

## *Hazards of General Anesthesia in the Reserpinized Patient*

Alan Jay Ominsky, M.D.,\* and Harry Wollman, M.D.†

THE POTENTIAL DANGERS of general anesthesia in reserpinized patients were first reported in 1955.<sup>1</sup> Additional reports in the following six years<sup>2, 3, 4, 5</sup> suggested that more than half of the patients being treated for hypertension with reserpine developed hypotension and bradycardia during general anesthesia. In addition, occasional electrocardiographic changes suggestive of ischemia occurred in some during anesthesia. Pressors were said not to be uniformly effective in restoring normal circulatory patterns, and anticholinergic drugs were recommended by some. On the basis of these findings a ten-day to two-week pause in reserpine therapy prior to elective surgery was advocated.

On these studies, and a few individual case reports (none recording permanent postanesthetic complications) rested the case for suspending antihypertensive reserpine therapy preoperatively. The value of this information was difficult to assess since control groups were lacking. The incidence of hypotension in hypertensives might have been just as high if reserpine had been discontinued prior to anesthesia. Furthermore, hypertensive patients may have a wide range of preoperative blood pressures, and this information was not supplied. Moreover, the real measure of circulatory competence is not the arterial blood pressure but the adequacy of tissue blood flow. The only evidence offered in the above reports

that any tissue suffered compromised blood flow was the occasional transient occurrence of S-T segment depression; this must be considered nonspecific with regard to both etiology and clinical significance. Finally, discontinuing an antihypertensive regimen that has proved therapeutically effective is not without danger. Stoppage of the drug may permit the return of hypertension with all its complications.

Since emergency surgery in reserpinized patients was unavoidable, Munson and Jenicek in 1962 were able to compare the results in patients undergoing elective surgery whose reserpine therapy had been discontinued prior to anesthesia with results in emergency cases in which reserpine had not been discontinued.<sup>6</sup> No significant difference in the incidences of intraoperative hypotension in the two groups was noted. In the group whose therapy had been discontinued, 7 of 16 experienced intraoperative hypotension. When a third (non-emergency) group where reserpine was electively continued until surgery was compared with the patients in whom reserpine was discontinued two weeks prior to surgery there was no significantly increased incidence of intraoperative hypotension. These investigators found that when hypotension did occur in their patients, on or off reserpine, it was responsive to such measures as reduction in anesthetic concentration, administration of intravenous fluids, or the reflex effect of surgical stimulation.

In 1963, Morrow and Morrow studied the incidence of hypotension in five *nonhypertensive* patients, aged 16-35 years, undergoing cardiac surgery. The patients were given 0.5 mg or more of reserpine for 38 to 68 days up to the day of operation.<sup>7</sup> None of these patients became hypotensive during anesthesia.

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† Associate Professor of Anesthesia.

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Thus, the high incidence of hypotension during anesthesia in hypertensive patients appeared to be due to their disease rather than to reserpine therapy. This fact was demonstrated in a well-controlled study in 1964 which showed significant hypotension in 18 of 100 hypertensive patients anesthetized while taking reserpine, and in 30 of 100 matched patients who were hypertensive, but were not undergoing reserpine therapy.<sup>8</sup> Furthermore, the hypotension was usually associated with blood loss, rapid anesthetic induction, surgical manipulation, positional changes, or excessive anesthesia. Ephedrine proved to be an effective pressor drug in countering the hypotension.

The theoretical grounds for fearing bradycardia and hypotension in the reserpinized patient undergoing anesthesia and surgery center on depletion of chemical transmitter stores (norepinephrine) at the postganglionic nerve endings of the sympathetic nervous system.<sup>9</sup> Compensation for the cardiac depressant effects of anesthetic drugs is dependent at least in part on responses of the sympathetic nervous system.<sup>10</sup> Furthermore, sympathoadrenal responses form an important defense against the circulatory alterations induced by postural changes, positive-pressure ventilation, and blood loss.<sup>11, 12, 13</sup> In addition, cardiac slowing due to digitalis and reserpine may be additive. In fact, one might wonder why reserpine does not cause bradycardia and hypotension more frequently during anesthesia and surgery. This may be explained in several ways. Probably catecholamines are still being liberated in effective concentrations at the receptor sites of the myocardium and peripheral vessels, although the "spillover," and hence the measurable plasma concentrations, may be lower than usual.<sup>14, 15</sup> Indeed, less than the normal amount of catecholamines might be required since reserpine pretreatment produces increased sensitivity to catecholamines.<sup>16</sup> Furthermore, some autoregulatory mechanisms independent of the sympathetic nervous system probably persist in the vascular bed following catecholamine depletion. Alper, Flacke, and Krayer pointed out that reserpine, unlike the ganglionic blocking agents, does not cause significant postural hypotension when used in antihypertensive dosages up to 0.45 mg per

day for 13 weeks, or when these responses are studied four hours after a single intramuscular dose of 2.5 mg.<sup>9</sup> In addition, it has been shown that cardiac output increases in the usual manner following hypoxemia and exercise in reserpinized patients,<sup>17</sup> and reserpine pretreatment in hypertensive patients does not prevent the pressor response to stimuli such as immersion of the hands in ice water.<sup>18</sup>

Tests of the adequacy of circulatory homeostasis have been devised utilizing drugs such as ephedrine or tyramine which depend partly on catecholamine release from sympathetic nerve endings for their pressor effect. Theoretically, compromise of sympathetic integrity might diminish the effectiveness of such indirectly-acting agents. However, virtually all pressors have some direct vasomotor action independent of catecholamine release, and this direct action increases in the presence of sympathetic denervation.<sup>16</sup> Further, standard dose of pressor drug is apt to produce widely varying responses when administered to different representatives of the "normal" population. Thus, such tests have generally failed to predict whether a patient will become hypotensive during anesthesia.<sup>19, 20, 21</sup> Other tests attempt to utilize the response of the circulation to tilting or to the Valsalva maneuver as an index of homeostatic integrity. Again, the wide range of "normal" responses and the many unpredictable stresses during anesthesia have prevented these tests from accurately prognosticating who may be anesthetized safely.<sup>22</sup>

If hypotension does occur during anesthesia, routine measures such as reduction in anesthetic concentration, modification of position, correction of ventilatory abnormalities, appropriate use of blood or intravenous fluids, or initiation of surgical stimulation should be considered first. If a vasopressor drug is required in a reserpinized patient, one with direct action (methoxamine, phenylephrine, metaraminol, or norepinephrine) should probably be chosen in preference to one with mixed actions (ephedrine) or with mainly indirect actions (mephentermine). However, at most all the pressor amines have some element of mixed action, and if used in sufficient doses could be effective even if transmitter stores were greatly depleted.<sup>9, 16</sup>

A special problem is presented by patients given massive doses of reserpine for psychiatric therapy (5 to 10 mg per day in the adult) who then require general anesthesia for electroshock therapy. In these individuals catecholamine depletion and sympathetic blockade are virtually complete and the hazards may be greater. There are case reports of profound irreversible hypotension and death<sup>1, 2, 23</sup>; but the difficulties might have been related to the autonomic effects of electroshock, rather than to anesthesia. Still, on the basis of the available fragmentary data, it may be more hazardous to administer general anesthesia to these patients. Since the use of large doses of rauwolfia alkaloids in psychiatry is now quite rare,<sup>23</sup> there are few such cases from which we can gather useful information.

As with reserpine, the theoretical arguments for continuing or suspending antihypertensive therapy with alpha-methyl dopa and guanethidine before elective surgery are inconclusive. Both of these drugs can deplete catecholamines and produce the equivalent of adrenergic blockade. Though homeostatic reflexes are not totally abolished, these drugs are more apt to cause postural hypotension and to interfere with the cold pressor response, thus increasing the potential danger during anesthesia.<sup>24, 25, 26</sup> However they are also likely to be used in the treatment of more serious hypertension where the hazards of suspending therapy would be proportionately greater. For lack of adequate studies, at the present time, the advisability of suspending therapy prior to the time of surgery remains unknown for both alpha-methyl dopa and guanethidine. Perhaps the most important protection to the patient is the anesthetist's knowledge of the potential hazards and effective methods of treatment. While one does not know how to evaluate the clinical impression that less general anesthesia is required by the reserpined patient,<sup>9</sup> there is objective evidence that alpha-methyl dopa can reduce the amount of anesthetic required.<sup>27</sup>

### Summary

A review of the literature suggests that the hypertensive patient offers a higher risk of intraoperative hypotension and other complications than the normotensive patient. There is

no evidence that discontinuing reserpine therapy in such patients one to two weeks preoperatively diminishes the likelihood of hypotension or other complications during anesthesia. Anesthesia for electroshock therapy in patients receiving massive doses of reserpine for psychiatric reasons (5 to 10 mg per day) may present an increased hazard, but data on this point are fragmentary. Preoperative use of alpha-methyl dopa or guanethidine may affect the anesthetic course, but the discontinuance of an effective therapeutic regime in a hypertensive patient may result in more serious sequelae.

If hypotension does occur during surgery in reserpined patients, it is usually related to blood loss, depth of anesthesia, speed of induction, surgical manipulation, or positional change; and it should respond to appropriate therapy. Should a pressor drug be required, one with a direct action is preferable, but indirectly-acting pressors should be effective in sufficient dose. Preoperative tests such as the ephedrine challenge have not proved useful in prognosticating intraoperative difficulties.

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### Erratum

In the second line of the abstract of the article, "Tachyphylaxis to Decamethonium and Reversibility of the Block by Anticholinesterase Drugs," by Felix G. Freund (*Anesthesiology* 30: 7, 1969), the dose should be 0.05 mg/kg, not 0.5 mg/kg.