Hormonal and Hemodynamic Changes Induced by Pentolinium and Propranolol during Surgical Correction of Scoliosis

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Deliberate hypotension has had variable success in decreasing blood losses and facilitating extensive surgical procedures. In this study, hemodynamic variables, catecholamines, plasma renin activity, and angiotensin II levels were studied in 11 patients undergoing operative correction of idiopathic scoliosis. Deliberate hypotension with mean arterial blood pressures ranging from 55 to 42 torr was provided with the ganglionic blocking agent, pentolinium tartrate, supplemented by beta blockade with propranolol during morphine-nitrous oxide anesthesia. Stroke volume index, systemic vascular resistance, and left ventricular stroke work index decreased 16, 19, and 40 per cent, respectively, with blood pressure reduction. Following the return to normal blood pressure, stroke volume index increased to a value 28 per cent greater than control, while systemic vascular resistance remained decreased. At this time left ventricular stroke work index increased slightly, but the increase was not statistically significant compared with control. The epinephrine level had risen from 59 to 270 pg/ml an hour after hypotension, probably secondary to infiltration of the skin prior to the surgical procedure. It had decreased to control levels by the end of the procedure. Norepinephrine and dopamine concentrations and plasma renin activity were unchanged. The angiotensin II level was significantly decreased, from 60 to 40 pg/ml, during deliberate hypotension. Blood loss correlated with left ventricular stroke work index, while changes in systemic vascular resistance and heart rate correlated well with changes in angiotensin II and plasma renin activity, respectively. The ability of ganglionic blockade and propranolol to inhibit the increases in catecholamines and angiotensin II during morphine-nitrous oxide anesthesia, hypotension, and surgical intervention may be of considerable importance. (Key words: Anesthesia, orthopedic. Anesthetic techniques: hypotension, induced. Hormones: adrenal. Polypeptides: renin–angiotensin. Sympathetic nervous system: catecholamines; ganglionic blocking agents, pentolinium; sympatholytic agents, propranolol.)

Induced hypotension is well recognized as a useful adjunct to anesthesia in a wide variety of surgical procedures. It decreases intraoperative blood loss and provides a dry surgical field. There are, however, occasional failures to provide the desired response in spite of a satisfactory decrease in blood pressure. Elevation of cardiac output has been suggested as a potential reason for such failures. Since the sympathetic nervous system and the renin–angiotensin system are important hemodynamic regulators, it is possible that increases in their levels of activity may account for the intermittent failures of hypotension therapy to reduce blood loss and/or to maintain vital organ function.

The present study documents the concurrent changes in hemodynamic responses, plasma renin activity, and concentrations of angiotensin II and catecholamines during hypotension induced by ganglionic blockade and facilitated by beta-receptor blockade in patients undergoing anesthesia for correction of scoliosis. Clarification of these interactions should identify preferable techniques, permit improved clinical control, and increase the success and safety of deliberate hypotension.

Materials and Methods

Eleven patients (two male and nine female) undergoing general anesthesia for correction of idiopathic scoliosis were studied. Patients ranged in age from 12 to 17 years, weighed 36–61 kg, and were free of cardiovascular, metabolic, or respiratory disease. The plan for induced hypotension and the investigative interventions were discussed and informed consent obtained preoperatively from both the patient and his or her parents. The experimental protocol was approved by the Committee to Review Grants for Clinical Research and Investigation Involving Human Beings of the University of Michigan. Patients were admitted three or four days preoperatively and maintained on a regular diet containing 6–10 g of sodium daily.

Patients were premedicated with morphine, 0.2 mg/kg, im, and diazepam, 0.2 mg/kg, p.o. Anesthesia was induced with diazepam, 0.25 mg/kg, iv, and sodium thiopental, 2 mg/kg, iv. Pancuronium bromide, 0.1 mg/kg, was used to facilitate tracheal intubation, and
anesthesia was maintained with morphine (0.5 mg/kg, total dose excluding premedication), and nitrous oxide (4 l/min) and oxygen (2 l/min). Morphine was given intravenously in 2-mg increments such that the total dose was administered prior to incision.

Following induction of anesthesia, a 20-gauge radial-artery catheter and a 7-Fr Swan-Ganz catheter with thermodilution output capability were placed. The patient was then turned prone on a Relton frame and positioned carefully for the operation so as to avoid vertebral venous congestion. After the initial collection of blood samples and measurement of hemodynamic variables, pentolinium tartrate was administered in 2-mg increments over a 15-20-min period in an attempt to decrease the systolic blood pressure to approximately 80 torr. The skin and intraspinal ligaments were infiltrated with 20 ml of a 1/200,000 epinephrine solution, and the surgical procedure was begun. Additional pentolinium was given after incision, to a total of 0.3–0.4 mg/kg as needed to cause a decrease in bleeding and provide an adequate surgical field, i.e., one in which bleeding did not interfere with surgical dissection. Propranolol in 0.25-mg increments was given to a total dose of 0.08–0.1 mg/kg such that heart rate was controlled at the postinduction rate. All patients received some propranolol. Data from two patients were not included in those reported for the 11 patients studied, although the hemodynamic data other than initial systemic vascular resistance and blood pressure did not differ significantly from those for the rest of the patients in the series. In these two patients, despite very large doses of pentolinium (greater than 0.4 mg/kg) and signs of ganglionic blockade, i.e., dilated pupils, systemic vascular resistance remained high and arterial blood pressure decreased only slightly. A phentolamine drip was utilized in these two patients during the period of deliberate hypotension to provide a satisfactory decrease in arterial blood pressure and resistance.

Blood loss from the surgical procedure was determined by careful measurement of the contents of the suction container and the weight of the sponges. Irrigation volume was carefully monitored and subtracted from these values. This deficit was replaced by Ringer’s Injection®, 3 ml for each ml of blood lost. Packed erythrocytes were given to maintain a hematocrit of 30 per cent. In addition, intravascular plasma volume was determined by Evans blue dye dilution technique. This technique has been shown in our laboratory not to affect the hormonal response or hormonal assays used in this study. Blood volume was determined by using the equation:

\[
\text{Blood volume} = \frac{\text{plasma volume}}{1 - \text{hematocrit}}
\]

Blood volume was determined twice during the procedure, once during the control period prior to any hypotension or blood loss and again prior to “wake up” during satisfactory hypotension and after the period of major blood loss.

Following the completion of decortication of the vertebrae and placement of the Harrington rods, surgical stimulation was stopped and nitrous oxide discontinued. The patient was then asked to move his feet. This event did not necessitate reversal of the muscle relaxant or narcotic, and the patient was able to comply (“wake up”) with uncanny reproducibility within 3 min after administration of nitrous oxide was terminated. With demonstration of satisfactory neurologic function, namely movement of both feet on command, anesthesia was reinstalled by use of a small bolus of thiopental (0.5 mg/kg) supplemented by nitrous oxide. The blood pressure was returned to normal by transfusion of the expanded vascular space (secondary to ganglionic blockade) with Ringer’s solution and whole blood. Reversal of hypotension took approximately 15–30 min. The trachea was extubated in the operating room. Careful monitoring of pulmonary-artery wedge pressure was used postoperatively to aid in fluid administration during recovery from pentolinium as the intravascular space contracted.

Intraoperatively, the electrocardiogram (lead 2), systemic arterial blood pressure, pulmonary arterial pressure, urinary output from a Foley catheter, and a precordial Doppler probe (to detect air embolism) were monitored continuously. Pressures were measured by Hewlett-Packard® transducers and were recorded continuously on a Hewlett-Packard strip recorder. Every 30 min, or when intraoperative intervention warranted, cardiac output (as determined by thermodilution technique using an Electronics for Medicine® cardiac output computer) and central venous and pulmonary capillary wedge pressures were measured. Cardiac output determinations were performed in triplicate. Variation among the individual determinations was 5 per cent. The derived hemodynamic values (cardiac index, stroke volume index, systemic vascular resistance, and left ventricular stroke work index) were calculated from these measurements.

Arterial blood and mixed venous blood from the pulmonary artery were obtained for measurements of pH, PCO₂, P O₂, HCO₃⁻, hematocrit, and hemoglobin at the time of hemodynamic determinations. All blood gases were analyzed and standardized for body tem-
perature using a Radiometer® ABL-2 blood-gas
machine. Concomitant with hemodynamic determina-
tions and blood-gas measurements, mixed venous
blood samples were drawn from the pulmonary
artery for determination of plasma renin activity,
and angiotensin II, epinephrine, norepinephrine,
and dopamine concentrations, on three occasions:
first, following induction of anesthesia but prior to
morphine administration or induction of hypoten-
sion; second, 60 min after induction of deliberate
hypotension; finally, at the time blood pressure
was increased to prehypotensive levels 15–30 min after
“wake up.”

Angiotensin II was measured by radioimmunoassay
using an antibody previously characterized. Plasma
renin activity was determined by a radioimmunoas-
say from a commercially available kit. The radionu-
clid assay method of Peuler and Johnson was
used to determine plasma epinephrine, norepineph-
rine, and dopamine levels. Assay variability was
determined by measuring plasma renin activity, angio-
tensin II, epinephrine, norepinephrine, and dopa-
mine in aliquots from a single plasma pool in con-
secutive assay runs. The coefficients of variation were:
11.4 per cent for plasma renin (20 assays); 11.2 per
cent for angiotensin II (12 assays); 9.6, 8.0, and 30
per cent for norepinephrine, epinephrine, and dopa-
mine, respectively (8 assays). The intraassay variation
from 12 analyses of the same sample was always less
than interassay variability. Results of assays of known
standards were linear with concentrations within
the range of values studied. The assay limit of detec-
tion for the catecholamines and angiotensin was 5
pg/ml. All catecholamine concentrations were
tested with an internal standard in every sample.

The high coefficient of variation for dopamine is a
result of the low (close to the limit of detection) dopa-
mine levels in this study. All samples from any one
patient were analyzed in a single assay run for each
of the above assays.

Statistical analyses were performed using a com-
puterized system that provides a two-way analysis of
variance to test whether the measured and derived
variables had changed over time. Specific compar-
isons were made using the Student t test for paired
data. When appropriate, correlation between specific
variables was tested with a linear regression model.

Values were considered significant when \( P < 0.05 \). All data are expressed as means ± SEM.

### Results

During hypotension, arterial blood \( pH \) and cal-
culated base excess were within the normal range
and remained unchanged; however, the pulmonary
artery–mixed venous blood ratio \( P_{a} / P_{v} \) decreased signif-
ically from a mean of \( 44 ± 1 \) torr to a mean low of
34 ± .3 torr during hypotension. The values rose to
control levels again with restoration of blood pressure.
\( P_{a} / P_{v} \) was greater than 100 torr in all patients during
the entire procedure. \( P_{a} / P_{v} \) was 33 ± 2 torr and mixed
venous blood \( P_{v} \) was 35 ± 3 torr throughout the
procedure. Temperature decreased significantly from
a mean of 35.4 ± .3 to 34.5 ± .2°C. At no time during
the procedure was air embolism detected by the pre-
cordial Doppler probe. Urinary output was absent
during the period of hypotension and returned to
normal (1 ml/kg/h) following restoration of arterial
blood pressure. Postoperatively, urinary output was
satisfactory.

### Hemodynamics (Table 1)

An hour after induction of satisfactory hypotension,
as judged by an acceptably dry surgical field, mean
arterial pressure had decreased from 74 ± 2 to 51
± 2 torr. The initial response to ganglionic blockade
in these patients was a variable increase in heart rate.
Propranolol was given intravenously in 0.25-mg
increments to control this increase in heart rate.

An hour after attainment of a satisfactory surgical
field, the heart rate was not significantly different
from the normotensive control value. Central venous
and pulmonary capillary wedge pressures both
would have been below normal, 5 ± 2 and 7 ± 3 torr, respec-
tively. To 0 torr as blood pressure decreased, probably
secondary to the increase in venous capacitance
brought about by pentolinium administration. Stroke
volume index decreased in a similar manner from
32 ± 3 to 27 ± 3 ml/beat/m² at one hour. The magni-
tudes of the individual changes in cardiac index or
stroke volume index did not correlate with the changes
in mixed venous blood \( P_{v} \), although all three decreased.
Systemic vascular resistance decreased signifi-
cantly also, from 1491 ± 111 to 1206 ± 128 dynes
sec cm⁻². Cardiac index decreased significantly from
2.81 ± .2 to 2.50 ± 15 l/min.

Left ventricular stroke work index (LVSWI) was
significantly decreased by 58 per cent with induction
of stable hypotension, and was the only hemodynamic
index that showed a significant correlation with the
amount of blood lost (actual blood, not loss minus
replacement) during the procedure \( r = .76, P < 0.05, \) blood loss = 82.2 × LVSWI ± 69. The mean
blood loss was 1,040 ± 106 ml, which was 30 ± 5 percent of the individual patient's calculated total blood volume.

As shown in table 1, all hemodynamic values remained relatively stable during the period of reduced blood pressure and surgical intervention and until the time of "wake up." After "wake up" the patients needed volume to restore their original mean arterial pressures due to the expanded vascular space as a result of continued pentolinium activity. Following restoration to control blood pressure ("reversal"), cardiac index, 3.8 ± .4 l/min/m², and stroke volume index, 42 ± 4 ml/beat/m², were elevated over control values, 2.8 ± .2 l/min/m² and 32 ± 3 ml/beat/m², recorded prior to induction of hypotension. Stroke work index was elevated compared with control values; however, this change was not statistically significant. Pulmonary capillary wedge and central venous pressures remained zero after return of control blood pressure. Systemic vascular resistance also remained below control levels. These values would be expected due to the continued action of pentolinium. Intravascular blood volume as measured by the Evans blue dye dilution technique was not significantly different (P > .05) at the end of deliberate hypotension prior to restoration of control blood pressure (3,679 ± 397 ml), compared with the value attained prior to induction of hypotension (3,671 ± 382 ml). The hemodynamic changes observed therefore, were the result not of decreased vascular fluid volume, but of an increased intravascular space with normal volume.

**Table 1. Systemic Hemodynamic Values (Mean ± SEM) in Patients (n = 11) before and after Deliberate Hypotension**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Deliberate Hypotension</th>
<th>Normotensive</th>
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<tbody>
<tr>
<td></td>
<td>1 Hour</td>
<td>2 Hours</td>
<td>&quot;Wake Up&quot;</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>74 ± 2</td>
<td>51* ± 2</td>
<td>50* ± 2</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>91 ± 2</td>
<td>92 ± 3</td>
<td>91 ± 2</td>
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<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.81 ± 0.20</td>
<td>2.50* ± 0.15</td>
<td>2.45* ± 0.17</td>
</tr>
<tr>
<td>Stroke volume index (ml/beat·m²)</td>
<td>32 ± 3</td>
<td>27* ± 2</td>
<td>27* ± 2</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes·sec·cm⁻¹)</td>
<td>1491 ± 111</td>
<td>1206* ± 128</td>
<td>1123* ± 85</td>
</tr>
<tr>
<td>Left ventricular stroke work index (g·m·m⁻²)</td>
<td>24.1 ± 2.3</td>
<td>14.1* ± 1.6</td>
<td>13.3* ± 1.6</td>
</tr>
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* P < 0.05 paired with control.
† P < 0.05 paired with successive values.
‡ P < 0.05 paired with one-hour values.

**Catecholamines during Hypotension**

Plasma epinephrine levels were increased significantly after an hour of deliberate hypotension, from 59 ± 20 to 270 ± 80 pg/ml, but these higher levels were presumably contributed to or caused by the earlier infiltration of epinephrine in the operative area (fig. 1). By the time of reversal, plasma epinephrine had declined to levels observed prior to hypotension. Plasma norepinephrine and dopamine levels did not change significantly from basal values of 99 ± 14 and 49 ± 25 pg/ml, respectively. With the exception of the one-hour epinephrine values, catecholamine levels were within or below the range of values obtained from normal awake supine patients: epinephrine, 30–100 pg/ml; norepinephrine, 150–250 pg/ml; dopamine, 0–100 pg/ml.

**Effects of Deliberate Hypotension on the Renin–Angiotension System**

Angiotensin II levels after induction of anesthesia were somewhat higher (mean 60 ± 14 pg/ml) than those in normal awake supine patients (20–50 pg/ml), perhaps as a result of tracheal intubation and manipulation of the patient. Plasma renin activity was always within the normal range (0.6–4.0 ng/ml/h). Following the induction of deliberate hypotension, angiotensin II levels decreased significantly from 60 ± 14 to 40 ± 8 pg/ml.

Changes in plasma renin activity and angiotensin II levels after the first hour of deliberate hypotension were compared with concurrent alterations in hemo-
dynamic variables. The most striking correlation was between concurrent changes in plasma angiotensin II (A-II) levels and systemic vascular resistance (SVR), \( r = 0.98, P < 0.001, \ A-II = 0.061 \times \text{SVR} - 6 \) (fig. 2). Lesser, but statistically significant, correlations were observed between plasma renin activity (PRA) and heart rate (HR), \( r = 0.81, P < 0.05, \ PRA = 0.02 \times \text{HR} + 15 \) and between plasma renin activity and angiotensin II \( (r = 0.76, P < 0.05, \ A-II = 10.21 \times \text{PRA} + 20.3) \). In three large patients (50–61 kg) additional plasma renin activity, and angiotensin II and catecholamine levels, were determined after two hours of hypotension, at “wake up” and in the recovery room. There was no significant difference between these values and those obtained in samples drawn after one hour of hypotension and after “reversal” in the other eight patients.

**Discussion**

The autonomic nervous system and the renin–angiotensin system are important physiologic regulators of blood pressure, distribution of blood flow, fluid volume, and electrolyte balance. The actions of these two systems are intricately linked, and stimulation of either may enhance the activity of the other by positive-feedback mechanism, the autonomic nervous system being a potent regulator of renin release, and angiotensin II activating the autonomic nervous system at a number of sites. Acute stimulation of these systems results in an increase in myocardial contractility and constriction of the peripheral vasculature, resulting in elevation of total peripheral resistance and an increase in blood pressure.

Stimuli such as pain, alteration in electrolyte balance, and a decrease in effective circulating volume, either by increasing intravascular space or by decreasing intravascular fluid volume, may cause activation of these two systems. Anesthesia with halothane or morphine does not appear to elevate catecholamines and/or to activate the renin–angiotensin system in man, although angiotensin II has been shown to play a significant role in the maintenance of blood pressure in rats anesthetized with either halothane or enflurane. With the addition of surgical trauma and blood loss or the use of a hypotensive agent such as sodium nitroprusside in the anesthetic technique, both systems are activated.

Sympathetic stimulation and activation of the renin–angiotensin system may not be advantageous in patients undergoing anesthesia and operation, and may even be potentially harmful. Activation of these two systems may result in vasoconstriction, with an increase in systemic vascular resistance and cardiac contractility, resulting in a marked hypertensive response. The varying sensitivities of vessels in different organs may cause major changes in the distribution of blood flow, resulting in shunting of blood from nonvital tissues and maldistribution of circulation in others, such as the kidney. In addition, considerable evidence suggests that very high circulating concen-
Stimulation of the sympathetic and renin–angiotensin systems may adversely affect the operative courses of patients undergoing deliberate hypotension and surgical procedures. First, there may be difficulty in controlling the blood pressure. Second, although blood pressure may be controlled adequately, cardiac output may remain elevated, making it difficult to decrease bleeding. Finally, rebound hypertension and its possible sequelae of bleeding from the operative site, cerebral edema, and cerebral vascular accidents are undesirable complications that may occur during recovery from hypotensive anesthesia and operation.

Miller has shown in rats that saralasin, an angiotensin II inhibitor, blocks rebound hypertension following nitroprusside administration. Our data show that surgically induced activation of the autonomic and renin–angiotensin systems can be prevented in spite of light anesthesia and considerable hypotension by the use of ganglionic (pentolinium) and beta-receptor blockade. Ganglionic blockade with pentolinium acts to diminish sympathetic outflow in general and would be expected to inhibit renin release, since the sympathetic system is of primary importance in the renin responses to a number of stimuli. Beta-blocker (propranolol) administration in the current studies also would inhibit renin release, as beta receptors mediate the activity of the autonomic nervous system on the juxtaglomerular apparatus.

We were able to maintain stable hypotension by decreasing systemic vascular resistance and cardiac output with pentolinium, while also providing a “dry” surgical field. Stroke volume was reduced in our patients because of a decrease in venous return and with-

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**Fig. 2.** Changes in systemic vascular resistance (SVR) vs. changes in angiotensin II (A-I) levels before and after one hour of deliberate hypotension in patients treated with pentolinium and propranolol. Notice the linear relationship between these changes: r = 0.98, P < 0.001, A-II = 0.001 × SVR – 6.

**Fig. 3.** Comparison of methods of delivering deliberate hypotension (↑ signifies an increase, ↓ signifies a decrease, and ? data not conclusive).
PHYSIOLOGIC CHANGES DURING DELIBERATE HYPOTENSION

Physiologic changes during deliberate hypotension

The withdrawal of sympathetic drive to the heart. Several reports have suggested that both a reduction in total peripheral resistance and a reduction in cardiac output or stroke volume are necessary to provide a satisfactory (dry) surgical field.1,2 We found, indeed, a positive correlation between blood loss and left ventricular stroke work index.

A hemodynamic role of angiotensin II could be seen in our patients. Despite an overall decrease in angiotensin II levels there was a strong positive correlation between the change in systemic vascular resistance and the concomitant change in blood levels of angiotensin II.

The ability to inhibit activation of the autonomic and renin–angiotensin systems during light anesthesia with hypotension and surgical stimulation should allow adequate tissue perfusion and distribution of cardiac output in the patient during and after the surgical procedure. Adequacy of cerebral and spinal blood flows was demonstrated in the present study by the promptness with which the patients awakened and responded to commands to move their feet even when mean arterial blood pressure was very low, and also by the rapid awakening at the completion of the procedure.

The current technique can be compared with deliberate hypotension produced by other methods (fig. 3). Sodium nitroprusside has been reported to increase blood catecholamine levels15 and to activate the renin–angiotensin system when given alone or during anesthesia.16,17 During treatment with sodium nitroprusside, cardiac output and stroke volume can be elevated, and bleeding is less easily controlled.21,22 Moreover, hypotension itself may be difficult to control, particularly in young patients.21 Recently, in patients 18–60 years of age who received hypotensive anesthesia for surgical correction of cerebral aneurysms, Khambatta et al. showed that plasma renin activity increased during the use of sodium nitroprusside and remained elevated 30 min following its discontinuation. Arterial pressure increased after discontinuation of nitroprusside administration to levels significantly elevated over awake values despite continued anesthesia with halothane.23 In contrast to these observations, rebound hypertension did not occur in our patients, and plasma renin activity was unchanged during hypotension and significantly decreased 15 min following restoration of the patient’s blood pressure.

Hypotension may be induced with high concentrations of halothane, with satisfactory control of bleeding. This technique, however, relies on myocardial depression with a marked decrease in cardiac output, which is considered undesirable by some.24 Deep halothane anesthesia was not satisfactory for our patients because we desired intraoperative “wake up” during the period of hypotension to test for integrity of neurologic function. Angiotensin II levels in plasma have rarely been measured during anesthesia and surgery. It is at least theoretically possible that one or more of the agents used in our study might alter the normally close relationship between renin activity and the activities of an active end product of the system, angiotensin II. That this did not occur was shown by the similar fluctuations in plasma renin activity and angiotensin II levels. We can state, therefore, that plasma renin levels may be used to reflect circulating angiotensin II values under the conditions of our study.

The autonomic system and the renin–angiotensin system are two factors of major importance in blood vessel function and in maintenance of the viability of important tissues, including myocardium and renal tubules. It is, therefore, of more than academic interest that in spite of surgical stress and deliberate hypotension, we were able to prevent increases in plasma renin activity and in circulating levels of angiotensin II and catecholamines, to induce the desired hemodynamic changes, to reduce the need for transfusion, and finally, to facilitate the surgical procedure by maintaining a “dry” surgical field. This method of inducing hypotension deserves formal comparison with other accepted techniques, which may activate the sympathetic and renin–angiotensin systems.

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