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Effects of Propranolol on the Cardiovascular and Renin-Angiotensin Systems during Hypotension Produced by Sodium Nitroprusside in Humans

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The authors examined the effects of controlled hypotension induced with sodium nitroprusside (SNP) with and without propranolol on the cardiovascular, pulmonary, and renin-angiotensin systems in 10 consecutive anesthetized patients with kyphoscoliosis undergoing posterior spinal fusion. SNP infusion ($4.1\ \mu g \cdot kg^{-1} \cdot min^{-1}$) alone decreased mean systemic arterial pressure ($\overline{SAP}$) by 25 torr ± 3 SE ($P < 0.001$), systemic vascular resistance index (SVRI) by 1113 $dyne \cdot sec \cdot cm^{-5} \cdot m^2$ ± 125 SE ($P < 0.001$), mean pulmonary artery pressure ($\overline{PAP}$) by 6 torr ± 2 SE ($P < 0.02$), pulmonary capillary wedge pressure (PCWP) by 4 torr ± 1 SE ($P < 0.01$), pulmonary vascular resistance (PVR) by 50 $dyne \cdot sec \cdot cm^{-5}$ ± 18 ($P < 0.05$), and Pa_{O_2} by 16 torr ± 7 SE ($P < 0.05$), whereas cardiac index increased by 1.08 $l \cdot min^{-1} \cdot m^2$ ± 0.24 SE ($P < 0.01$) and heart rate increased 16 beats/min ± 5 SE ($P < 0.02$). After 40 min of hypotension, 0.03 mg/kg propranolol was injected intravenously while the SNP infusion rate was held constant. Ten min later there was a significant decrease in the heart rate (10 beats/min ± 4 SE, $P < 0.02$) and cardiac index ($0.65\ l \cdot min^{-1} \cdot m^{-2}$ ± 0.21, $P < 0.02$). Plasma renin activity (PRA) increased from 2.37 $ng \cdot ml^{-1} \cdot h^{-1}$ ± 0.7 SE before anesthesia to 6.50 $ng \cdot ml^{-1} \cdot h^{-1}$ ± 1.45 SE ($P < 0.05$) after 40 min of nitroprusside infusion. Forty min after propranolol there was a significant reduction in PRA to 4.07 $ng \cdot ml^{-1} \cdot h^{-1}$ ± 0.73 SE ($P < 0.05$). Thus propranolol, when given during SNP hypotension, exhibits an early cardiovascular response manifested as a decrease in cardiac output and heart rate and a delayed action on the kidney resulting in an inhibition of renin release. (Key words: Anesthetic technique: hypotension, induced, nitroprusside. Polypeptides: renin-angiotensin. Surgery: orthopedic. Sympathetic nervous system: sympatholytic agents, propranolol.)

ALTHOUGH the cardiovascular and pulmonary consequences of kyphoscoliosis in awake unanesthetized individuals have been well-documented,[1–9] data pertaining to the hemodynamic and respiratory effects of anesthesia and/or induced hypotension in these patients are limited. Controlled hypotension with sodium nitroprusside (SNP) has been shown to be effective in reducing blood loss associated with mandibular surgery[10] and total hip arthroplasty.[11] SNP dose requirement can be reduced by giving propranolol in a dose large enough to slow heart rate during controlled hypotension,[12] thus decreasing the likelihood of developing cyanide toxicity. The precise mechanism of action of propranolol in this circumstance has not yet been defined, although a possible effect on the renin-angiotensin system has been suggested.[13]

The present study examined the following areas in patients with kyphoscoliosis: 1) the effects of anesthesia and hypotension induced with SNP on the pulmonary, cardiovascular, and renin-angiotensin systems; and 2) the effects of propranolol on the pulmonary, cardiovascular, and renin-angiotensin systems during hypotension induced with SNP.

Methods

The subjects were ten consecutive patients with moderately severe kyphoscoliosis, ages 13–36 yr, undergoing posterior spinal fusion and Harrington rod insertion. The study protocol was reviewed by the Institutional Human Studies Committee and detailed informed consent was obtained from the subjects and/or their legal guardians on the day prior to operation.

Premedication consisted of morphine (0.1 mg/kg) and scopolamine (0.005 mg/kg), intramuscularly (IM), one hour prior to induction of anesthesia. After the patient arrived in the operating suite, a peripheral intravenous infusion was begun and a venous blood sample was obtained for plasma renin activity (PRA) measurement. Gallamine, 10–20 mg, was given intravenously (iv), and anesthesia was induced with sodium thiopental, 3–4 mg/kg, iv, and maintained with 70 per cent nitrous oxide in oxygen and morphine, 0.5 mg/kg, iv. Endotracheal intubation was facilitated with succinylcholine, 1 mg/kg, iv, after topical laryngotracheal anesthesia with 4 per cent lidocaine 160 mg. Curare, 0.3 mg/kg, iv, was then

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TABLE 1. Calculations and Formulae

$\overline{SAP} = \left(\frac{\text{Systolic} - \text{Diastolic}}{3}\right) + \text{Diastolic}$	(torr)
$\overline{PAP} = \left(\frac{\text{Systolic} - \text{Diastolic}}{3}\right) + \text{Diastolic}$	(torr)
$CI = \frac{CO}{BSA\ (m^2)}$	$(l \cdot min^{-1} \cdot m^{-2})$
$SVRI = \frac{(\overline{SAP} - CVP) \times 79.92}{CI}$	$(dyne \cdot sec \cdot cm^{-5} \cdot m^2)$
$PVR = \frac{(\overline{PAP} - PCWP) \times 79.92}{CO}$	$(dyne \cdot sec \cdot cm^{-5})$
$SVI = \frac{CI}{HR}$	$(ml \cdot m^2)$

given and constant controlled mechanical ventilation was instituted to maintain the arterial CO_2 tension (Pa_{CO_2}) near 35 torr throughout the operation.

After induction of anesthesia, a 20-gauge radial arterial catheter and a 7-French thermistor-tipped triple-lumen pulmonary artery catheter were introduced percutaneously. The latter was localized using pressure waveform control. The legs were wrapped with elastic bandages and patients were placed prone on a chest frame for operation.

Radial arterial, pulmonary arterial, and central venous pressures were continuously monitored (Bentley® Model 500 transducers) and recorded throughout the study period. The following variables were determined: heart rate (HR); mean systemic arterial pressure ($\overline{SAP}$); mean pulmonary artery pressure ($\overline{PAP}$); pulmonary capillary wedge pressure (PCWP); central venous pressure (CVP); and body temperature. Cardiac output (CO) was measured by thermal dilution technique in triplicate (Edwards® 9520-A computer). Body surface area (BSA) was calculated from standard nomograms using height and weight, and the following hemodynamic variables were calculated from appropriate formulae (table 1): cardiac index (CI); systemic vascular resistance index (SVRI); pulmonary vascular resistance (PVR); and stroke volume index (SVI). Arterial and mixed venous blood samples were obtained anaerobically for analysis of *p*H, oxygen, and CO_2 tensions (Corning® model 175 *p*H/blood-gas analyzer). Mixed venous blood samples were obtained for analysis of plasma renin activity (PRA; measured using radioimmunoassay, method of Haber; New England Nuclear Kit); and whole blood cyanide (by the method of Rodkey[14,15]).

Hemodynamic measurements and blood samples were obtained: 1) prior to induction of anesthesia (blood samples only); 2) after anesthetic induction and placement in the prone position; 3) 10 min after incision (and infiltration with 1:500,000 epinephrine-saline mixture 25–50 ml); 4) after 10 min of constant SNP infusion sufficient to maintain $\overline{SAP}$ at 71 torr ± 3 (SE); and 5) after 40 min of SNP while the SNP infusion rate was held constant (4.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ± 0.53 SE). Propranolol, 0.03 mg/kg, iv, was then administered as a bolus. The SNP infusion rate continued at 4.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ± 0.53 SE and data were again collected: 10 min and 40 min after propranolol. The study was then terminated. All PRA samples were drawn from the pulmonary artery ex-

TABLE 2. Hemodynamic and Laboratory Values before and during Nitroprusside Infusion

	Awake	Prone Anesthetized	Incision + 10 min	SNP + 10 min	SNP + 40 min	Propranolol + 10 min	Propranolol + 40 min
HR (beats/min)		64 ± 4	64 ± 6	78 ± 7	80 ± 7†	70 ± 6‡	69 ± 5‡
$\overline{SAP}$ (torr)		79 ± 2	99 ± 3*	71 ± 3†	74 ± 3*	76 ± 2	74 ± 3
$\overline{PAP}$ (torr)		18 ± 2	22 ± 2*	14 ± 2†	16 ± 2†	17 ± 2	18 ± 2
PCWP (torr)		14 ± 2	16 ± 2*	8 ± 2†	12 ± 2†	13 ± 2	13 ± 2
CVP (torr)		9 ± 1	10 ± 1	6 ± 1†	8 ± 1*	9 ± 2	9 ± 1‡
CI $(l \cdot min^{-1} \cdot m^{-2})$		2.71 ± 0.09	2.91 ± 0.15	3.58 ± 0.41	3.99 ± 0.34†	3.34 ± 0.27‡	3.43 ± 0.20
PVR $(dyne \cdot sec \cdot cm^{-5})$		91 ± 18	103 ± 18	74 ± 10	54 ± 6†	71 ± 9‡	71 ± 9‡
SVRI $(dyne \cdot sec \cdot cm^{-5} \cdot m^2)$		2075 ± 87	2502 ± 163	1625 ± 145†	1389 ± 114†	1695 ± 137‡	1574 ± 129
SVI (ml/m^2)		43.47 ± 2.5	47.75 ± 3.9	48.92 ± 5.4	52.56 ± 5.6	49.90 ± 4.5	51.05 ± 3.7
Pa_{O_2} (torr)		139 ± 12	126 ± 9	120 ± 7†	110 ± 7†	120 ± 6	123 ± 7
Pa_{CO_2} (torr)		34 ± 2	34 ± 2	34 ± 2	35 ± 1	35 ± 1	35 ± 2
pH_a		7.46 ± 0.02	7.46 ± 0.02	7.43 ± 0.02	7.43 ± 0.02	7.44 ± 0.01	7.45 ± 0.02
$P\bar{v}_{O_2}$ (torr)		40 ± 1	38 ± 1	42 ± 2†	41 ± 1	39 ± 1	36 ± 1‡
Hct		36 ± 1	36 ± 1	35 ± 1	34 ± 1	34 ± 1	34 ± 1
PRA $(ng \cdot ml^{-1} \cdot h^{-1})$	2.37 ± 0.7	5.35 ± 1.43*	5.42 ± 1.29	6.66 ± 1.69	6.50 ± 1.45	5.47 ± 1.01	4.07 ± 0.73‡
CN^- $(\mu mol/l)$		1.02 ± 0.26			5.64 ± 0.85*		13.19 ± 2.26‡
Temperature (°C)		36.1 ± 0.1	35.6 ± 0.2	35.3 ± 0.2	35.1 ± 0.2	35.1 ± 0.3	35.0 ± 0.3

All values are means ± SE. * Indicates $P < 0.05$ *vs.* preceding value; †Indicates $P < 0.05$ *vs.* values 10 minutes after incision; ‡ Indicates $P < 0.05$ *vs.* values after 40 minutes of SNP (just before propranolol).

cept for those obtained before anesthetic induction which were from a peripheral vein.

All data were analyzed using Student's t test for paired data. $P < 0.05$ was regarded as significant.

Results

Incision resulted in significant increases in $\overline{SAP}$, $\overline{PAP}$, and PCWP as compared with control values (table 2). SNP infusion produced significant decreases in $\overline{SAP}$, SVRI, $\overline{PAP}$, PCWP, and PVR, accompanied by significant increases in HR and CI and a progressive reduction in Pa_{O_2} despite a constant inspired oxygen fraction of 0.3.

After propranolol administration there were significant decreases in HR and CI whereas SVRI, PVR, and CVP increased. The progressive reduction in arterial oxygen tension (Pa_{O_2}) observed during SNP infusion did not continue following propranolol.

PRA was 2.37 $ng \cdot ml^{-1} \cdot h^{-1} \pm 0.78$ SE prior to induction of anesthesia and increased significantly after induction of anesthesia, intubation, cannulation, and turning into the prone position. No further increase in PRA was observed after incision and SNP infusion. Propranolol administration significantly decreased PRA as compared with values measured just before propranolol was given. Control PRA values varied markedly between individuals, a finding also observed by others.[16]

Whole blood cyanide increased progressively during SNP infusion with a peak value of 13.19 μmol/l $\pm$ 2.26 SE being reached 40 min after propranolol was administered.

Discussion

The basic derangement in kyphoscoliosis is compression of lung tissue from chest wall distortion, with consequent loss of thoracic volume leading to ventilation-perfusion mis-match, hypoxia, and eventual pulmonary hypertension.[5] Our data after anesthesia and intubation agree well with the observations of Bergofsky *et al.*[2] in five unanesthetized patients with moderately severe kyphoscoliosis who were clinically comparable to our patients. They observed a $\overline{PAP}$ of 16 torr $\pm$ 2 (SE), a CI of 3.2 $l \cdot min^{-1} \cdot m^{-2} \pm 0.1$, and a normal PCWP.[3]

Infusion of the vasodilator SNP caused reductions in SVRI and PVR with resultant reductions in $\overline{SAP}$, $\overline{PAP}$, and PCWP. The concomitant increases in CI and HR are thought to be reflex responses to the decrease in $\overline{SAP}$[17,18] and may be baroceptor-mediated.[19] The hemodynamic response to propranolol was characterized by decreases in HR and CI within 10 min of the administration of the drug. These observations are in agreement with previously published data demonstrating that intravenous propranolol decreases HR and CI within minutes.[20]

The significant increase in PRA after anesthesia and the absence of a further increase after epinephrine infiltration, surgical incision, and SNP infusion apparently reflect a near-maximal renin response to induction of anesthesia, endotracheal intubation, vascular cannulation, and turning prone.[21,22] Propranolol significantly decreased PRA as compared with levels observed just before propranolol was given, but this was not seen until 40 min after the drug was administered. Davies and Slater also found a 15–30 min delay after propranolol before observing decreased PRA response to head-tilt maneuvers in healthy subjects.[23] In the rat PRA supports blood pressure during SNP-induced hypotension and this effect can be blocked by propranolol.[24] In addition, propranolol is known to block the renal release of renin in response to both generalized sympathetic stimulation[25] and direct stimulation of the renal nerves.[26] Thus, our data appear to indicate two distinct effects of propranolol during SNP hypotension: 1) an early, direct effect on the heart characterized by decreases in HR and CI; and 2) an effect on the kidney manifested by a decrease in PRA occurring later.

Arterial oxygenation decreased progressively during SNP infusion, despite a constant inspired oxygen fraction of 0.30. This may have been related to release of hypoxic pulmonary vasoconstriction by SNP, a significant phenomenon known to occur in dogs,[27,28] but as yet unproven in humans.[29] PVR increased after propranolol, and it is possible that propranolol reversed the effect of SNP on hypoxic pulmonary vasoconstriction by restoring pulmonary vascular tone. This is highly speculative since propranolol has no apparent effect on arterial vasodilation caused by nitroglycerin, histamine, or acetylcholine.[30] In addition, the pulmonary vasculature is unresponsive to angiotensin-II[31] which should have decreased along with the decrease in PRA values after propranolol. An alternative explanation for the effect of propranolol on oxygenation is that it reversed the progressive increase in cardiac output caused by SNP infusion. As recently pointed out by Cheney and Colley, the effect of cardiac output on oxygenation may be variable, but in regional atelectasis, such as is seen with kyphoscoliosis, shunt fraction has been found most frequently to vary inversely with cardiac output.[32]

The continuous increase in CN^- levels during the study period was due to the constant rate of infusion of SNP. There was, however, no change in arterial pH or Pv_{O_2} suggestive of cyanide toxicity in any of the patients.

In summary, propranolol administration during SNP infusion decreases HR, CI, and PRA. These may be the mechanisms by which previously documented decreases in SNP dose requirement by propranolol[12] are achieved.

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