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Treatment of Proximal Aortic Hypertension after Thoracic Aortic Cross-clamping in Dogs

Phlebotomy versus *Sodium Nitroprusside/Isoflurane*

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Thoracic aortic cross-clamping causes proximal aortic hypertension. Theoretically, the method used to treat hypertension can influence spinal cord perfusion pressure and neurologic outcome. Phlebotomy was compared to sodium nitroprusside/isoflurane in terms of ability to treat increased proximal mean aortic pressure (MAP_p) after thoracic aortic cross-clamping in dogs. Dogs were assigned randomly to one of three groups depending on the method used to treat hypertension after cross clamping: 1) phlebotomy (n = 10); 2) sodium nitroprusside/isoflurane (n = 11); and 3) control (no treatment) (n = 8). In each dog, anesthesia was maintained with isoflurane in oxygen, 1.4% end-tidal. The thoracic aorta was occluded 2.5 cm distal to the left subclavian artery for 50 min and then was released. Hemodynamics, cerebrospinal fluid pressure (CSFP), and regional blood flows by the radioactive microsphere technique, were measured at 1) baseline; 2) 2 min after aortic cross-clamping; 3) after treatment of proximal aortic hypertension; 4) 5 min after aortic unclamping; and 5) 30 min after resuscitation. At 24 h, a neurologic assessment was performed. Thoracic aortic cross-clamping increased MAP_p, decreased distal MAP (MAP_d), and reduced lumbar spinal cord perfusion pressure ($SCPP_l$), [$SCPP_l = MAP_d - CSFP$], in all three groups. Control of increased MAP_p necessitated removal of 36 ± 9 ml/kg of blood in the phlebotomy group. In the sodium nitroprusside/isoflurane group, sodium nitroprusside (16 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused and end-tidal isoflurane concentration increased to 2.5 ± 0.7 %, restoring MAP_p to baseline level. After treatment of increased MAP_p in the phlebotomy and sodium nitroprusside/isoflurane groups and nontreatment in controls, $SCPP_l$ was similar in the control and phlebotomy groups (7 ± 3 *vs.* 5 ± 6 mmHg) but significantly lower in the sodium nitroprusside/isoflurane group (−12 ± 5 mmHg, $P = 0.04$; group × time interaction). The uniformly negative $SCPP_l$ after sodium nitroprusside/isoflurane was associated with significant increases in total cerebral blood flow, cervical spinal cord blood flow, and CSFP. In contrast, phlebotomy decreased central venous pressure and, secondarily, CSFP, without changing cerebral blood flow or cervical spinal cord blood flow. The intergroup differences in $SCPP_l$ were not associated with measurable differences in lumbar spinal cord blood flow. After aortic unclamping, lumbar spinal cord blood flow exhibited a hyperemic response in all three groups. Higher MAP_d in the control group during the period of aortic cross-clamping was associated with significantly more favorable acid–base status immediately after unclamping. Twenty-five dogs survived for 24 h. Eight of eight dogs in the sodium nitroprusside/isoflurane group and seven of eight in the control group had spastic paraplegia. In the phlebotomy group, three of nine dogs could walk. Neurologic outcome did not differ significantly between groups. In this experimental model (50 min of thoracic aortic cross-clamping in isoflurane-anesthetized dogs), the method of treating proximal aortic hypertension did not significantly influence either lumbar spinal cord blood flow or neurologic outcome. (Key words: Complications: paraplegia. Pharmacology: isoflurane; sodium nitroprusside. Spinal cord: blood flow. Surgery: thoracic aorta, vascular.)

SURGERY of the descending thoracic aorta normally requires aortic cross-clamping, which in turn causes proximal aortic hypertension and increased cardiac filling pressures. Acute cardiac decompensation can follow in patients with heart disease. The hemodynamic consequences of thoracic aortic cross-clamping can be controlled by the use of partial cardiopulmonary bypass. Partial bypass, however, is technically demanding, usually involves anticoagulation, and does not clearly improve outcome.[1–3] Consequently, many thoracic aortic cross-clamping procedures are performed without bypass. When bypass is not used, proximal aortic hypertension caused by cross clamping usually is controlled by administration of either vasoactive agents or volatile anesthetics, or both. The specific combination of sodium nitroprusside and a volatile agent such as isoflurane has been recommended.[4]

The method of controlling proximal aortic hypertension may influence spinal cord perfusion distal to the clamp. Agents such as sodium nitroprusside and isoflurane may decrease mean aortic pressure distal to the clamp (MAP_d) while increasing cerebrospinal fluid pressure (CSFP).[5,§§] These changes may adversely affect lumbar

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spinal cord perfusion pressure ($SCPP_l$), which is determined as follows: $SCPP_l = MAP_d - CSFP$.[6] Therefore, treatment of proximal aortic hypertension with vasodilators and volatile anesthetics theoretically may worsen lumbar spinal cord ischemia and increase the risk of paraplegia.

We have found that phlebotomy effectively reverses proximal aortic hypertension after thoracic aortic cross-clamping in dogs. Unlike treatment with vasodilators and volatile agents, phlebotomy does not compromise $SCPP_l$ further.[7] This is because phlebotomy decreases central venous pressure (CVP) and consequently CSFP. We hypothesized that phlebotomy would be superior to sodium nitroprusside/isoflurane for treatment of proximal aortic hypertension after thoracic aortic cross-clamping in dogs. We included a control group of dogs whose proximal aortic hypertension was not treated. Efficacy criteria included systemic hemodynamics, SCPP, spinal cord blood flow, and neurologic outcome.

Materials and Methods

This study was approved by the Committee for Animal Experimentation at the University of Manitoba. Twenty-nine mongrel dogs (21 ± 3 kg [mean ± standard deviation]) were randomly assigned to one of three groups depending on the method used to treat proximal aortic hypertension after aortic cross-clamping: 1) phlebotomy (n = 10); 2) sodium nitroprusside/isoflurane (n = 11); and 3) control (no treatment) (n = 8).

Preparation

After induction of anesthesia with an intravenous infusion of thiopental (25 mg/kg), the trachea was intubated and mechanical ventilation instituted. Anesthesia was maintained with isoflurane in oxygen, 1.4% end-tidal, and Pa_{CO_2} was adjusted to 35–40 mmHg. Dogs were placed in a modified sphinx position with the head fixed in a stereotactic frame. A nasopharyngeal temperature probe was inserted, and body temperature was maintained at 37 ± 1° C by a servocontrolled heating lamp and pad. Through the right femoral vein, a flow-directed catheter was advanced to the right ventricle and withdrawn slightly into the right atrium. A right femoral arterial catheter was advanced into the distal aorta. A 7.5-Fr double-lumen catheter was inserted in the right brachial artery and advanced to the proximal aorta. Scalp tissues were reflected, a midline burr hole made, and the superior sagittal sinus cannulated with a 22-G catheter. With a micromanipulator, a 22-G spinal needle was inserted in the cisterna magna to measure CSFP. Through a left thoracotomy, the left atrium was exposed and cannulated with a 16-Fr catheter and the descending thoracic aorta was dissected free. Animals received 5,000 IU of heparin intravenously.

Experimental Protocol

At least 30 min elapsed between completion of preparatory invasive procedures and the start of the experiment. Measurements of hemodynamics, CSFP, and regional blood flow were then made (baseline). The aorta was cross clamped 2.5 cm distal to the left subclavian artery, and 2 min later, all measurements were repeated (clamp on). Increased proximal MAP (MAP_p) then either was restored to baseline level or was left untreated in control dogs. In the phlebotomy group, this was done by removal of blood from the left atrial cannula during a period of approximately 5 min. The blood was drawn into bags containing CPDA-1 anticoagulant and stored at room temperature. In the sodium nitroprusside/isoflurane group, sodium nitroprusside was infused at 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The end-tidal isoflurane concentration then was increased until MAP_p was restored to baseline. After restoration of MAP_p to baseline, or after 30 min in control dogs, all measurements were repeated (treatment). The aortic cross-clamp was left in place for 50 min. In the phlebotomy and sodium nitroprusside/isoflurane groups, MAP_p was increased to 30% above baseline, immediately before release of the aortic cross-clamp. This was accomplished by reinfusion of stored blood or by discontinuation of sodium nitroprusside and reduction of end-tidal isoflurane concentration in the phlebotomy and sodium nitroprusside/isoflurane groups, respectively. No attempt was made to control MAP_p or Pa_{CO_2} immediately after unclamping. Five minutes after unclamping, all measurements were repeated (clamp off). The dogs then were resuscitated by blood volume expansion with crystalloid and, in the phlebotomy group, with any remaining stored blood. Ventilation was adjusted to restore Pa_{CO_2} to baseline, and $NaHCO_3$ was administered if the base deficit exceeded 10 mM. A final set of measurements was made 30 min after complete resuscitation (resuscitation). All wounds then were sutured and infiltrated with 0.5% bupivacaine. Isoflurane was discontinued, and the trachea was extubated. Oxygen was administered by face cone, and Ringer's lactate was infused at 100 ml/h until the next day. Buprenorphine (0.015 mg/kg) was administered intramuscularly for analgesia and, if necessary, repeated the next morning. Exactly 24 h after application of the aortic cross-clamp, neurologic assessment was performed by a veterinarian who was unaware of the treatment group to which the dogs belonged. She assessed the severity of

†† Shine T, Nugent M: Sodium nitroprusside decreases spinal cord perfusion pressure during descending thoracic aortic cross-clamping in the dog. Journal of Cardiothoracic Anesthesia 4:185–193, 1990.

paraplegia in each dog, using Tarlov's scale[8]: grade 0 = no voluntary movement, spastic paraplegia; grade 1 = perceptible movement of joints; grade 2 = good movement of joints but unable to stand; grade 3 = ability to stand and walk; grade 4 = complete recovery. The dogs were then killed by Euthanyl® injection.

Data Acquisition

At each of the five measurement periods (control, clamp on, treatment, clamp off, and resuscitation), temperature, MAP_p, MAP_d, CVP, and CSFP were recorded and radiolabeled microspheres were injected to measure regional blood flow. Before each microsphere injection, arterial and superior sagittal sinus blood gases and hemoglobin were measured by an acid–base laboratory (ABL 300, Radiometer, Copenhagen, Denmark). Pressures were measured by calibrated transducers (Gould P23®) positioned either at the level of the cisterna magna or, for the CVP transducer, at the right atrial level. Data were recorded on paper continuously by a polygraph (Gould Recorder 2600S®) and intermittently on hard disk (Gateway 2000 386®) by a computer-based digital acquisition system (Dataq Instruments). Data presented are from the digital acquisition system unless otherwise noted.

Regional Blood Flows

Regional blood flows were determined by left atrial injection of radiolabeled microspheres of 15-μm diameter, as previously described.[9] Approximately 2.5×10^6 microspheres were injected for each flow determination. Microspheres labeled with one of five different radioisotopes (^{46}Sc, ^{85}Sr, ^{141}Ce [3M Company, St. Paul, MN]; ^{95}Nb, ^{113}Sn [New England Nuclear] were used in random sequence. A Harvard pump withdrew blood (25 ml) from the brachial artery for 300 s, starting 15 s before each microsphere injection. After the dogs were killed, tissue was obtained from both kidneys. The brain was excised and, after removal of the pia mater, sectioned into specific regions (left and right frontal, parietal, occipital cortex, basal ganglia, cerebellum, and brain stem). The spinal cord was processed similarly and sectioned into cervical (foramen magnum to first thoracic vertebra), thoracic, and lumbar (first lumbar vertebra to cauda equina) regions. The organ and blood samples, including the entire brain and spinal cord, were weighed and placed in a gamma counter (LKB Compugamma®). Standard formulas were used to convert counts per minute to units of regional blood flow (milliliters per gram per minute).[10]

Total cerebral blood flow (tCBF) (in milliliters per gram per minute) was determined by summing weight-corrected regional flows and dividing by total brain weight. Other regions of the brain with blood flows of interest were the cerebral cortex, cerebellum, and brain stem. Cerebral perfusion pressure was calculated as [MAP_p − mean CSFP]. Cerebral metabolic rate for oxygen was calculated as [tCBF × (arterial − superior sagittal sinus oxygen content)].

Data Analysis

Data were evaluated by analysis of variance for repeated measures. When analysis of variance revealed a significant treatment × time interaction ($P < 0.05$), we rejected the null hypothesis that the method of treating increased MAP_p did not influence the variable in question. When analysis of variance revealed either a significant group × time interaction or a time effect, appropriate multiple comparisons were made by the least squares means test. Bonferroni's correction was applied ($P < 0.05/n$, where n = number of comparisons) when multiple comparisons were made. The corrected P-value was considered statistically significant. The data were pooled (n = 29) for the first two measurement periods to examine the hemodynamic and regional blood flow consequences of cross clamping the proximal thoracic aorta (Student's t-test for paired data, $P < 0.05$). Tarlov scores were analyzed by the Mann–Whitney rank-sums test ($P < 0.05$).

Results

The hemodynamic consequences of cross clamping the proximal thoracic aorta in the 29 dogs are shown in table 1. The MAP_p,cerebral perfusion pressure, CSFP, and CVP all increased significantly from baseline values ($P < 0.0001$ for each variable). Of note is that the CVP and CSFP increased by an identical magnitude (3.1 mmHg). The MAP_d and SCPP decreased significantly (for each, $P < 0.0001$). The effects of thoracic cross-clamping on regional blood flows are shown in table 2. An increase in total cortical blood flow was seen ($P = 0.04$ *vs.* baseline); CBF_t was increased but not significantly ($P = 0.09$). Cerebellar and total brain stem flow were not increased ($P = 0.53$ and 0.79, respectively). Regional blood flow to

TABLE 1. Hemodynamic Consequences of Thoracic Aortic Cross-clamping

Variable	Baseline	Cross-clamp On	P
MAP_p	94 ± 19	142 ± 18	0.0001
CSFP	7.3 ± 5.8	10.4 ± 5.1	0.0001
CPP	87 ± 20	132 ± 20	0.0001
CVP	5.4 ± 4.0	8.5 ± 4.2	0.0001
MAP_d	92 ± 20	15 ± 5	0.0001
SCPP	85 ± 20	5.4 ± 5	0.0001

Mean ± SD; n = 29.
All pressures are mmHg.
MAP_p = mean arterial pressure, proximal; CSFP = cerebral spinal fluid pressure; CPP = cerebral perfusion pressure; CVP = central venous pressure; MAP_d = mean arterial pressure, distal; SCPP = spinal cord perfusion pressure.

TABLE 2. Effects of Thoracic Cross-clamping on Regional Blood Flow

Region	Baseline	Cross-clamp On	*P*
tCBF	0.74 ± 0.22	0.81 ± 0.26	0.0868
tCortex	0.74 ± 0.22	0.83 ± 0.27	0.0407
tCerebellum	0.80 ± 0.05	0.84 ± 0.23	0.5344
tBrainstem	0.68 ± 0.26	0.70 ± 0.24	0.7896
$SCBF_c$	0.31 ± 0.14	0.29 ± 0.13	0.5165
$SCBF_t$	0.26 ± 0.11	0.10 ± 0.09	0.0001
$SCBF_l$	0.32 ± 0.12	0.05 ± 0.06	0.0001
Renal	4.32 ± 1.36	0.94 ± 0.35	0.0001

Mean ± SD; n = 29.
Regional flows are milliliters per gram per minute.
tCBF = total cerebral blood flow; tCortex = total cortex blood flow; tCerebellum = total cerebellum blood flow; tBrainstem = total brainstem blood flow; $SCBF_c$ = spinal cord blood flow, cervical; $SCBF_t$ = spinal cord blood flow, thoracic; $SCBF_l$ = spinal cord blood flow, lumbar; Renal = renal blood flow.

structures below the cross-clamp site (thoracic and lumbar spinal cord and kidney) was decreased markedly (for each, $P < 0.0001$ *vs.* baseline).

Temperature and blood gas data for the three experimental groups are shown in table 3. No significant intergroup differences in temperature were noted. The treatment × time interaction for hemoglobin concentration approached significance ($P = 0.08$). The hemoglobin concentration tended to be lower in the phlebotomy group throughout the experiment. A significant group × time interaction was noted for Pa_{CO_2}. Immediately after unclamping, Pa_{CO_2} was significantly higher in the phlebotomy and sodium nitroprusside/isoflurane groups than in the control group. Base excess and HCO_3^- also were significantly lower in the phlebotomy and sodium nitroprusside/isoflurane groups at unclamping. Consequently, arterial *p*H was significantly lower in the phlebotomy and sodium nitroprusside/isoflurane groups after unclamping. During resuscitation, $NaHCO_3$ requirements in the phlebotomy, sodium nitroprusside/isoflurane, and control groups (25 ± 25 mEq, 23 ± 17 mEq, and 9 ± 11 mEq, respectively) did not differ significantly.

The hemodynamic data for the three groups are shown in table 4. There was no intergroup difference in MAP_d. Significant group × time interactions were noted for MAP_p, CVP, CSFP, and $SCPP_l$. Aortic cross-clamping caused a sharp increase in MAP_p in all three groups. Because of the experimental design, MAP_p was significantly higher in the control group after treatment of increased MAP_p in the other two groups. In the phlebotomy group, restoration of MAP_p to baseline values after aortic clamping necessitated withdrawal of 36 ± 9 ml/kg of blood. In the sodium nitroprusside/isoflurane group, a sodium nitroprusside infusion of 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and an increase in end-tidal isoflurane concentration to 2.5 ± 0.7% were required to control MAP_p. In the control group, MAP_p also was significantly higher immediately after unclamping. The CVP increased significantly, in all groups im-

TABLE 3. Temperature and Blood Gas Data

Variable	Baseline	Clamp On	Treatment	Clamp Off	Resuscitation
Temperature (° C)					
Control	36.5 ± 1.12	36.4 ± 1.11	36.1 ± 0.86	36.1 ± 1.04	36.0 ± 0.99‡
Phlebotomy	36.9 ± 0.96	36.9 ± 0.89*†	36.3 ± 0.73‡	36.2 ± 0.74‡	36.5 ± 0.85*†‡
SNP/ISO	36.7 ± 0.79	36.5 ± 0.84	36.3 ± 1.13	36.2 ± 0.98‡	36.0 ± 0.89
Pa_{CO_2} (mmHg)					
Control	37.1 ± 1.93	38.2 ± 2.25	39.3 ± 1.19	42.2 ± 3.05*‡§	37.2 ± 1.56
Phlebotomy	37.6 ± 2.24	37.0 ± 1.80	37.8 ± 1.60	49.9 ± 6.17‡	37.2 ± 2.05
SNP/ISO	37.1 ± 1.30	38.4 ± 2.00	37.2 ± 1.96	51.4 ± 6.38‡	37.3 ± 1.84
*p*H					
Control	7.36 ± 0.03	7.35 ± 0.04	7.34 ± 0.03	7.31 ± 0.04*§	7.36 ± 0.03
Phlebotomy	7.35 ± 0.05	7.35 ± 0.04	7.26 ± 0.08*‡	7.14 ± 0.11‡	7.36 ± 0.05
SNP/ISO	7.36 ± 0.04	7.36 ± 0.03	7.32 ± 0.06	7.15 ± 0.09‡	7.37 ± 0.03
Hgb (g/dl)					
Control	13.7 ± 1.9	13.2 ± 2.3	14.0 ± 2.4	14.2 ± 2.0	12.3 ± 2.4
Phlebotomy	11.1 ± 1.6	10.9 ± 1.5	12.4 ± 2.1	13.1 ± 2.0‡	10.8 ± 1.9
SNP/ISO	13.9 ± 1.8	13.9 ± 1.9	15.7 ± 2.8‡	15.1 ± 3.1	12.4 ± 1.9‡
HCO_3^- (mEq/l)					
Control	20.1 ± 2.1	20.7 ± 1.4	20.6 ± 1.4	20.7 ± 1.7*§	20.7 ± 1.1
Phlebotomy	20.3 ± 1.9	20.3 ± 1.4	16.7 ± 2.5*‡	16.3 ± 2.9‡	20.9 ± 1.9
SNP/ISO	20.9 ± 1.5	21.3 ± 1.8	19.0 ± 2.5	17.1 ± 2.4‡	21.1 ± 0.9
Base excess (mEq/l)					
Control	−4.6 ± 2.1	−4.1 ± 1.6	−4.4 ± 1.6	−4.8 ± 1.9*§	−4.1 ± 1.3
Phlebotomy	−4.7 ± 2.3	−4.6 ± 1.8	−9.1 ± 3.5*†‡	−11.4 ± 4.0‡	−3.8 ± 2.4
SNP/ISO	−3.8 ± 1.8	−3.4 ± 2.0	−6.2 ± 3.1	−10.7 ± 3.5‡	−3.5 ± 1.1

Mean ± SD; control n = 8; phlebotomy n = 10; SNP/ISO n = 11.
SNP = sodium nitroprusside; ISO = isoflurane.
* $P < 0.05$ phlebotomy *versus* control.
† $P < 0.05$ phlebotomy *versus* SNP/ISO.
‡ $P < 0.05$ *versus* baseline within groups.
§ $P < 0.05$ control *versus* SNP/ISO.

TABLE 4. Hemodynamic Data

Variable	Baseline	Clamp On	Treatment	Clamp Off	Resuscitation
MAP_p (mmHg)					
Control	101 ± 25	146 ± 18*	151 ± 17*†‡	93 ± 25†‡	86 ± 23
Phlebotomy	91 ± 18	142 ± 21*	92 ± 20	74 ± 12*	76 ± 12
SNP/ISO	89 ± 16	139 ± 16*	89 ± 16	64 ± 23*	81 ± 18
MAP_d (mmHg)					
Control	100 ± 26	17 ± 4*	19 ± 4*	93 ± 26†‡	86 ± 23
Phlebotomy	87 ± 17	15 ± 6*	11 ± 5*	70 ± 13*	73 ± 11*
SNP/ISO	88 ± 16	14 ± 3*	5 ± 3*	65 ± 18*	79 ± 20*
CVP (mmHg)					
Control	5.1 ± 3.7	8.1 ± 4.3	8.6 ± 4.9†	6.1 ± 3.2	8.0 ± 5.8
Phlebotomy	5.6 ± 2.4	9.3 ± 3.2*	2.4 ± 2.1*	4.6 ± 2.5	6.3 ± 3.4
SNP/ISO	5.2 ± 5.0	8.1 ± 5.0*	7.4 ± 4.3§	5.8 ± 4.9	5.7 ± 3.1
CSFP (mmHg)					
Control	8.0 ± 8.0	11.0 ± 6.6	11.2 ± 5.1	13.4 ± 7.0*	10.8 ± 6.0‡
Phlebotomy	7.3 ± 3.8	10.4 ± 4.6	7.0 ± 4.6	14.2 ± 5.4*	7.1 ± 3.3
SNP/ISO	7.3 ± 5.8	10.3 ± 4.8	17.0 ± 4.7*§	11.3 ± 4.5*	5.8 ± 3.9
CPP (mmHg)					
Control	93 ± 26	135 ± 20	140 ± 20*†‡	80 ± 28	75 ± 23
Phlebotomy	84 ± 19	132 ± 23	85 ± 21	60 ± 15	70 ± 13
SNP/ISO	82 ± 19	128 ± 18	72 ± 14	54 ± 18*	75 ± 19
SCPP (mmHg)					
Control	92 ± 27	6 ± 6*	7 ± 3*	79 ± 30†‡	75 ± 24
Phlebotomy	80 ± 17	5 ± 6*	5 ± 6*	56 ± 15*	66 ± 12
SNP/ISO	80 ± 19	3 ± 7*	−12 ± 5*‡§	53 ± 20*	73 ± 21
Isoflurane concentration (%)					
Control	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.1	1.4 ± 0.1	1.4 ± 0.1
Phlebotomy	1.4 ± 0.1	1.4 ± 0.2	1.6 ± 0.2	1.5 ± 0.2	1.5 ± 0.2
SNP/ISO	1.4 ± 0.1	1.4 ± 0.1	2.5 ± 0.7‡§	1.3 ± 0.4	1.4 ± 0.1

Mean ± SD; control n = 8, phlebotomy n = 10, SNP/ISO n = 11.
MAP_p = mean arterial pressure, proximal; SNP/ISO = sodium nitroprusside≠isoflurane; MAP_d = mean arterial pressure, distal; CVP = central venous pressure; CSFP = cerebral spinal fluid pressure; CPP = cerebral perfusion pressure; SCPP = spinal cord perfusion pressure.

* $P < 0.05$ *versus* baseline within groups.
† $P < 0.05$ control *versus* phlebotomy.
‡ $P < 0.05$ control *versus* SNP/ISO.
§ $P < 0.05$ SNP/ISO *versus* phlebotomy.

mediately after aortic clamping. It was significantly lower, however, in the phlebotomy group during treatment compared to the other two groups. After aortic cross-clamping, CSFP was similar in all groups. Treatment of increased MAP_p was associated with a significant increase in CSFP in the sodium nitroprusside/isoflurane group (from 10.3 ± 4.8 mmHg to 17.0 ± 4.7 mmHg) ($P < 0.05$), a decrease in CSFP in the phlebotomy group (from 10.4 ± 4.6 mmHg to 7.0 ± 4.6 mmHg), and no change in CSFP in controls (11.0 ± 6.6 mmHg to 11.2 ± 5.1 mmHg). Aortic cross-clamping caused dramatic decreases in $SCPP_l$ in all groups. After treatment of increased MAP_p, $SCPP_l$ was similar in the control and phlebotomy groups (7 ± 3 mmHg *vs.* 5 ± 6 mmHg, respectively). However, $SCPP_l$ was significantly lower in the sodium nitroprusside/isoflurane group (−12 ± 5 mmHg [$P = 0.04$, group × time interaction]) at this time. In fact, administration of sodium nitroprusside/isoflurane resulted in a negative $SCPP_l$ in all dogs. The hemodynamic consequences of sodium nitroprusside infused at 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before an increase in isoflurane concentration are shown in table 5. Administration of sodium nitroprusside/isoflurane resulted in a negative SCPP (−6 ± 2 mmHg) before any increase in inspired isoflurane concentration. These latter data were obtained from the polygraph records for 10 of 11 dogs, not from the digital acquisition system. This difference in methodology accounts for apparent discrepancies in measured values between tables 4 and 5.

Regional blood flow data are shown in table 6. No intergroup differences were noted for renal blood flow or thoracic spinal cord blood flow ($SCBF_t$). Significant group × time interactions were noted for tCBF, cervical SCBF

TABLE 5. Effects of Sodium Nitroprusside at 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$

Variable	Clamp On	Clamp On + SNP (Pre-ISO)
MAP_d (mmHg)	15 ± 3	10 ± 3*
MAP_p (mmHg)	141 ± 16	129 ± 22*
		(n = 9)
CSFP (mmHg)	11.2 ± 4.1	15.6 ± 6.0*
CVP (mmHg)	8.4 ± 5.1	6.3 ± 16.1

Mean ± SD; sample size n = 10.
MAP_d = mean arterial pressure, distal; MAP_p = mean arterial pressure, proximal; CSFP = cerebral spinal fluid pressure; CVP = central venous pressure.
* $P < 0.05$ *versus* clamp on.

TABLE 6. Regional Blood Flow Data

Variable	Baseline	Clamp On	Treatment	Clamp Off	Resuscitation
tCBF (ml·g^{-1}·min^{-1})					
Control	0.70 ± 0.27	0.79 ± 0.34	0.66 ± 0.19	0.76 ± 0.23§†	0.69 ± 0.21
Phlebotomy	0.77 ± 0.16	0.84 ± 0.28	0.95 ± 0.22	1.20 ± 0.31*	0.64 ± 0.18
SNP/ISO	0.74 ± 0.25	0.78 ± 0.18	1.19 ± 0.36*†‡	1.25 ± 0.37*	0.81 ± 0.35
$SCBF_c$ (ml·g^{-1}·min^{-1})					
Control	0.24 ± 0.10	0.23 ± 0.16	0.17 ± 0.09	0.41 ± 0.36	0.36 ± 0.27
Phlebotomy	0.34 ± 0.14	0.34 ± 0.14	0.38 ± 0.09	0.54 ± 0.16*	0.27 ± 0.09
SNP/ISO	0.31 ± 0.16	0.29 ± 0.10	0.56 ± 0.12*†	0.57 ± 0.16*	0.38 ± 0.18
$SCBF_t$ (ml·g^{-1}·min^{-1})					
Control	0.21 ± 0.11	0.11 ± 0.13	0.10 ± 0.14	0.42 ± 0.08*	0.49 ± 0.36*
Phlebotomy	0.31 ± 0.12	0.12 ± 0.08*	0.13 ± 0.04*	0.52 ± 0.18*	0.41 ± 0.14*
SNP/ISO	0.24 ± 0.08	0.06 ± 0.03*	0.12 ± 0.07	0.39 ± 0.14	0.56 ± 0.12*
$SCBF_l$ (ml·g^{-1}·min^{-1})					
Control	0.26 ± 0.12	0.06 ± 0.07	0.06 ± 0.04	0.87 ± 0.39*	0.97 ± 0.28*
Phlebotomy	0.39 ± 0.13	0.07 ± 0.08*	0.03 ± 0.03*	0.84 ± 0.46*	0.93 ± 0.33*
SNP/ISO	0.29 ± 0.08	0.02 ± 0.02*	0.04 ± 0.06*	0.44 ± 0.26†‡	1.06 ± 0.28*
Content difference (vol %)					
Control	4.5 ± 0.9	4.2 ± 1.5	4.1 ± 0.9	3.7 ± 1.0	4.6 ± 0.8
Phlebotomy	3.7 ± 1.2	3.2 ± 0.9§	3.0 ± 1.4	2.6 ± 1.0*	4.3 ± 0.9
SNP/ISO	4.4 ± 1.1	4.0 ± 0.9	2.9 ± 0.8*	3.4 ± 1.7*	4.8 ± 0.9
CMR_{O_2} (ml O_2·g^{-1}·min^{-1})					
Control	0.030 ± 0.006	0.030 ± 0.009	0.027 ± 0.003	0.029 ± 0.010	0.033 ± 0.013
Phlebotomy	0.028 ± 0.009	0.027 ± 0.010	0.027 ± 0.012	0.029 ± 0.007	0.027 ± 0.007
SNP/ISO	0.031 ± 0.009	0.031 ± 0.008	0.028 ± 0.006	0.037 ± 0.013	0.039 ± 0.016
Renal (ml·g^{-1}·min^{-1})					
Control	5.49 ± 1.34	1.18 ± 0.30*	1.16 ± 0.37*	3.83 ± 0.69*	4.60 ± 2.59
Phlebotomy	3.82 ± 1.26	0.88 ± 0.34*	0.45 ± 0.35*	3.00 ± 0.92	3.33 ± 0.79
SNP/ISO	3.99 ± 1.06	0.84 ± 0.35*	0.54 ± 0.37*	3.66 ± 1.13	3.86 ± 0.87

Mean ± SD; control n = 8; phlebotomy n = 10; SNP/ISO n = 10.
tCBF = total cerebral blood flow; SNP/ISO = sodium nitroprusside/isoflurane; $SCBF_c$ = cervical spinal cord blood flow; $SCBF_t$ = thoracic spinal cord blood flow; $SCBF_l$ = lumbar spinal cord blood flow; CMR_{O_2} = cerebral metabolic rate for oxygen.

* $P < 0.05$ *versus* baseline within groups.
† $P < 0.05$ SNP/ISO *versus* control.
‡ $P < 0.05$ SNP/ISO *versus* phlebotomy.
§ $P < 0.05$ phlebotomy *versus* control.

($SCBF_c$), and lumbar SCFB ($SCBF_l$). In the control group, tCBF was stable throughout the experiment. With treatment of increased MAP_p, tCBF increased significantly in the sodium nitroprusside/isoflurane group and was significantly increased compared to the other groups. Immediately after unclamping, tCBF was significantly higher in the phlebotomy and sodium nitroprusside/isoflurane groups compared to controls. After resuscitation, tCBF returned to baseline levels in all three groups. The $SCBF_c$ data exhibited the same pattern as did the tCBF results. Aortic clamping caused profound decreases in $SCBF_l$ in all three groups. Lumbar SCBF remained low, regardless of the method used to treat proximal aortic hypertension. After unclamping, $SCBF_l$ increased significantly above baseline levels in the control and phlebotomy groups. This immediate hyperemic response was significantly attenuated in the sodium nitroprusside/isoflurane group. After resuscitation, a similarly increased $SCBF_l$ was evident in all groups.

Twenty-five of 29 dogs survived for 24 h. The incidence and severity of paraplegia is shown in table 7. The three groups did not differ significantly with respect to neurologic outcome.

Discussion

Cross clamping of the proximal descending thoracic aorta in dogs anesthetized with 1.0 MAC isoflurane was associated with the following overall effects (n = 29): 1) increased MAP_p; 2) decreased MAP_d;3) increased CVP; and 4) increased CSFP.

Increased CSFP, which contributed to decreased $SCPP_l$, was presumably passive and secondary to increased CVP. The identical increase in CSFP and CVP seen in this study confirms previous work from our Neuroanesthesia Research Laboratory that has demonstrated this interrelationship.[7] After an induction dose of sodium

TABLE 7. Incidence and Severity of Paraplegia

Tarlov Scale	0	1	2	3	4
Control	7				1
Phlebotomy	6			3	
SNP/ISO	8				

SNP/ISO = sodium nitroprusside/isoflurane.
Mann-Whitney rank-sums test: phlebotomy *versus* SNP/ISO $P = 0.08$, two-tailed test.

thiopental and maintenance anesthesia with isoflurane (1 MAC end-tidal) CBF, was increased significantly only in the cerebral cortex ($P = 0.04$ *vs.* baseline [table 2]) when cerebral perfusion pressure was increased markedly with cross clamping of the proximal thoracic aorta. As has been demonstrated previously in this laboratory, cerebellar and brain stem blood flow autoregulated during isoflurane anesthesia.[11] The decreased MAP_d and increased CSFP reduced $SCPP_l$ and decreased $SCBF_l$ dramatically. The resulting severe spinal cord ischemia, when sustained for 50 min, was associated with an 87.5% incidence of spastic paraplegia in control dogs.

Both phlebotomy and sodium nitroprusside/isoflurane were effective in restoring MAP_p to baseline values, but they had different effects on other variables. Both CVP and CSFP were significantly lower after phlebotomy than after sodium nitroprusside/isoflurane. Consequently, phlebotomy resulted in a significantly higher $SCPP_l$ than did sodium nitroprusside/isoflurane (5 ± 6 mmHg *vs.* −12 ± 5 mmHg). Also, the $SCPP_l$ after phlebotomy was not different than that seen in control dogs (7 ± 3 mmHg). Therefore, in the narrow context of $SCPP_l$, phlebotomy was superior to sodium nitroprusside/isoflurane for treatment of proximal aortic hypertension after thoracic aortic cross-clamping. These results validate our previous observations regarding the effects of phlebotomy after aortic cross-clamping in thiopental-anesthetized dogs.[7]

The observed intergroup difference in $SCPP_l$ reflects the decrease in CSFP accompanying phlebotomy, compared to the increase seen after sodium nitroprusside/isoflurane, because MAP_d was similar in both groups. By reducing CVP, without altering cerebrovascular tone, phlebotomy decreases CSFP. In contrast, by causing cerebral vasodilation, sodium nitroprusside/isoflurane presumably increases cerebral blood volume and CSFP. In this regard, we noted significant increases in CBF after sodium nitroprusside/isoflurane, despite stable cerebral metabolic rate for oxygen and a 44% decrease in cerebral perfusion pressure. An increase in CSFP after sodium nitroprusside administration, during aortic cross-clamping, has been observed by other investigators.[5,§§] We also quantified the effect of administering sodium nitroprusside alone, before increasing the inspired isoflurane concentration (table 5). Sodium nitroprusside alone caused a significant increase in CSFP and a negative SCPP in all dogs. Other vasodilators and volatile anesthetics are likely to cause similar, undesirable changes in $SCPP_l$.

As we hypothesized, phlebotomy resulted in a significantly higher $SCPP_l$, compared to sodium nitroprusside/isoflurane. Despite this theoretical advantage, phlebotomy did not significantly improve either $SCBF_l$ or neurologic outcome. There are several possible explanations for these findings. First, the 17-mmHg difference in $SCPP_l$ between the phlebotomy and sodium nitroprusside/isoflurane groups during treatment is a statistical exaggeration. The negative $SCPP_l$ (−12 mmHg) in the sodium nitroprusside/isoflurane group is likely no worse than a perfusion pressure of 0 mmHg. In that case, the relevant intergroup difference in perfusion pressure was actually 5 mmHg. A difference of this magnitude may have been insufficient to alter either $SCBF_l$ or neurologic outcome. Second, $SCBF_l$ was extremely low after aortic clamping in all groups, and small differences in blood flow in this range would be difficult to resolve. Third, the 50-min cross-clamp duration we employed was undoubtedly too long. The extremely high (87.5%) incidence of paraplegia in the control group would make it very difficult to demonstrate that sodium nitroprusside/isoflurane worsens outcome compared to either phlebotomy or no treatment.

In the sodium nitroprusside/isoflurane group, we deliberately limited the sodium nitroprusside infusion to 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ because larger doses cause cyanide release in dogs.[12] Therefore, an increase in end-tidal isoflurane concentration was needed in all dogs to control MAP_p. Other investigators have administered much larger doses of sodium nitroprusside to control increased MAP_p after aortic clamping in dogs.[13,§§] Neuronal cyanide toxicity may have contributed to the poor neurologic outcome they observed. Our study demonstrates that uniformly poor outcome can be expected even when smaller doses of sodium nitroprusside are used to control MAP_p.

There were significant metabolic advantages associated with nontreatment of increased MAP_p after aortic clamping. Immediately after unclamping, Pa_{CO_2} was significantly lower and arterial *p*H significantly higher in the control group. The higher MAP_p in control dogs was associated with apparently better overall tissue perfusion distal to the clamp. Despite its theoretical advantages, nontreatment of increased MAP_p is frequently not a viable option in patients undergoing thoracic aortic surgery because they frequently have significant heart disease.

In conclusion, when used to control increased MAP_p after thoracic aortic cross-clamping, phlebotomy results in a significantly higher lumbar SCPP than does sodium nitroprusside/isoflurane. Improved perfusion pressure, however, was not associated with either a measurable difference in $SCBF_l$ or a significant improvement in neurologic outcome. Nontreatment of proximal aortic hypertension is associated with an improved acid–base status immediately after declamping. The combination of sodium nitroprusside and isoflurane increased CBF and CSFP and was invariably associated with negative $SCPP_l$. Phlebotomy alone does not improve neurologic outcome after thoracic aortic cross-clamping of 50-min duration in isoflurane-anesthetized dogs.

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