Connecting Links to Solve Discrepancies of Actions of Pressor Drugs

About five years ago, the cardiovascular effects of some commonly used pressor amines were reviewed in the Journal.1 The review article ended as follows: "It is important to emphasize the fact that the available information on the mechanism of cardiovascular effects of pressor agents has been derived from two types of preparations: anesthetized animals and unanesthetized human subjects. The connecting link of studies on anesthetized subjects would be a welcome addition that might help resolve some of the existing discrepancies.

It is pleasant to note that elsewhere in this issue, one "connecting link" is offered to resolve the discrepancies regarding the cardiovascular effects of one pressor drug, mephenetermine. Li, Shimosato and Etsten2 report the hemodynamic effects of mephenetermine in human subjects under spinal anesthesia. The three conclusions and the significance of each are as follows:

1. The hemodynamic responses following the administration of mephenetermine to hypertensive subjects under spinal anesthesia consist largely of a combined increase in cardiac output and total peripheral vascular resistance. The increase in cardiac output is to be expected because of the known positive chronotropic and inotropic actions of mephenetermine. The simultaneous increase in total peripheral vascular resistance is surprising because, heretofore, mephenetermine has been shown to be free of any local vasoconstrictor action when tested in various preparations, with the exception of two abstracts describing a local vasoconstrictor action.3-4 Two possibilities remain to explain the increase in peripheral vascular resistance, other than a local vasoconstrictor action. First, is the release of circulating catecholamines when mephenetermine is administered intravenously, a possibility demonstrated in the isolated heart perhaps readily tested in the patient by measurements of blood levels. Secondly, is a stimulation of the medullary vasoconstrictor centers by mephenetermine, a likely explanation requiring direct proof.

2. The simultaneous occurrence of increase in blood pressure, cardiac output and peripheral resistance reported to occur following the administration of mephenetermine in subjects under spinal anesthesia5 has been previously described for norepinephrine in human subjects with either atropine or ganglionic blocking drugs.6 A hemodynamic change in which all three measurements simultaneously increase cannot be elicited by any pressor drug if the autonomic nervous system is not blocked. For example, mephenetermine in normotensive individuals, initially increases output and later increases peripheral vascular

References
resistance but not both simultaneously. Noradrenaline, in the absence of autonomic blockade, causes an increase in vascular resistance but a decrease in cardiac output. As long as the autonomic nervous system is intact the baroreceptor reflexes can automatically compensate for a primary increase in output or peripheral resistance by a secondary decrease of the other.

(3) The hemodynamic response of the human subject under spinal anesthesia to mephenesin depends upon the initial circulatory status prior to the administration of the drug. When the initial cardiac output values are low, there is a significant increase of the cardiac output following the administration of mephenesin, but when the initial output values are high, the changes in output are minimal. Li and his collaborators emphasized that such a pattern of response obeys the law of initial values which states that "the intensity and direction of the response of any function of the organism to a stimulus depends to a great extent upon the initial value (level) of that function at the moment of the stimulus." The observations supporting the law would have been more convincing if they were based on multiple observations in the same individual, each one with two or more hypotensive levels of blood pressure and cardiac output, rather than single observations from several individuals. Specifically, mephenesin could have been tested under two levels of spinal anesthesia and hypotension in the same individual. In the anesthetized dog, the increase in cardiac output during anoxia was compared at various levels of cardiac output. When cardiac output was intentionally reduced by bleeding, the percentage increase during anoxia was about two times greater than that encountered in the same animal prior to bleeding. These observations, derived from each of a group of dogs, support the law of initial values. On the other hand, not all cardiovascular responses follow such a pattern. For instance, when the common carotids are temporarily occluded, the pressor response is less intense if the control level of blood pressure is reduced. The law of initial values will require direct proof in each situation.

The above comments should not detract from the scientific value of the article under consideration. The most significant feature of the article is the availability for the first time of a complete study of the hemodynamic effects of a drug directly on hypotensive patients. The results have served the purposes of identifying which of the known actions of the drug are of primary importance clinically and also of raising additional questions which require further studies.

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