny the existence and the potential importance of acute local regulation of tissue blood flow. At our present level of understanding, however, it is prudent not to extrapolate the theory of autoregulation too far beyond our understanding of these mechanisms based on short-term studies. It is difficult, for example, even to prove whether autoregulatory mechanisms are indeed responsible for the gradually occurring increases of TPR observed in volume-expanded forms of hypertension. Nevertheless, such a theory readily explains the hemodynamic changes observed in these conditions. It is considerably more difficult to make a strong case for a role of autoregulation in the antihypertensive action of beta-blockers on the basis of the observations of the present study.

References


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