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High Spinal Anesthesia for Cardiac Surgery

Effects on β-Adrenergic Receptor Function, Stress Response, and Hemodynamics

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Background: **This double-blind, randomized, controlled trial examined the effect of high-dose intrathecal bupivacaine in combination with general anesthesia on atrial β-adrenergic receptor function, the stress response, and hemodynamics during coronary artery bypass graft surgery.**

Methods: **Thirty-eight patients were randomized to either control (n = 19) or intrathecal bupivacaine (ITB) groups (n = 19). Patients in the ITB group received 37.5 mg intrathecal hyperbaric bupivacaine before induction of general anesthesia. Control patients received an injection of local anesthetic into the skin and subcutaneous tissues (sham spinal). Comparisons were made between groups with respect to atrial receptor desensitization and down-regulation, in addition to circulating catecholamines and hemodynamics.**

Results: **In patients with cardiopulmonary bypass (CPB) times in excess of 1 h, the ITB group had significantly less atrial β-receptor dysfunction, as measured by maximal isproteronol, 50% maximal isoproterenol, sodium fluoride–stimulated activity, and zinterol stimulation assays of adenylyl cyclase activity ($P \leq 0.02$) and β-adrenergic receptor density ($P = 0.02$). Serum epinephrine, norepinephrine, and cortisol concentrations were significantly lower in the ITB group, independent of CPB times ($P < 0.0001$, $P < 0.001$, and $P < 0.05$, respectively). ITB patients had a higher cardiac index and a lower pulmonary vascular resistance index in the post-CPB time period ($P < 0.01$ and $P < 0.05$, respectively). In the pre-CPB period, mean arterial pressure and systemic vascular resistance index were significantly lower in the ITB group.**

Conclusions: **High-dose intrathecal bupivacaine, when combined with general anesthesia, resulted in less β-receptor dysfunction and a lower stress response during coronary artery bypass graft surgery.**

CARDIAC surgery is a highly provocative stimulus for the release of endogenous catecholamines and stress hormones.[1–3] In particular, the initiation of cardiopulmonary bypass (CPB) is well known to increase blood norepinephrine, epinephrine, and cortisol concentrations.[3–5] These hormones, the concentrations of which remain variably elevated in the postoperative period, have the potential for adverse systemic effects, including the disruption of the myocardial oxygen supply/demand ratio, increased catabolism, and impaired immune function.[6,7] Attenuation of the stress response has the potential to prevent some of the adverse sequelae following cardiac surgery.[8,9] Although it is possible to minimize the stress response with high doses of intravenous opioids, it is not possible to completely block the stress response to CPB.[1,10–12] In addition, these high-dose techniques generally prolong intubation times, which for numerous reasons is no longer the standard of care for cardiac surgery.[13–19]

High circulating catecholamine concentrations have been linked, *via* desensitization, to β-adrenergic receptor (βAR) dysfunction after CPB.[20,21] This desensitization may be a contributing factor to the decreased myocardial performance that can occur immediately following cardiac surgery. Measurement of intraoperative right atrial βAR density and adenylyl cyclase activity have served as good indices for gauging the effectiveness of various techniques in blunting catecholamine-mediated stress responses.

Thoracic epidural anesthesia (TEA) has previously been shown to blunt the stress hormone response to coronary artery bypass graft surgery (CABG)[22] and to decrease troponin release after cardiac surgery.[9] In a number of small studies, TEA reduces myocardial oxygen consumption and intraoperative and postoperative arrhythmias, and improves analgesia, pulmonary function, and hemodynamic stability.[2,8,9,23] However, its utility has been questioned because of the fear of traumatic insertion of the large epidural needle and catheter, with the accompanying risk of neuraxial hematoma subsequent to full heparinization.[24–28] Although a survey of cardiac anesthesiologists suggests that the use of TEA is relatively common,[29] the actual number of patients reported to have received epidural anesthesia for cardiac surgery is relatively small.[17] An estimate of the safety of TEA for cardiac surgery is therefore not possible at this stage. Similarly, the use of intrathecal opiates in cardiac surgery is also common,[29] but large numbers of patients have been reported without any adverse neurologic sequelae.[17] Kowalewski *et al.*[30] reported the technique of general anesthesia combined with intrathecal bupivacaine (ITB)–morphine for cardiac surgery. High-dose ITB may be an anesthetic technique that could provide some of the benefits of TEA without some of the potential risks.

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This double-blind, randomized, placebo-controlled trial was designed to test the primary hypotheses that high-dose ITB will decrease right atrial βAR desensitization and reduce the catecholamine stress hormone response to CABG surgery. The study was also designed to test the secondary hypothesis that high-dose ITB combined with general anesthesia would provide stable intraoperative hemodynamics. We additionally hypothesized that the technique would provide improved intraoperative left ventricular regional wall motion and would improve respiratory function for 24 h postoperatively.

Materials and Methods

Perioperative Management and Anesthetic Technique

After we obtained University of Manitoba Health Sciences Center Ethics Committee approval and written informed consent, consecutive patients undergoing primary CABG surgery were enrolled in the study. Exclusion criteria included age greater than 80 yr; body mass index greater than 35 kg/m^2; emergency surgery; previous cardiac surgery; coagulopathy as defined by platelet count less than 100,000/ml; any anticoagulant medications other than acetylsalicylic acid, nonsteroidal antiinflammatory drugs, or low-dose subcutaneous heparin; infection at the lumbar puncture site; serum creatinine concentration greater than 180 μM; systolic blood pressure greater than 180 mmHg or diastolic blood pressure greater than 110 mmHg; known or anticipated difficult airway; the use of clonidine or corticosteroids preoperatively; and history of tolerance to narcotics.

Patients were premedicated with 0.1 mg/kg oral diazepam 90 min preoperatively. On arrival to the operating room, patients were further sedated with 0.015 mg/kg intravenous midazolam and 0.1 μg/kg sufentanil. Before the intrathecal injection, patients received a lactated Ringer's fluid bolus of either 6 ml/kg if admitted on the same day of surgery or 3 ml/kg if an inpatient. Invasive hemodynamic monitors were placed, including radial arterial cannula and right internal jugular central venous access, through which a pulmonary artery catheter was placed.

An anesthesiologist not directly involved in the management of the case consecutively randomized patients into either the control group or the ITB group, using a previously generated randomization table, and performed the intrathecal injection. Patients were placed in the right lateral position, and the skin was prepared and draped in an aseptic fashion. Patients in the control group received only local infiltration of the skin with 2 ml of 2% preservative-free lidocaine with a 25-gauge, 3.8-cm needle, but did not receive an intrathecal injection. In the ITB group, after local infiltration, placement of the spinal bupivacaine was accomplished in the region of the second to fourth lumbar interspace using a 25-gauge Whitacre spinal needle (Becton Dickinson Anesthesia Systems, Franklin Lakes, NJ). A maximum of three attempts to successfully locate the subarachnoid space was allowed before the patient was removed from the study. Similarly, in the event of blood returning in the spinal needle, the spinal anesthetic technique was discontinued, heparinization was delayed for 1 h, and the patient was removed from the study. When clear, free-flow of cerebrospinal fluid was established, 5 ml of 0.75% preservative-free, hyperbaric bupivacaine was injected. All patients were placed in 30° Trendelenburg position for 7 min. The study design was such that the initial two hemodynamic measurements would be performed before the administration of any chronotropic or vasoactive medications. The level of spinal anesthesia was determined by checking for the onset of loss of cold sensation. In the absence of at least a T1 level of anesthesia, the ITB-group patients were removed from the study. Immediately before induction, the anesthesiologist who performed and tested the block was then replaced by a second anesthesiologist who remained blinded to the treatment group assignment. Anesthesia was subsequently induced with 2–4 mg/kg thiopental, 0.6 mg/kg rocuronium, and 0.4 μg/kg sufentanil.

Isoflurane (0.4–2.0%, inspired) was titrated to maintain a mean arterial blood pressure (MAP) of 60–90 mmHg. Intravenous nitroglycerin and phenylephrine were also used to control hemodynamic parameters. Intravenous glycopyrrolate (0.2 mg) or atropine (0.3 mg) was used to treat bradycardia of less than 35 beats/min. Ventilation was set to a tidal volume of 10 ml/kg, with positive end-expiratory pressure of 5 cm H_2O, and respiratory rate was titrated to maintain an arterial carbon dioxide partial pressure of 35–40 mmHg. Heparin was administered to establish an activated clotting time of greater than 500 s.

The CPB circuit was primed with a small crystalloid volume (1 l). CPB was conducted with a roller pump and a membrane oxygenator at 33–35°C. Flow was maintained at 2.2–2.5 $l \cdot min^{-1} \cdot m^{-2}$. Alpha-stat blood gas management was used throughout. Five grams of ε aminocaproic acid was given before CPB, and 5 g was also added to the CPB prime. During CPB, all patients received a minimum of 1% isoflurane, titrated to maintain a MAP of 50–80 mmHg.

Before aortic cross-clamp removal, all patients received 4 g magnesium sulfate. A standard dose of 7 mg/kg intravenous $CaCl_2$ was given 2 min before separation from CPB. On separation from CPB, isoflurane was discontinued, and anesthesia was maintained using a propofol infusion of 0.5–5.0 $mg \cdot kg^{-1} \cdot h^{-1}$. Lactated Ringer's and 10% Pentaspan (B. Braun Medical Inc., Bethlehem, PA) were used as required for volume resuscitation in the post-CPB period. Protamine (1 mg/100 U of heparin) was given for heparin reversal. Blood product use was at the discretion of the attending anes-

thesiologist. Fluid balance for the intraoperative period was calculated by subtracting the urine output as well as weighed and suctioned blood loss from the total fluids administered and the CPB balance. Muscle relaxation was reversed with the administration of 0.04 mg/kg intravenous neostigmine and 0.008 mg/kg glycopyrrolate. All patients received 4 μg/kg intravenous flumazenil to ensure no residual benzodiazepine effects. Patients were extubated either before leaving the operating room or immediately on arrival to the postanesthesia care unit (PACU).

Postoperative antihypertensive therapy consisted of 5–15 mg intravenous labetalol as needed, sublingual nifedipine, or intravenous nitroglycerin infusion, titrated according to protocol. Phenylephrine was used to treat hypotension. Time of discharge from the PACU to the low-intensity step-down unit was at the discretion of the attending anesthesiologist, as per established institutional practice. Postoperative analgesia consisted of intravenous morphine patient-controlled analgesia (PCA) for 24 h, followed by oral acetaminophen with or without codeine titrated to visual analog scale (VAS) pain score. Nonsteroidal antiinflammatory drugs were not prescribed perioperatively. Patients were assessed on a daily basis until discharged from hospital.

Physiologic Data Collection and Sampling

Atrial adenylyl cyclase activity and βAR density were measured both before and after CPB. Right atrial biopsy specimens were taken before and after CPB for β-receptor function analysis. Approximately 100 mg (wet weight) of right atrial tissue was obtained immediately before venous cannulation. The second atrial biopsy specimen was taken after rewarming, immediately following decannulation of the atrium, from a tissue site that remained perfused during CPB. Samples were immediately frozen (−70°C) and subsequently processed for βAR density and functional assays of the receptor complex activity as per Booth *et al.*[21] These functional assays measure the different units of the β-receptor complex: (1) basal activity of the receptor complex; (2) maximal activity after stimulation with the nonselective βAR stimulant isoproterenol; (3) 50% maximal activity after stimulation with isoproterenol; (4) zinterol-stimulated activity, which measures maximum β_2 activity; (5) manganese-stimulated activity (manganese is a direct stimulant of adenylyl cyclase); and (6) sodium fluoride–stimulated activity, which directly stimulates the G-protein.

Serum epinephrine, norepinephrine, and cortisol samples from arterial blood were taken at six standardized time points: immediately before administration of ITB, 5 min after tracheal intubation, 5 min after sternotomy, 30 min after the initiation of CPB, 30 min after separation from CPB, and 4 h after arrival in PACU. Samples were processed immediately and flash-frozen at −70°C until analysis.[21]

Hemodynamic measurements, including heart rate, MAP, cardiac index, mean pulmonary artery pressure, pulmonary artery wedge pressure, systemic vascular resistance index, and pulmonary vascular resistance index were recorded at 13 standardized time points: immediately before administration of the spinal bupivacaine, 2 min after spinal but before induction, 1 min after tracheal intubation, 10 min after tracheal intubation, 1 min after sternotomy, 10 min after sternotomy, 20 min after sternotomy, 1 min after separation from CPB, 10 min after separation from CPB, 20 min after separation from

Table 1. Preoperative Patient Characteristics

Characteristic	Control (n = 19)	ITB (n = 19)	Significance
Age, yr	65.4 ± 1.3	61.0 ± 2.5	NS
Sex (male), n	18	16	NS
Weight, kg	84.0 ± 3.3	89.0 ± 3.5	NS
BMI, kg/m^2	27.50 ± 0.67	29.30 ± 0.67	NS
Creatinine, μm	89.5 ± 5.0	85.6 ± 7.4	NS
Smoking history	15	12	NS
Smoking, pack years	24.0 ± 7.0	16.0 ± 4.4	NS
Coexisting disease, n			
Diabetes	4	4	NS
Hypertension	10	11	NS
Atrial fibrillation	0	0	NS
Medications, n			
β-Blockers	16	16	NS
Calcium channel blockers	6	7	NS
Long-acting nitrates	9	8	NS
Digoxin	0	0	NS
Other antiarrhythmics	0	1	NS
Diuretics	4	3	NS
ACE inhibitors	8	3	NS

Results are expressed as mean ± SEM. *P* values are given for unpaired *t* test or chi-square analysis where appropriate.

ACE = angiotensin converting enzyme; BMI = body mass index; ITB = intrathecal bupivacaine; NS = not significant.

Table 2. Intraoperative and Postoperative Patient Characteristics

Characteristic	Control (n = 19)	ITB (n = 19)	Significance
Pre-CPB			
Sodium thiopental dose, mg/kg	2.92 ± 0.31	2.10 ± 0.10	$P = 0.02$
Rocuronium dose, mg/kg	0.65 ± 0.02	0.69 ± 0.03	NS
Mean %Et isoflurane	0.98 ± 0.04	0.49 ± 0.02	$P < 0.0001$
Sufentanil dose, μg/kg	0.51 ± 0.01	0.49 ± 0.01	NS
Phenylephrine total, μg/kg	5.65 ± 2.04	14.85 ± 3.20	$P = 0.02$
Nitroglycerine total, μg/kg	0.61 ± 0.38	0	NS
During CPB			
Mean %Et isoflurane	1.07 ± 0.05	1.02 ± 0.03	NS
Phenylephrine total, μg/kg	14.80 ± 2.14	23.30 ± 6.67	NS
Nitroglycerine total, μg/kg	0	0	NS
Lowest temperature, °C	34.80 ± 0.14	34.20 ± 0.22	$P = 0.05$
Total number of distal grafts per patient	3.26 ± 0.26	3.26 ± 0.21	NS
Post-CPB			
Propofol dose, mg/kg	3.08 ± 0.23	3.10 ± 0.28	NS
Phenylephrine total, μg/kg	0.92 ± 0.43	2.22 ± 0.56	NS
Nitroglycerine total, μg/kg	0.85 ± 0.47	0.59 ± 0.22	NS
Aortic cross-clamp time, min	31.80 ± 2.28	32.50 ± 2.29	NS
Total CPB time, min	59.40 ± 4.91	58.10 ± 4.48	NS
Fluid balance for entire case, ml/kg	36.50 ± 2.54	35.75 ± 3.62	NS
PACU			
Extubation time, min	19.40 ± 2.50	10.90 ± 2.11	NS
Patients requiring mechanical ventilation, n	0	1	NS
Patients requiring post-CPB inotropic therapy, n	0	1	NS
Patients failing to meet PACU discharge criteria after 4 h, n	0	1	NS
Bromage score in PACU (immediately postextubation)	0.40 ± 0.20	1.70 ± 0.40	$P = 0.003$
Length of stay (postoperative), days	4.50 ± 0.18	5.10 ± 0.48	NS

Results are expressed as mean ± SEM.

CPB = cardiopulmonary bypass; ITB = intrathecal bupivacaine; NS = not significant.

CPB, immediately on arrival in the PACU, 1 h after arrival in PACU, and 4 h after arrival in PACU.

Where possible, patients received a transthoracic echocardiography study to determine preoperative 16-segment left ventricular wall motion score indexes.[31] Intraoperative transesophageal echocardiography studies were undertaken 10 min after induction, 5 min before CPB, and 15 min after separation from CPB. The studies were recorded and subsequently interpreted by a cardiologist certified in echocardiography who was blinded to group assignment. The left ventricular wall motion score index, a quantitative measure of wall motion abnormalities, was calculated.[31] Perioperative spirometry, arterial blood gases, and cardiac enzymes were

Table 3. Adenylyl Cyclase Activity and β-Adrenergic Receptor Density Pre-CPB and Post-CPB in Patients with CPB Duration from 0 to 60 min

Experimental Parameter	Activation Target	Group	Pre-CPB	Post-CPB	*P*
Isoproterenol (maximum)	β-AR	Control	1,363 ± 137	1,139 ± 124	0.52
		ITB	1,327 ± 694	1,100 ± 111	0.12
Isoproterenol (EC_{50})	β-AR	Control	792.0 ± 74.6	636.0 ± 64.3	0.29
		ITB	755 ± 100	605 ± 65.1	0.23
Zinterol	β_2-AR	Control	919 ± 95	811 ± 89	0.35
		ITB	757 ± 99	571 ± 55	0.09
Sodium fluoride	G protein	Control	2,146 ± 160	1,901 ± 120	0.47
		ITB	1,813 ± 213	1,569 ± 116	0.66
Manganese	Adenylyl cyclase	Control	1,447 ± 107	1,200 ± 100	0.28
		ITB	1,242 ± 172	932 ± 97	0.34
β-AR B_{max}		Control	68.0 ± 5.4	63.0 ± 7.0	0.53
		ITB	54 ± 16	52.0 ± 6.8	0.70

Selective activation of the β-adrenergic receptor (β-AR and β_2-AR) by isoproterenol (maximum), isoproterenol (EC_{50}), and zinterol; activation of G protein by sodium fluoride; or activation of adenylyl cyclase moiety by manganese are shown (control group, n = 10; intrathecal bupivacaine [ITB] group, n = 9). Adenylyl cyclase activity and β-adrenergic receptor density (β-AR B_{max}) are reported as picomoles of cyclic adenosine monophosphate per milligrams of protein every 15 min and femtomoles per milligram of protein, respectively. *P* values are given for the log-transformed, least-squared means multiple comparisons test. Results are expressed as mean ± SEM.

CPB = cardiopulmonary bypass.

Table 4. Adenylyl Cyclase Activity and β-Adrenergic Receptor Density Pre-CPB and Post-CPB in Patients with CPB Duration from 61 to 120 min

Experimental Parameter	Activation Target	Group	Pre-CPB	Post-CPB	*P*
Isoproterenol (maximum)	β-AR	Control	1,339 ± 244	973 ± 186	0.02
		ITB	1,657 ± 238	1,361 ± 179	0.23
Isoproterenol (EC_{50})	β-AR	Control	720 ± 127	507 ± 84	0.02
		ITB	959 ± 170	773 ± 109	0.22
Zinterol	β_2-AR	Control	876 ± 147	620 ± 113	0.01
		ITB	1,107 ± 153	873 ± 98	0.16
Sodium fluoride	G protein	Control	2,189 ± 259	1,514 ± 157	0.003
		ITB	2,572 ± 215	2,110 ± 167	0.10
Manganese	Adenylyl cyclase	Control	1,434 ± 141	936 ± 134	0.002
		ITB	1,682 ± 180	1,396 ± 164	0.14
β-AR B_{max}		Control	60 ± 5.9	45 ± 4.3	0.02
		ITB	74 ± 7.3	69 ± 6.3	0.66

Selective activation of the β-adrenergic receptor (β-AR and β_2-AR) by isoproterenol (maximum), isoproterenol (EC_{50}), and zinterol; activation of G protein by sodium fluoride; or activation of adenylyl cyclase moiety by manganese are shown (control group, n = 9; intrathecal bupivacaine [ITB] group, n = 10). Adenylyl cyclase activity and β-adrenergic receptor density (β-AR B_{max}) are reported as picomoles of cyclic adenosine monophosphate per milligrams of protein every 15 min and femtomoles per milligram of protein, respectively. *P* values are given for the log-transformed, least-squared means multiple comparisons test. Results are expressed as mean ± SEM.

CPB = cardiopulmonary bypass.

measured. All patients completed a validated, intraoperative awareness questionnaire. Postoperative VAS pain scores and total analgesic use were also measured.

Statistical Analysis

Statistical analyses were provided by the University of Manitoba Biostatistical Consulting Unit, using the Statistical Analysis System version 7.0 (SAS Institute Inc., Cary, NC). Patient demographic, intraoperative and postoperative characteristics data were examined using unpaired *t* tests and chi-square analyses. Because βAR desensitization is a time-dependent process, patients with CPB times greater than 60 min were *a priori* analyzed separately from those patients with CPB times less than 60 min.[20,21] Hemodynamic and pulmonary function data were examined using least-squared means multiple comparisons tests. Stress hormone and atrial biopsy data were tested for homoscedasticity using the Shapiro-Wilk test for normality, and data were log-transformed where appropriate.[32,33] Sample size was determined using the data from Booth *et al.*[21] regarding βAR dysfunction after CPB, and indicated that an enrollment of 30 patients per group would provide an 80% power in detecting a 25% reduction in βAR desensitization in the treatment group compared with the control group. Significance was set at $P \leq 0.05$.

Results

Patient Characteristics

A total of 38 patients were enrolled in the study. The target sample size of 30 patients per group could not be achieved because of time limitations and financial constraints. There were no significant differences in the preoperative patient characteristics (table 1). Sixteen patients in each group were taking β-blockers preoperatively. No patient had a history of preoperative atrial fibrillation.

Intraoperative and postoperative patient characteristics are shown in table 2. No patients were removed from the study once enrolled. Because all patients had given informed consent and were informed of the possible occurrence of dyspnea and upper and lower extremity paresthesia and weakness as a result of the intrathecal injection, no patients had complaints in this respect. Pre-CPB phenylephrine use was significantly higher in the ITB group (5.65 ± 2.04 μg/kg control *vs.* 14.5 ± 3.20 μg/kg ITB; $P = 0.02$). Phenylephrine use during and after CPB did not differ between groups. The ITB group received significantly less pre-CPB isoflurane (0.98 ± 0.04% control *vs.* 0.49 ± 0.02% ITB; $P < 0.0001$). The total fluid balance did not differ between groups. Mean extubation times (measured from the time of sternotomy dressing application) were short and not significantly different (19.4 ± 2.5 min control *vs.* 10.8 ± 2.1 min ITB). The modified Bromage score[34] was used to assess the residual motor block in the PACU and was higher in the ITB group (0.4 ± 0.2 control *vs.* 1.7 ± 0.4 ITB; $P = 0.003$). All patients had a Bromage scale of 0 before discharge from the PACU. One patient in the ITB group required a dopamine infusion (2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for postoperative hypotension (MAP < 60 mmHg and cardiac index < 2.2 $l \cdot min^{-1} \cdot m^{-2}$). This was initiated 1 h before the final catecholamine and cortisol sampling. This patient also required postoperative mechanical ventilation for 8 h. The patient was admitted to the surgical intensive care unit and discharged to the step-down ward the following day. Because exogenous dopamine increases serum catecholamine concentrations, this patient's postoperative stress hormone data were excluded from the study. Perioperative atropine and glycopyrrolate for bradycardia were

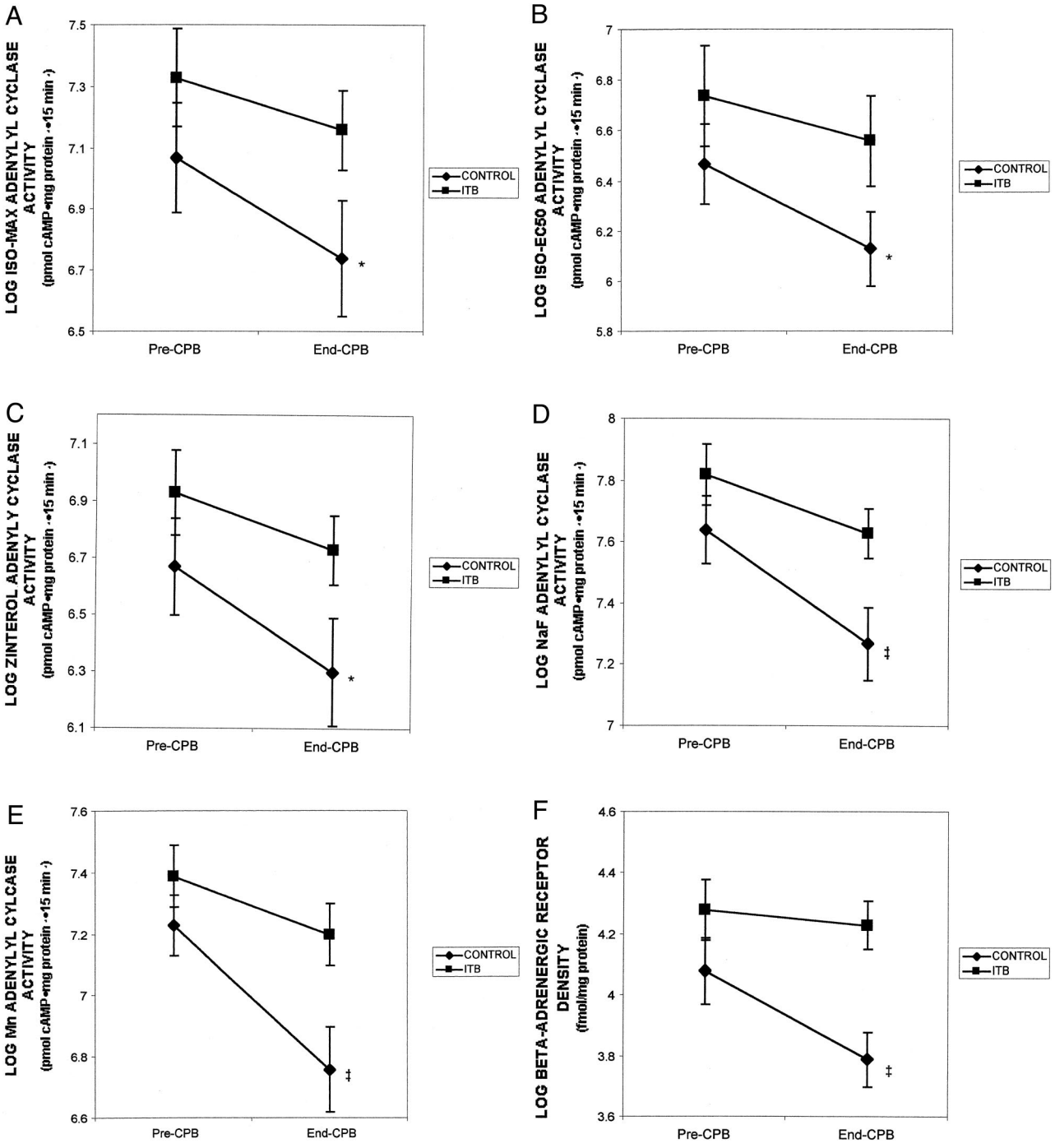

Fig. 1. (*A*) Maximal isproteronol (ISO MAX), (*B*) 50% maximal isoproterenol (ISO EC_{50}), (*C*) zinterol, (*D*) sodium fluoride (NaF)-stimulated, and (*E*) manganese (Mn)-stimulated β-adrenergic receptor (βAR) responsiveness, as measured by adenylyl cyclase activity in control and intrathecal bupivacaine (ITB) groups with cardiopulmonary bypass (CPB) times from 61–120 min. The control group shows a significant decline in adenylyl cyclase activity in each of these measures, whereas the ITB group does not. (*F*) βAR density in control and ITB groups with CPB times from 61–120 min. The control group shows a significant decline in βAR density at $P = 0.02$. Adenylyl cyclase activity and βAR density (βAR Bmax) are reported as picomoles of cyclic adenosine monophosphate per milligram of protein per 15 min and femtomoles per milligram of protein, respectively. The data were log-transformed. Results are expressed as mean ± SEM (*$P < 0.05$, ‡$P < 0.005$).

not required. Postoperative labetalol and nifedipine were also not required. No patients in the ITB group and only one patient in the control group received postoperative intravenous nitroglycerin therapy, which was discontinued before discharge from the PACU. No patients required medical intervention for new-onset atrial fibrillation, and at the time of discharge from hospital, all patients were in sinus rhythm. There were no reports of

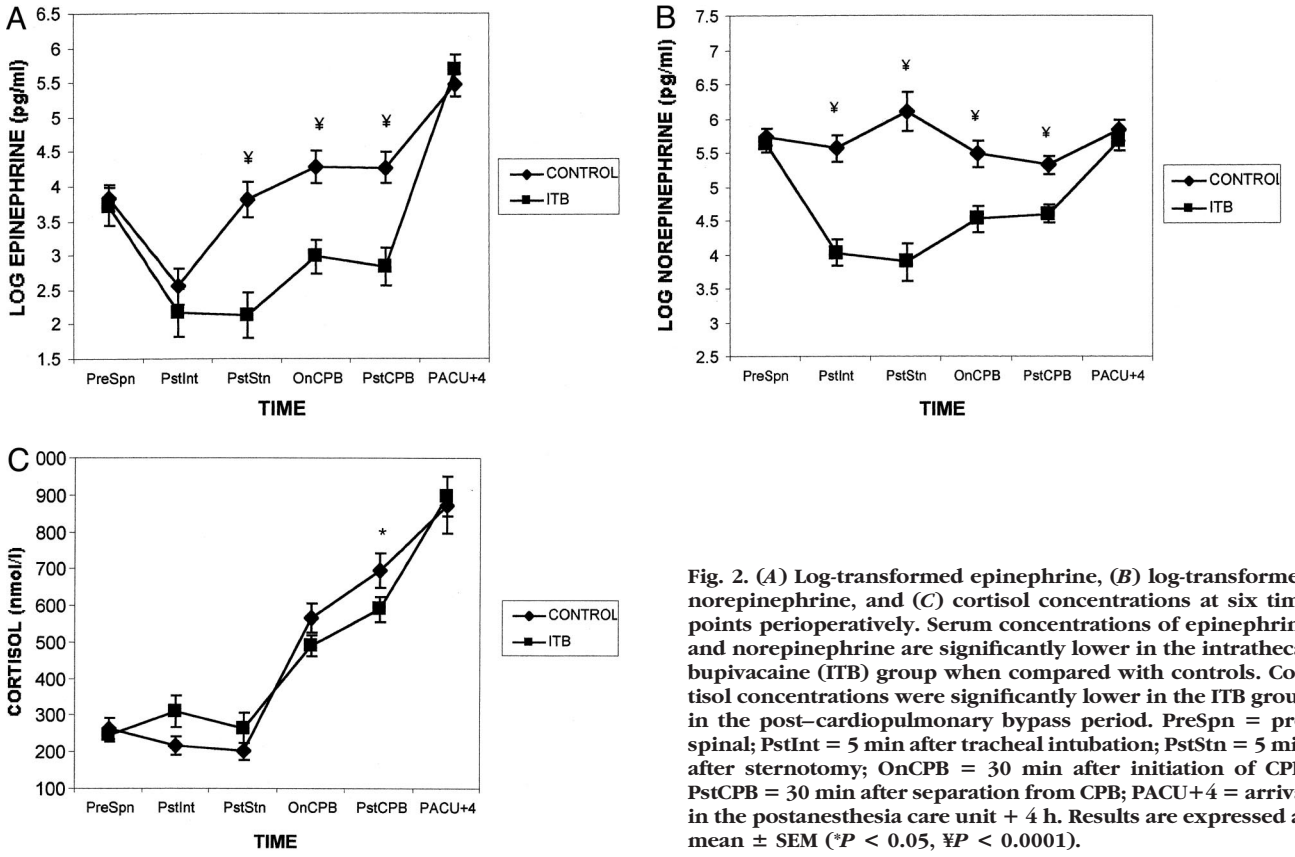

Fig. 2. (*A*) Log-transformed epinephrine, (*B*) log-transformed norepinephrine, and (*C*) cortisol concentrations at six time points perioperatively. Serum concentrations of epinephrine and norepinephrine are significantly lower in the intrathecal bupivacaine (ITB) group when compared with controls. Cortisol concentrations were significantly lower in the ITB group in the post–cardiopulmonary bypass period. PreSpn = prespinal; PstInt = 5 min after tracheal intubation; PstStn = 5 min after sternotomy; OnCPB = 30 min after initiation of CPB; PstCPB = 30 min after separation from CPB; PACU+4 = arrival in the postanesthesia care unit + 4 h. Results are expressed as mean ± SEM (*$P < 0.05$, ¥$P < 0.0001$).

intraoperative awareness. Postoperative hospital length of stay did not differ, with mean times of 4.5 ± 0.18 and 5.1 ± 0.48 days for the control and ITB groups, respectively.

Primary Outcomes

Adenylyl Cyclase Activity and β-Adrenergic Receptor Density. Adenylyl cyclase activity and βAR density are shown in tables 3 and 4. Control patients in the 0–60-min CPB group (table 3) did not show a significant βAR desensitization effect and had a constant βAR density. In contrast, control patients exposed to CPB times greater than 60 min (table 4) showed statistically significant declines in βAR function, as measured by each experimental parameter. βAR density in this subset also declined by 20% ($P = 0.02$). In the 61–120-min subgroup, the ITB patients did not show any significant changes in adenylyl cyclase activity, nor did the βAR density show a significant decline (fig. 1).

Plasma Catecholamines and Cortisol. Plasma epinephrine, norepinephrine, and cortisol concentrations were measured at six time points, as shown in figure 2. Epinephrine concentrations were significantly lower in the ITB group after sternotomy and on CPB, as well as in the post-CPB period ($P < 0.0001$). Similarly, norepinephrine concentrations were lower in the ITB group from the postintubation period to the 30 min post-CPB time point ($P < 0.0001$). The plasma cortisol concentrations were significantly lower in the post-CPB period ($P = 0.03$). When the data were substratified according to CPB times of 0–60 min and greater than 60 min, the analysis yielded the same statistical results.

Secondary Outcomes

Hemodynamics. The hemodynamic data are shown in figure 3. Time points 1 and 2 represent periods where no intravenous vasopressors or chronotropic agents were administered to the patient, *i.e.*, unmedicated hemodynamic points. Heart rate remained stable in both the control and ITB groups. When measured 1 min after separation from CPB, the cardiac index in the ITB group was transiently but significantly higher ($P < 0.01$). MAP remained lower in the ITB group until the recovery period ($P < 0.05$ to $P < 0.0001$). Mean pulmonary artery and pulmonary artery wedge pressures were significantly lower 2 min after spinal injection ($P < 0.0001$ and $P < 0.005$, respectively), but thereafter remained relatively constant between groups. The systemic vascular resistance index was significantly lower in the ITB group from the postspinal to the 1-min postseparation from CPB periods ($P < 0.05$ to $P < 0.0001$). The pulmonary vascular resistance index was significantly lower in the ITB group at 1 min after separation from CPB ($P \leq 0.05$).

Left Ventricular Wall Motion Score Indices. Preoperative transthoracic echocardiograms were obtained in a subset of eight control patients and seven ITB patients.

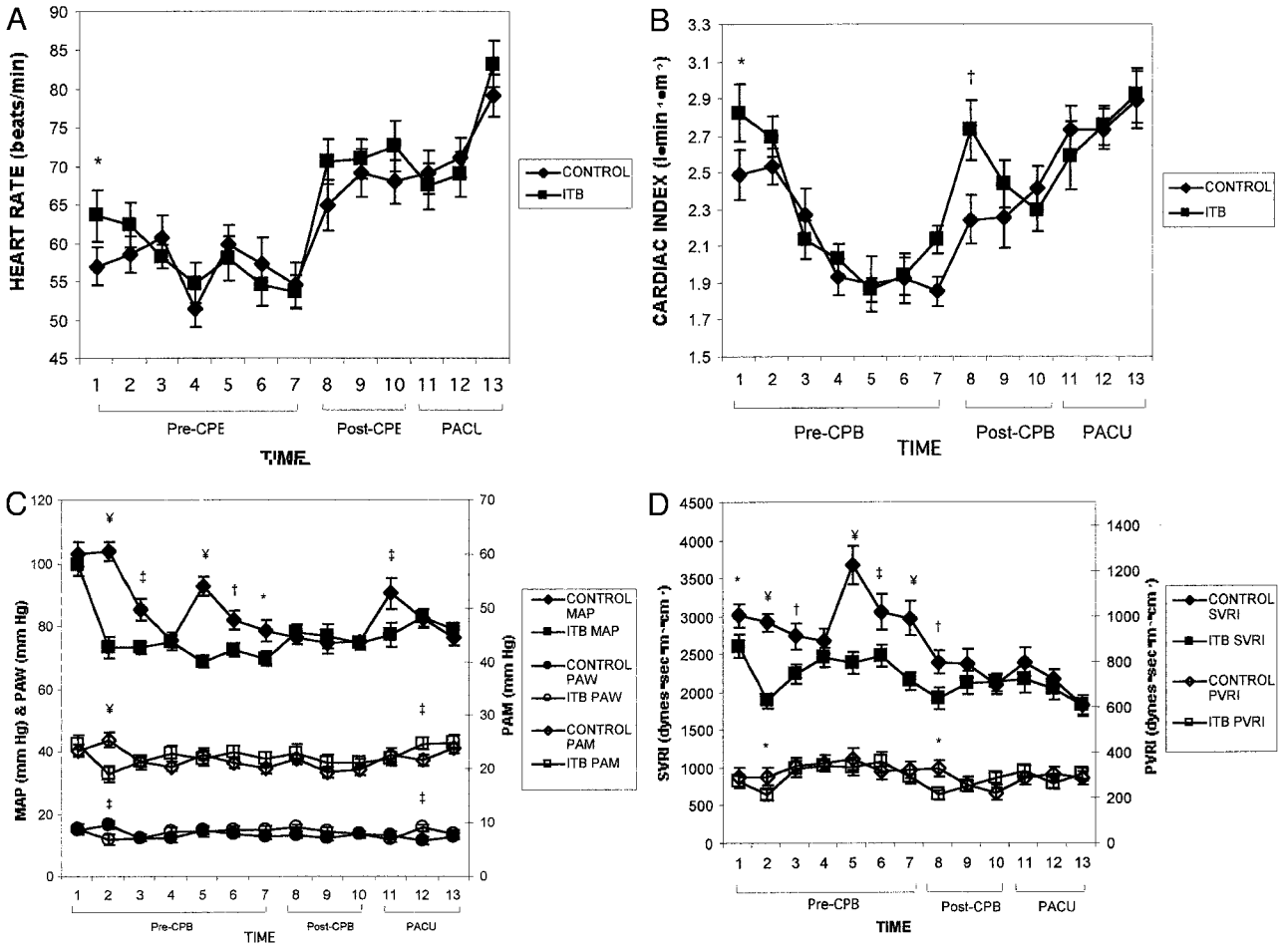

Fig. 3. Hemodynamic data: (*A*) heart rate; (*B*) cardiac index; (*C*) mean arterial pressure (MAP), pulmonary artery wedge (PAW), and pulmonary artery (PA) pressures; and (*D*) vascular resistance indices. MAP, PAW pressure, and systemic vascular resistance index were lower in the intrathecal bupivacaine (ITB) group. The cardiac index was significantly higher in the ITB group at 1 min after separation from cardiopulmonary bypass (CPB). Time points 1 to 13 represent the standardized sampling points: 1 = prespinal; 2 = 2 min after spinal preinduction; 3 = 1 min after tracheal intubation; 4 = 10 min after induction; 5 = 1 min after sternotomy; 6 = 10 min after sternotomy; 7 = 20 min after sternotomy; 8 = 1 min after separation from CPB; 9 = 10 min after separation from CPB; 10 = 20 min after separation from CPB; 11 = immediately on arrival in the postanesthesia care unit (PACU); 12 = PACU + 1 h; 13 = PACU + 4 h. Results are expressed as mean ± SEM (*$P < 0.05$, †$P < 0.01$, ‡$P < 0.005$, ¥$P < 0.0001$).

Transthoracic studies could not be obtained in all patients because of local health care system limitations and booking restrictions. All patients received intraoperative transesophageal echocardiography evaluations. Echocardiography tapes were interpreted off-line by an echocardiographer blinded to the group assignment. Left ventricular wall motion score indices were calculated for each patient and entered into the database for statistical analysis.[31] As demonstrated in figure 4, left ventricular wall motion score indices were significantly lower in the ITB group at the postintubation and pre-CPB periods ($P < 0.05$).

Respiratory Function and Gas Exchange Data. There were no significant differences in baseline or perioperative bedside spirometry between groups (table 5). When compared with controls, the ITB group had a significantly lower mean arterial carbon dioxide partial pressure at the 4-h postoperative time point (48 ± 1.4 mmHg control *vs.* 44 ± 1.1 ITB; $P < 0.01$). HCO_3^- was also lower in the ITB group when compared with controls (24 ± 0.34 mmHg control *vs.* 23 ± 0.39 mmHg ITB; $P < 0.05$).

Visual Analog Pain Scores and Analgesic Requirements. Visual analog scale pain scores, cumulative PCA morphine attempts, and the cumulative PCA morphine dose delivered were measured in the postoperative period. There were no significant differences in postoperative VAS pain scores or PCA use (table 6).

Discussion

The sympathectomy induced when using TEA with local anesthesia has previously been shown to be more efficacious than intravenous narcotics in blunting the stress response to CABG surgery.[9,22] In addition, high TEA has been shown to reduce the release of troponin T

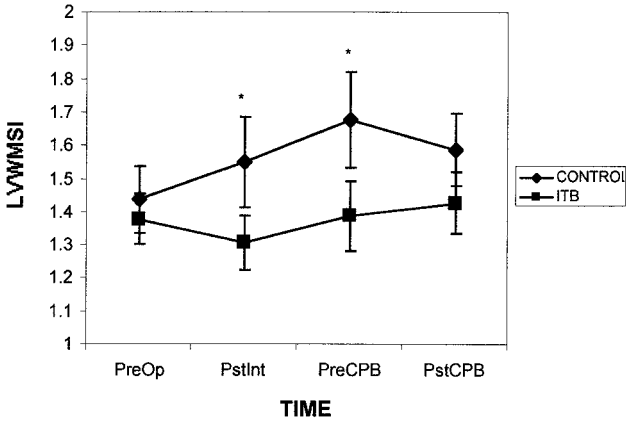

Fig. 4. Left ventricular wall motion score index (LVWMSI) values. LVWMSI values were significantly lower in the intrathecal bupivacaine (ITB) group after intubation and before cardiopulmonary bypass, suggesting improved left ventricular wall motion in the ITB group. 1 = normal; 2 =hypokinetic; 3 = akinetic; 4 = dyskinetic; PreOp = preoperative transthoracic echocardiography; PstInt = postintubation transesophageal echocardiography; PreCPB = pre-CPB transesophageal echocardiography; PstCPB = post-CPB transesophageal echocardiography. Results are expressed as mean ± S.E.M (*$P < 0.05$).

after CABG surgery.[9] However, TEA requires the use of a large needle in the thoracic epidural space, and in the event of a traumatic insertion of the needle or catheter, the risk of neuraxial hematoma, although not clearly known, may be greater. ITB may represent a suitable alternative to TEA. It provides many of the benefits of sympathectomy, but because of the smaller needle and lack of catheter insertion, it may have a lower risk. In a retrospective study by Kowalewski *et al.*,[30] the use of ITB combined with general anesthesia produced stable hemodynamics. There has been no previous investigation that has quantitatively determined if ITB, like TEA, blunts the stress response to CABG. Also, the hemodynamic effects of a high-spinal sympathectomy have not previously been studied in a prospective, controlled manner.

One of the benefits of ITB may relate to its ability to modulate catecholamine responses. High catecholamine concentrations can lead to βAR desensitization.[3–5,21] Acute myocardial βAR desensitization, followed by receptor internalization and destruction (down-regulation), has previously been demonstrated in humans following CPB and may be a contributing factor to myocardial contractile problems after cardiac surgery. Direct uncoupling of the adenylyl cyclase moiety appears to be the mechanism accounting for this acute βAR dysfunction and has two components: a decrease in adenylyl cyclase activity and a down-regulation in the β-adrenergic receptor numbers. As previously shown by Schwinn *et al.*, these events have also been shown to occur over different time courses.[5,20,21] Because of the association between the duration of CPB and the extent of β-receptor dysfunction, we examined the relation between CPB time and the various components of the atrial βAR function. With CPB times in excess of 1 h, we have shown that the technique of high-dose ITB anesthesia helps to prevent this receptor dysfunction, as measured by maximal activity after stimulation with isoproterenol, 50% maximal activity after stimulation with isoproterenol, sodium fluoride–stimulated activity, and zinterol stimulation assays of adenylyl cyclase activity and βAR density. Based on these findings, it is therefore

Table 5. Respiratory Function and Gas Exchange Data

	Group	Preoperative	Prespinal	Preextubation	PACU Arrival + 2 h	PACU Arrival + 4 h	PACU Arrival + 24 h	PACU Arrival + 48 h
*p*H	Control	7.41 ± 0.006	7.40 ± 0.006	7.40±0.014	7.32 ± 0.009	7.32 ± 0.009	7.40 ± 0.009	7.46 ± 0.009
	ITB	7.40 ± 0.007	7.40 ± 0.006	7.40 ± 0.013	7.32 ± 0.005	7.33 ± 0.008	7.40 ± 0.007	7.46 ± 0.006
Pao_2, mmHg	Control	107 ± 8.9	146 ± 9.8	328 ± 32	100 ± 9.7	97 ± 10.3	58 ± 3.3	60 ± 2.2
	ITB	103 ± 8.4	133 ± 7.3	314 ± 31	92 ± 2.2	85 ± 7.3	61 ± 3.8	62 ± 1.9
$Paco_2$, mmHg	Control	41 ± 0.95	44 ± 0.71	38 ± 1.8	47 ± 1.1	48 ± 1.4	40 ± 0.87	48 ± 0.72
	ITB	41 ± 0.92	43 ± 1.3	39 ± 1.64	45 ± 0.73	44 ± 1.2†	40 ± 1.3	37 ± 1.2
Bicarbonate, mm	Control	26 ± 0.39	27 ± 0.35	24 ± 0.52	23 ± 0.32	24 ± 0.36	25 ± 0.49	26 ± 0.53
	ITB	25 ± 0.52	27 ± 0.58	24 ± 0.47	23 ± 0.35	23 ± 0.40*	25 ± 0.50	26 ± 0.70
Fio_2	Control	0.25 ± 0.016	0.44 ± 0.0059	0.90 ± 0.044	0.37 ± 0.034	0.32 ± 0.027	0.21 ± 0.004	0.21 ± 0
	ITB	0.24 ± 0.014	0.34 ± 0.0045	0.87 ± 0.05	0.37 ± 0.044	0.34 ± 0.034	0.21 ± 0.0063	0.21 ± 0
$AADo_2$, mmHg	Control	20 ± 6.1	44 ± 12	265 ± 24	153 ± 23	87 ± 13	43 ± 4.4	41 ± 2.5
	ITB	21 ± 5.1	43 ± 9.0	258 ± 21	119 ± 26	91 ± 18	41 ± 4.6	40 ± 2.3
Percent predicted FEV_1	Control	87.1 ± 5.8	NA	NA	NA	23.8 ± 2.0	34.0 ± 2.0	36.3 ± 2.2
	ITB	86.1 ± 4.8	NA	NA	NA	24.8 ± 2.6	35.4 ± 2.8	39.4 ± 2.4
Percent predicted FVC	Control	93.3 ± 5.2	NA	NA	NA	26.5 ± 2.2	35.3 ± 2.2	40.3 ± 2.5
	ITB	91.3 ± 4.0	NA	NA	NA	28.2 ± 2.4	36.2 ± 2.4	42.6 ± 3.0
Percent predicted FEV_1/FVC	Control	90.9 ± 2.7	NA	NA	NA	89.0 ± 4.5	94.9 ± 2.2	90.4 ± 3.9
	ITB	90.8 ± 2.8	NA	NA	NA	85.5 ± 3.7	92.8 ± 3.2	90.5 ± 2.6

There were no significant differences in baseline or perioperative bedside spirometry between groups. When compared to the control group, the intrathecal bupivacaine (ITB) group had a significantly lower mean $Paco_2$ at the 4 h postoperative time point. Bicarbonate was also lower in the ITB group when compared to the control group. Values are expressed as mean ± SEM.

*$P < 0.05$. †$P < 0.01$.

$AADo_2$ = arterial–alveolar oxygen tension difference; FEV_1 = forced expiratory volume in 1 s; Fio_2 = fraction of inspired oxygen; FVC = forced vital capacity.

Table 6. Postoperative VAS Pain Scores at Rest and with Coughing

Time Point	Group	VAS at Rest	VAS with Cough	Cumulative PCA Attempts	Cumulative PCA Dose, mg
PACU arrival + 2 h	Control	6.7 ± 0.76	6.5 ± 0.77	15.6 ± 4.9	4.2 ± 0.67
	ITB	5.8 ± 0.70	6.7 ± 0.71	15.9 ± 5.6	4.7 ± 1.0
PACU arrival + 4 h	Control	4.9 ± 0.67	5.5 ± 0.64	30.1 ± 7.5	11.6 ± 1.8
	ITB	4.2 ± 0.55	5.3 ± 0.42	31.3 ± 8.5	9.7 ± 1.4
PACU arrival + 24 h	Control	5.2 ± 0.74	6.3 ± 0.89	89.9 ± 19	40.9 ± 6.1
	ITB	4.9 ± 0.48	5.4 ± 0.44	106.5 ± 26.5	40.9 ± 5.1

Cumulative patient-controlled analgesia (PCA) attempts and morphine dose delivered for the postoperative time course are shown. There were no significant differences in postoperative visual analog scale (VAS) scores or PCA morphine use. Data are expressed as mean ± SEM.

ITB = intrathecal bupivacaine.

reasonable to conclude that the technique may have the most utility in patients likely to have CPB times in excess of 1 h.

Epinephrine and norepinephrine concentrations were significantly reduced in the ITB group. In addition, serum cortisol concentrations were significantly lower in the ITB group immediately after separation from CPB. This observation that epinephrine, norepinephrine, and cortisol concentrations are decreased in the ITB group suggests the primary mechanism through which high-bupivacaine intrathecal anesthesia preserves adenylyl cyclase activity and βAR density. The significant reduction in sympathetic activity seen in this study may be due to a decreased release of epinephrine and norepinephrine mediated by the adrenal response, as well as from the neuraxial reflex mechanisms. Because the preoperative chronic administration of β-blockers has been associated with higher baseline adenylyl cyclase activity, preoperative β-blocker use was examined.[21] Although this may have been a potential confounding variable, there was found to be no difference between groups in the number of patients receiving preoperative β-blockers, as well as calcium channel blockers and angiotensin converting-enzyme inhibitors.

This study has outlined the hemodynamic consequences of high-dose bupivacaine spinal anesthesia in patients undergoing cardiac surgery. This technique, in conjunction with general anesthesia, provided acceptable hemodynamic control. ITB patients showed a trend toward a higher cardiac index in the pre-CPB period and significantly higher cardiac index after separation from CPB, with mean arterial pressure and systemic vascular resistance index being significantly lower in the ITB group during the pre-CPB period. As a result, more α-agonists were required to maintain MAP in the ITB group, but in the pre-CPB period only. Although the technique can result in substantial hypotension, hemodynamic goals were easily met by the administration of phenylephrine. Because of the significant improvement in cardiac index and reduction in afterload, high-dose ITB anesthesia may be an appropriate anesthetic adjunct for patients presenting with depressed cardiac function. The reduction in mean pulmonary artery pressure and pulmonary vascular resistance index that is also seen may be of particular benefit for those patients presenting with an element of right ventricular dysfunction and pulmonary hypertension.

To provide a functional measure of myocardial contractility, regional wall motion was examined using transesophageal echocardiography, and left-ventricular wall motion score indices were calculated and compared. As demonstrated by a lower left ventricular wall motion score index, patients in the ITB group had significantly improved regional wall motion in the postintubation and pre-CPB periods. This occurred despite the control group receiving twice as much isoflurane as the ITB group. It is now well established that volatile anesthetics have a strong antiischemic effect by stimulating mitochondrial and sarcolemmal adenosine triphosphate–sensitive potassium channels.[35,36] By using a different approach, a recent study in a canine model has shown that esmolol administration during CPB may also improve ventricular function by the prevention of βAR desensitization.[37]

In the post-CPB period, the trend for improved left ventricular wall motion continued but was not significantly different between the two groups. The benefits of cardiac sympathectomy on the left ventricular wall motion score index and hemodynamics is in keeping with previous work that has shown that TEA-induced cardiac sympathectomy relieves angina, improves ST segment depression, favorably alters the oxygen supply/demand ratio in ischemic myocardium, increases the diameter of stenotic epicardial coronary arteries, and improves global and regional left ventricular function.[38–41]

Although there was no effect on perioperative spirometry, it is interesting to note that patients in the ITB group had lower arterial carbon dioxide partial pressure and HCO_3^- concentrations in the PACU. This is perhaps because the ITB technique allows for a reduction in the amount of volatile anesthetic agent required. This decreased exposure to inhaled anesthetic agent may lead to a higher minute ventilation in the postoperative period. PCA morphine use and VAS scores did not differ between groups. A preemptive analgesic effect of high-dose ITB was not seen. We have also shown that the technique allows for very early extubation and safely bypassing routine intensive care unit admission.

The effects of high-dose ITB on the release of inflammatory mediators during CABG surgery has yet to be determined. In addition, an effect on postoperative cardiac arrhythmias was not demonstrated. Future studies might also examine the use of high-dose ITB in combination with low-dose intrathecal morphine (5 μg/kg) for cardiac surgery.

This randomized, double-blinded, controlled study has shown that, for cases with CPB times in excess of 1 h, high-dose ITB attenuates βAR desensitization and downregulation. In addition, the sympathectomy induced by this technique results in a significant intraoperative reduction in the stress hormone response to surgery.

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Appendix: The Winnipeg High-Spinal Anesthesia Group

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The members of the Winnipeg High-Spinal Anesthesia Group participated in the study by helping to ensure similar anesthetic and surgical conditions during the study, assisting in obtaining atrial biopsy and catecholamine samples, administering the spinals or sham spinals, providing their valuable advice and experience with the high-dose spinal bupivacaine technique, supervising the intraoperative transesophageal echocardiography examinations, obtaining informed patient consent where appropriate, collecting data and maintaining the database, analyzing the echocardiogram tapes, and performing the β-receptor and catecholamine assays.